PROMISING CANCER THERAPEUTIC DRUG TARGETS:

RECENT ADVANCEMENTS

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Promising Cancer Therapeutic Drug Targets: Recent Advancements

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PREFACE

The development of a population of cells that can invade tissues and spread to distant sites, resulting in significant morbidity, is what is known as cancer. Cancer is an abnormal growth of cells brought on by multiple changes in the gene expression, which result in a dysregulated balance of cell proliferation and cell death. A group of illnesses affecting higher multicellular organisms include cancer. The capacities to invade locally, disseminate to nearby lymph nodes, and metastasize to distant organs in the body distinguish malignant cancer from benign tumors. The acquisition of multidrug resistance and relapse pose the biggest challenge in the development of anticancer drugs. Traditional cancer treatments directly affect the DNA of the cell, but modern anticancer medications use molecularly focused therapy, such as focusing on proteins that have an aberrant expression in cancer cells. Conventional methods for completely eliminating cancer cells were found to be ineffective. Although targeted chemotherapy has been beneficial in treating some cancers, its efficacy has frequently been constrained by drug resistance and adverse effects on healthy tissues and cells. The aberrant tumor signaling, however, involves pathways for phosphoinositide 3-kinase (PI3K)/Akt, mammalian target of rapamycin (mTOR), Wnt/-catenin, mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3 (STAT3), and notch signaling. Targeted chemotherapy has been beneficial in some cases of cancer, but its efficacy has frequently been constrained by drug resistance and adverse effects on healthy tissues and cells. On the other hand, the majority of researchers are interested in the promising field of immunotherapy. Targeting cancer stem cells and microRNAs generally play a vital role in cancer medication development together with aberrant tumor signaling pathways. The main cause of medication resistance and tumor recurrence is recognized to be cancer stem cells. MicroRNAs are brief non-coding molecules that are 20-22 nucleotides long. It has the propensity to control a number of important signaling pathways that encourage cancer. Therefore, the current book discusses several of these important anticancer targets, such as cancer stem cells, microRNAs, (PI3K)/Akt, mTOR, Wnt/-Catenin, MAPK, STAT3, and notch signaling pathways. Additionally, numerous clinical trial phases for promising natural and synthetic medication candidates are outlined.

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CHAPTER 1

Exosomal Delivery of CRISPR/CAS9 Assembly: Approach towards Cancer Therapeutics

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Abstract: Exorbitant cancer malignancy is at the helm of multiple organ malfunction in humans and is considered a cause of increased cancer mortality worldwide. Clustered regularly interspaced short palindromic repeats (CRISPR) are powerful machinery for the therapeutic approach to tumors because of their substantial peculiarity, focusing on modulatory molecules, both oncogenes and tumor suppressors, to preclude tumor metastasis and enable apoptosis. Exosomes are considered an ideal delivery system because of their specificity and ability to prevent premature release of cargo. Exosomes are accessed as an effective conveyance of CRISPR/Cas9 elements and other attractive biomolecules to recipient cancer cells. The CRISPR/Cas9 loaded exosomes are endocytosed for further alteration of cellular metabolic pathways, either by knock-in or knock-out of the designed destined gene using sgRNA and Cas9 protein. The current study provides a platform to address the alliance between the CRISPR/Cas9 model and exosomes, depicting a remarkable therapeutic approach against cancer and other fatal diseases.

Keywords: CRISPR Clustered regularly interspaced short palindromic repeats, Cas - CRISPR-associated protein, CrRNA - CRISPR RNA, EMT - Epithelial to mesenchymal transition, gRNA - Guide RNA, MHC - Major histocompatibility complex, TracrRNA - trans-activating CRISPR RNA.

INTRODUCTION

Cancer can be defined as the ungoverned multiplication of cells that propagate far and wide through discrete organs. The unbeatable accumulation of aggressive

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cells creates an aching mass called “Tumor” that is benign in the preliminary phase, however, it undergoes extension in later phases. The characteristics of cancer cells include evasion of cell cycle regulatory checkpoints, chromosomal aberrations leading to a gain of function of specific oncogenes influencing conventional splitting of cells, subjugation of tumor suppressors by mutation or its related molecules, blocking of the body’s immune system and its regular functions, prevention of caspase-mediated cell death, acquisition of mesenchymal cellular attributes, and blood vessel organization.

As reported by GLOBOCAN 2020, there are 19.3 million unprecedented cases of cancer with a survival rate of 9.3 million for the early detection of the disease [1]. The understanding of the occurrence of cancer can be extrinsic components, for instance, consumption of excessive nicotine present in cigarettes [2], consumption promoting foodstuffs such as processed meat, alcohol, junk food, and drinks, exposure to deadly radiation [3], and viral infections [4, 5]. Intrinsic abiogenetic records increase vulnerability to tumorigenesis [6]. By employing diagnostic tools corresponding to national databases, doctors can reveal different stages of cancer and advance further. The tumor of stage 0 is benign and exists at the place of its origin, and its early recognition can be remediable by eliminating the tumor through surgery. Stage I tumor is a minor protuberance that is settled at one site and neither augmented intensively in adjacent tissues nor stretched in another place towards lymph nodes. Stages II and III are regarded as the initiation of the migratory ability of cancer cells within easy-to-reach tissues along with lymph nodes. Treatment options for stages I-III include surgery, chemotherapy, and radiation therapy. Stage IV exhibits a highly precarious patient condition with a weakly favorable medicament since the tumor circulated rapidly to distant organs and recommended Targeted Immunotherapy in addition to the mentioned ones.

Cancer examinations can be performed through imaging trials, Endoscopy, Bioscopy, and discrete body fluid tests. Cancer metastasis is related to the expansion of unregulated cells that disrupt their prevailing morphology and attain locomotion efficiency in various parts of the human body (Fig. **1**). These metastatic cells breached the epithelial tissue lining and entered the biological fluids, such as blood, milk, saliva, semen, vaginal fluid, and urine, and further interfaced with healthy cells for their transition into tumor cells. This evolution of genes favors the synthesis of growth-promoting proteins, whereas it obstructs programmed cell death molecules [7]. Portments of metastatic carcinoma include pain, vomiting, body weight reduction, exhaustion, feverishness, infrequent excretion, and hemorrhage [8]. Therapeutic options for cancer that are currently used worldwide include chemotherapy, radiation therapy, and surgical removal of solid tumors coupled with either one of the aforementioned therapies. Targeted

therapeutic interventions are of prime focus these days in order to avoid any cytotoxicity exerted by chemotherapy on adjacent normal cells.

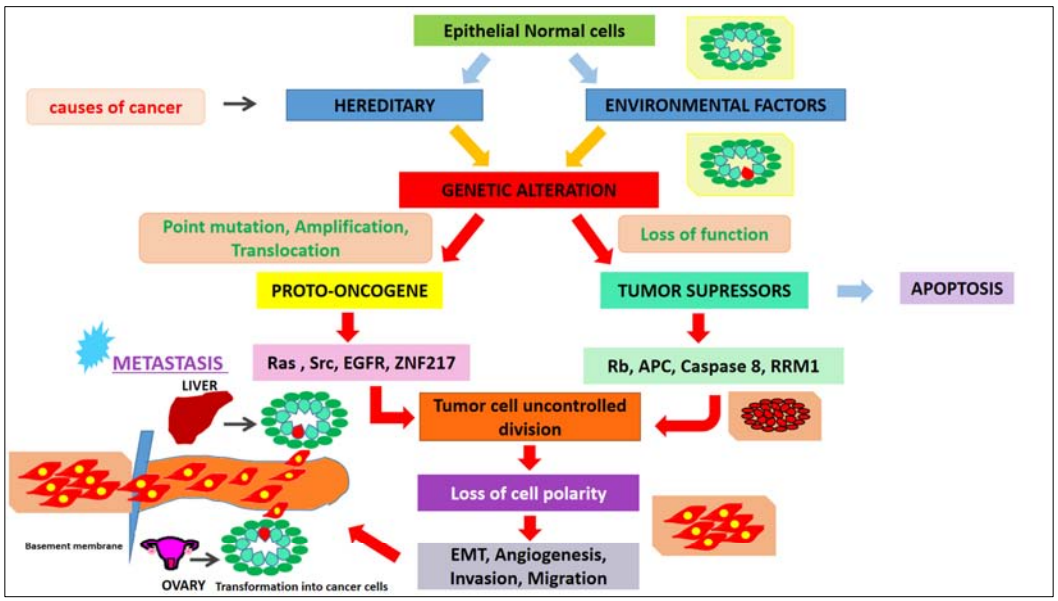

Fig. (1). Cancer metastasis.

Exosomes are nanovesicles of approximately 30-150 nm liberated by all types of living cells under natural as well as pathological conditions. The breakthrough in the discipline of extracellular vesicles emerged in the year 1983 searched out in Reticulocytes for endocytosis of iron [9] and it is composed of transferrin receptors, sphingomyelin, amino acid and glucose transporters liberated apart from the cell, therefore, designated as “Exosomes” [10]. Exosomes are produced by cellular machinery and further move out and mobilize in the extracellular space, interacting with other cells for the purpose of conveying specific molecules, consequently influencing the cellular metabolism of recipient cells. They are an exemplary means of proteins (CD63, CD81/82, Alix, TSG101, Rab) [11], nucleic acid family [12], and fatty acids (ATP-binding cassette transporter A1, low-density lipoprotein receptor, low-density lipoprotein receptor) [13], which are involved in immune response, modulate the tumor microenvironment, cancer infiltration, and evade cell death. Further studies have demonstrated that exosomes serve as clusters of biomarkers for the preliminary identification of malignancy.

Exosomes perform their function in cancer therapeutics by impeding the activity of constitutively expressed growth-promoting genes at former neoplastic spots, controlling their cellular habitat, and preventing affinity to different organs and

CHAPTER 2

Cancer Stem Cells and Their Role in Chemo-Resistance

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Abstract: Cancer stem cells (CSCs) are found to be responsible for chemoresistance and disease relapse because of their ability to self-renew and capacity to differentiate into heterogeneous lineages of cancer cells. The in-depth knowledge of molecular mechanisms and their characteristics that ultimately lead to treatment failure might help in finding novel targets and make the drugs effective for a longer time. In this chapter, we will try to understand the key features and characteristic mechanisms that regulate CSC function at the molecular level in drug resistance as well as recent developments in therapeutic approaches for targeting CSCs. The novel insights into the role of CSCs in chemo-resistance will provide better therapeutic rationales for treating cancer. This chapter will also discuss the basics of conventional chemotherapies, different theories of CSC, molecular and cellular mechanisms of CSC self-defense, and how all these factors are ultimately involved in chemoresistance.

Keywords: Cancer, Cancer therapy, Drug-resistant, Stem cells, Transporter proteins.

INTRODUCTION

Since the identification of cancer stem cells (CSCs) in the tumor, the understanding of carcinogenesis and chemotherapy approaches has changed a lot. Research has focused a lot on the involvement of cancer stem cells in carcinogenesis, drug resistance, and metastasis. Bone marrow stem cells are required for continuous replenishment of blood cells and they consist of long-term renewing stem cells, short-term renewing stem cells, and nonrenewable multipotent progenitors that can only differentiate into various types of blood cells in the bone marrow. There needs to be a proper balance in cell renewal and cell

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division and any aberrant changes can lead to blood cancer development. Pluripotent stem cells are present in the organs that have the ability of self-renewal and differentiate into organ-specific cells and aberrant proliferation of these cells is involved in or aggravates the solid cancer development and growth. In the mammary gland tissues, three types of cells have been identified-myoepithelial cells, ductal epithelial cells, and milk-producing alveolar cells- but the clonal population can develop into all the functional types of mammary gland cells. Human mammary epithelial cells can be developed into spheroids that consist of the three main types of mammary cells. One of the important characteristics of normal stem cells which remain quiescent and stay most of the time in the SubGo phase is self-renewal and pluripotency. Stem cells can repair DNA and also accumulate carcinogen-induced mutations with time. But whether cancer stem cells arise from pre-existing normal stem cells after the accumulation of mutation or cancer stem cells and normal stem cells are independent is still a topic of contention. Stem cells are relatively more resistant to toxins and radiation and this might be a possible cause of the development of resistance in cancer stem cells in a longer course of treatment. A better understanding of normal/cancer stem cell biology can give a better idea to deal with cancer development and resistance to the treatments.

Normal Stem Cells and Cancer Stem Cells Linked to Carcinogenesis

Cancer stem cells are present in the tumors and play an important role in different types of blood cancers and solid cancers. These stem cells might be the source of the development and reemergence of cancer after chemotherapy. Cancer stem cells, which are a very small fraction of the tumor have the potential to grow into tumors when transplanted at new sites but the rest of the tumor cells lack this regenerative power. It is a general perception that leukemia originates from the stem cell population that gets transformed and produces a large colony of cells that have lost the potential of self-renewal and differentiation. Teratocarcinoma is an important example of the presence of pluripotent cells in tumors [1]. Stem cells present in the tumor have been shown to express organ-specific biomarkers (Table **2**). The pluripotent stem cells present in the tumor might arise from the normal stem cells that had accumulated mutations or from the differentiated cells that had acquired the capacity of self-renewal and stem cell properties [2]. Cancer stem cells have many properties similar to normal stem cells and hence sometimes it becomes very tough to distinguish between them. Normal stem cells might provide the properties of drug resistance, a longer resting phase, active DNA repair capacity, and anti-apoptotic potential, and also similar characteristics are present in cancer stem cells [3]. The study of the detailed mechanism of development of drug resistance in normal or cancer stem cells of the tumor might prove new drug targets and a better strategy to manage the cancer disease.

Transporter Proteins in Stem Cells and Cancer

Stem cells have the properties of self-renewal and differentiation as well as quiescence for a longer time interval. They also require a special microenvironment consisting of unique cells, stroma, and growth factors for their survival and maintenance. Stem cells are shown to express very high levels of ABC drug transporter proteins [4]. Hematopoietic stem cells express very high levels of ABCG2 [5] proteins, and two of the most extensively studied ABC transporter genes are ABCB1 and ABCG2 [6]. ABCC1 gene has also been shown to be overexpressed in multidrug-resistant cancer cells [7]. The ABC transporter superfamily plays an important role in normal physiology and helps in transporting the drugs across the placenta and intestine. They have also an important role in the blood-testis barrier [8] and blood-brain barrier [9]. These transporters efflux the toxic chemicals from the cells utilizing the energy of ATP hydrolysis and protect the cells from harmful effects. The drug-transporting property of stem cells is also utilized for their isolation and analysis in blood cancers. Hoechst 33342 and rhodamine 123 dyes are accumulated inside the cells but the stem cells expressing ABCG2 and ABCB1 throw out these dyes outside the cell [10]. These low fluorescent stem cell populations because of efflux are called dull cells or side population (SP) cells [11]. The side population of stem cells can be isolated from many organs and they might represent lineage-specific stem cells.

Chemotherapy Resistance in Cancer and Cancer Stem Cells

There are multiple ways by which a cancer cell can acquire resistance to chemotherapeutic drugs such as drug efflux, mutation and/or overexpression of drug targets, metabolizing or inactivating the drugs [12]. Typically, cancer cells that re-emerge at primary or secondary sites after the chemotherapy cycles are multiple drug-resistant, and because of the selective advantage, they overtake the tumor population. Cancer stem cells have the natural tendency to resist chemotherapy because of the expression of ABC transporters, quiescence nature, and DNA repair capabilities, and these characteristics allow tumor cells to survive chemotherapy and help tumor cells regrow by releasing various factors. According to the acquired resistance model, cancer stem cells or their close progeny acquires resistance to the drugs [13]. Based on the recent experience with imatinib (Glivec) in leukemia, it was found that ABC-mediated efflux is not the only responsible factor behind drug resistance in cancer stem cells. In the case of leukemia, mutation in ABL is the stronger reason behind imatinib resistance as compared to the drug efflux [14]. DNA repair capacity and overexpression of antiapoptotic pathways also play an important role in drug resistance [15]. Since stem cells are quiescent and non-dividing cells hence, they are generally

CHAPTER 3

Importance of Natural Compounds Targeting the Mitophagic Process in Breast Cancer Treatment

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Abstract: Breast cancer is a serious concern among women and the second most common cancer worldwide with an estimated 2.3 million new cases reported in the year 2020 alone. Most breast cancers are *carcinomas*, which can be further classified into invasive and *in-situ* carcinomas depending on their infiltrating ability. Also, another classification of breast cancers exists based on the presence or absence of hormone receptors on the cell surface namely Triple-negative breast cancer (TNBC), Basal-like BC, Claudin low, HER2+, Luminal A and Luminal B. The diagnosis and treatment for the above-mentioned subtypes prove to be quite challenging. A special form of autophagy in which the damaged or defective mitochondria are detected by the autophagy machinery and are finally digested by the lysosomes is known as mitophagy. Recent investigations have reported that the mechanisms governing mitochondrial activities are critical for cancer therapy. Since most of the chemically synthesised drugs in recent times have not been shown to increase the overall survival rates in BC patients and on the contrary have resulted in many side effects, new strategies, and innovative chemo-preventive agents are required to augment the efficacy of existing cancer regimens. Phytochemicals, naturally occurring plant compounds, are important sources for new medications in cancer therapies which may thus prove to be better than their existing chemotherapeutic counterparts. Hence, the incorporation of such phytochemicals favouring mitophagic dysregulations alongside existing treatment regimes (endocrine therapy, chemotherapy, surgical exclusions) may prove to be effective in minimizing the side effects associated with these treatments.

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Keywords: Breast cancer, Chemo-preventive agents, Mitophagy, Natural compounds, Triple negative breast cancer.

INTRODUCTION

Cancer is a unique disease that can occur in different parts of the human body. Breast Cancer (BC) is very common in women and is better defined as the unchecked growth of malignant cells in the mammary epithelial tissues. This disease affects both genders, however, it is more predominant among females and its incidence rises dramatically with age [1]. Various studies have shown that lung cancer in the male population is seconded by breast cancer in women proving to be the main source of cancer-related mortality across the globe, with almost 1.7 million new cases and 521,900 deaths in 2012 alone, when contrasted with 1.38 million new cases and 458,000 deaths during 2008 [2, 3]. This records around 25% of all new disease cases and 15% of all cancer-related deaths among women [2, 4, 5]. An expected 231,840 (29%) new instances of the invasive form of breast cancer were analysed among females in the US during 2015, in contrast to 105,590 (13%) instances of lung cancers in a similar populace [6].

BC is a diverse condition with promising prospects with many biochemical modifications that occur throughout the disease's course. Similar to developments in other cancer types, current advances in tumour sequencing technology have led to the discovery of molecular targets and pathways that are engaged in the carcinogenesis development of BC and the advancement of the tumor [7, 8].

Mitophagy is an adaptive response that is reported to be induced by various stress factors thereby eventually aiding in the removal of damaged mitochondria [9]. When it pertains to carcinogenesis, autophagy, and mitochondrial clearance seem to function as a process that is recruited on demand by growing cancer cells in order to alter significant malignant characteristics throughout cancer onset and progression [10]. In recent years, there has been increasing evidence that mitophagy pathways are important regulators of cancer cell mitochondrial mass and dynamics, redox homeostasis, bioenergetics, oncogene-driven metabolic transformation, and cell death signals. This is associated with the fact that mitochondrial biology and metabolic adaptability are critical in the progression of cancer as well as in response to anticancer treatments. There is a growing consensus that mitophagy is a highly adaptable system that assists cancer cells in their metabolic transformations and survival inside the hostile tumour microenvironment [9].

Chemotherapeutic drugs harbour their advantages and drawbacks. Therefore, the National Comprehensive Cancer Network (NCCN) recommends combination therapy of anti-cancer drugs. Chemotherapy, however, has negative effects on

both malignant and normal cells. Recent findings have proven that chemotherapy for breast cancer might induce cardiotoxicity [11].

Flavonoids, alkaloids, polysaccharides, essential oils, quinonoids, terpenoids, coumarins, and saponins are endogenous chemical components of plant extracts. Numerous researchworks have shown that natural plant compounds have anti-inflammatory, antiviral, antioxidant, neuroprotective, and cardioprotective characteristics [12]. Many *in vitro* and *in vivo* research, as well as clinical trials, have shown that natural products possess anticarcinogenic and chemo-preventive benefits on malignant cells involving DNA repair, cell proliferation, differentiation, apoptosis, carcinogen metabolism, angiogenesis, and progression. Hence, the synergistic effects of natural products and chemotherapeutic medicines eventually reduce toxicity and drug resistance [11]. This review thus highlights the treatment strategies for breast cancer, their negative impacts, the role of mitophagy in breast cancer, and the use of various natural compounds as effective drugs against mitophagy to hinder tumor progression.

Breast Cancer Statistics

As per a precise examination of BC cases in 187 nations worldwide, the frequency of breast malignancy expanded from 641,000 cases in 1980 to 1,643,000 cases in 2010, suggesting a yearly increment of 3.1% [13]. It served as an important reason for malignancy-related mortality in ladies in the less developed regions (324,000 deaths accounting for 14.3% of the aggregate) and is presently considered the second most incessant reason for cancer-related deaths in females in developing countries too (198,000 deaths accounting to 15.4%) [2]. However, the rate of incidence greatly differed across nations like Northern America, Australia, and New Zealand having a higher occurrence in contrast with Africa and Asia having a lower incidence [3]. Though Europe reported the maximum BC cases with individual nations like Belgium and Denmark (119.9 and 105.0 per 100,000 separately) exceeding the incidence table (IARC 2014), North American and West European countries reported the maximum cases in region-wise distribution. The last occurrence was seen in Eastern Asia and Central America. Despite the fact that frequency rates stayed most elevated in the developed countries, mortality was generally a lot higher in the less developed regions [4]. According to recent reports, although the well-developed nations account for around 2.3 million new BC cases, approximately only 6,85,000 cases have been reported as mortality [2, 5].

Various surveys state that patterns in occurrence are influenced by ethnicity and age in various populations. For instance, in developing nations it had been accounted that females of reproductive age were twice as liable to develop BC

CHAPTER 4

Bioactive Natural Compounds as Inhibitors of Signal Transducer and Activator of Transcription 3: Prospects in Anti-Cancer Therapeutics

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Abstract: STAT3 is regarded as a latent transcription factor, which is activated by tyrosine phosphorylation at position 705 by non-receptor tyrosine kinase, leading to its dimerization, nuclear translocation, DNA binding, and activation of gene transcription. Activation of STAT3 is important for the transcription of genes related to cell cycle, growth, proliferation, migration, and angiogenesis. Under normal physiological conditions, its upstream signaling that leads to its activation is tightly regulated, but in cancer, the activation of STAT3 is dysregulated. Studies on various cancer models suggest that it is constitutively activated in cancer cells and plays a crucial role in the growth, progression, and metastasis of cancer. It is involved in the induced expression of procarcinogenic cytokines, such as interleukin-13, and suppressed expression of Anti-cancer cytokines, such as interleukin-12, indicating shifting of the balancer of tumor immunity toward tumor growth and progression. Thus it appears to be a potential target for cancer therapeutics. Several bioactive compounds from natural sources have been found to interfere with the signaling leading to deregulated STAT3 activation in cancer cells and subsequent cancer suppression/rejection. This chapter discusses a wide range of natural bioactive compounds that show antitumor effects by inhibiting STAT3 activation both *in vitro* and *in vivo*, as well as their future perspectives in anti-cancer therapeutics.

Keywords: Apoptosis, Anticancer therapeutics, Cell cycle, Cell proliferation, Cell migration, Lignans, Flavonoids, Metastasis, Polyphenols, STAT3, Tumor growth, Triterpenes.

INTRODUCTION

Transcription factors (TFs) are protein molecules that bind to the DNA-regulatory sequence of the genes and regulate gene expression. Its binding to regulatory

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sequence, *i.e.*, enhancers and silencers, upstream to target genes may result in increased or decreased gene expression and protein synthesis, and subsequent altered cellular function. Several families of transcription factors exist and members of each family may share structural characteristics. Signal transducer and activator of transcription (STAT) proteins are a distinct type of latent cytoplasmic transcription factors consisting of seven mammalian members, *viz*. STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6 [1]. They mediate many aspects of cellular immunity, cell proliferation, apoptosis, and differentiation in a tightly controlled way with finite kinetics in normal physiological conditions [2]. Initially, STAT3 has been identified as a transcription factor bound with interleukin-6 responsive element downstream to IL-6/gp130/JAK pathway in response to IL-6 [3]. It has been found to be expressed in response to several other cytokine growth factors, such as epidermal growth factor (EGF) [4], platelet-derived growth factor [5], hepatocyte growth factor (HGF) [6], transforming growth factor-alpha (TGF-α) [7], granulocyte-macrophage-colony stimulating factor (GM-CSF) [8], fibrocyte growth factor-1 (FGF-1) [9], *etc*., cytokines, such as IL-6, IL-7, IL-9, IL-10, IL-11, IL-15, IL-22, IFN-α/β, Leukemia inhibitory factor (LIF), oncostatin M (OSM), leptin, and growth hormone (GH) [3, 10, 11]. The activation of STAT3 proteins downstream to signaling in response to cytokines and growth factors regulates the expression of a multitude of genes related to cell proliferation, survival, differentiation, apoptosis, inflammation, *etc*., like other STAT proteins [12]. Notably, it has been found that STAT3 is also activated to induce gene expression in response to many environmental factors, including carcinogens, sunlight, infection, tobacco consumption, cigarette smoking, and stress (Fig. **1**) [13 - 15].

It has been noted that the deregulated signaling results in constitutive activation of these STAT proteins in the cell that results in aberrated control of cellular machinery. Constitutive or unregulated activation of STAT proteins, particularly STAT3 and STAT5, has been found to be associated with many tumor cell types. It shows that aberrant signaling associated with these STATs has some crucial role in oncogenesis and the process of malignant transformation [16]. Aberrant STAT3 signaling has been found to promote uncontrolled growth and survival of cells through dysregulated expression of various genes associated with cell cycle, survival, and apoptosis, such as cyclin D1, cMyc, B-cell lymphoma-extra-large (Bcl-xL), myeloid cell leukemia-1 (Mcl-1), and survivin. Moreover, aberrant/constitutive activation of STAT3 has been found to induce the expression of vascular endothelial growth factors that contribute to tumor angiogenesis and promote immune evasion of tumor cells or metastasis [17, 18]. These findings indicate that STAT3 may be a new target for cancer therapy [19]. Thus these studies provided the rationale for designing and developing small molecules that

could interfere with the signaling cascade that might otherwise lead to STAT3 activation.

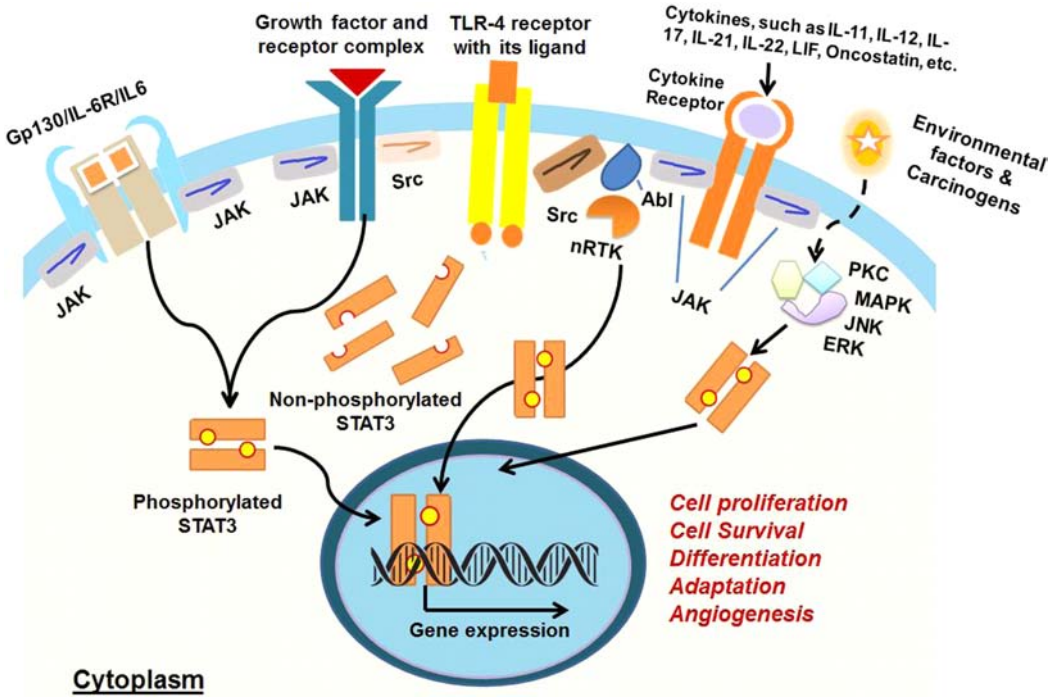

Fig. (1). Signaling pathway activating STAT3 in the cell. STAT3 is activated by a diverse array of molecules comprising both endogenous as well as exogenous origin. Different cytokines and growth factors bind to their corresponding receptor and activate receptor tyrosine kinase, such as JAK, which results in the phosphorylation of STAT monomer. STAT proteins then dimerise and translocate to the nucleus where they bind to the promoter region of the STAT3-inducible gene leading to the expression of a number of proteins involved in cell proliferation, survival, differentiation, adaptation, and angiogenesis. Upon internal stimuli, some serine/threonine kinases, such as Src and Abl with JNK activate cytoplasmic STAT3. Some environmental factors and carcinogens are able to activate STAT3 molecules through the activation of PKC/MAPK/ERK/JNK molecules.

THERAPEUTIC TARGETING OF STAT3 SIGNALING IN CANCER

The downstream signaling cascade that leads to STAT3 activation indicates several target points that can lead to disruption of the signaling pathway. There may therefore be several strategies to regulate or eliminate STAT3 signaling, like strategies to prevent the activation of STAT3 by preventing receptor-ligand interaction or by inhibiting kinases, to block the protein-protein molecule interaction of the signaling pathway, to block the nuclear translocation of STAT3 proteins, and further to block/inhibit binding of STAT3 with a promoter region of the genes.

CHAPTER 5

Targeting Cancer Stemness by Exosomes as a Therapeutic Approach against Ovarian Cancer

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Abstract: Early detection and effective treatment are daunting challenges in the field of cancer biology. Ovarian cancer has emerged as a third-ranked health issue among women worldwide. In recent decades, there have been numerous pieces of evidence regarding ovarian cancer depicting a high-grade cellular transformation leading to self-renewal, defining cancer stemness, aggressive growth, and distribution to other organs. Deregulated biological processes are activated, including the Wnt pathway, AKT/MAPK, and STAT3, in typical cells that turn down the governed cell division into uncontrolled expansion through cancer stem cell markers SOX2, CD133, CD44, CD117, and Aldehyde dehydrogenase, thereby suppressing the cell immune system and apoptotic activity. Currently, there has been the advent of innovative therapy for cancer known as "Exosomes," which are nanovesicles secreted by all cells conveying nucleic acids, proteins, lipids, and carbohydrates to the recipient cells. The upper-hand use of exosomes is marked by their immune tolerability, stability, and systemic delivery to target cells, which will contribute to cancer therapy. In this analysis, we will focus on the behavior of cancer stem cells in the EMT mechanism that promotes ovarian cancer and discusses exosome-based therapeutic applications that require further research to prevent tumor growth.

Keywords: Nanovesicles, Ovarian cancer, Wnt pathway.

INTRODUCTION

Ovarian cancer is classified as a leading gynecological carcinoma, with over 25,000 cases and an incidence rate between 5-8/100,000 in India. As stated by the WHO in the year 2020, there were 45,701 new cases of ovarian cancer with a mortality of 32,077 cases, thereby exhibiting lower chances of survival in India (Fig. **1**) [1].

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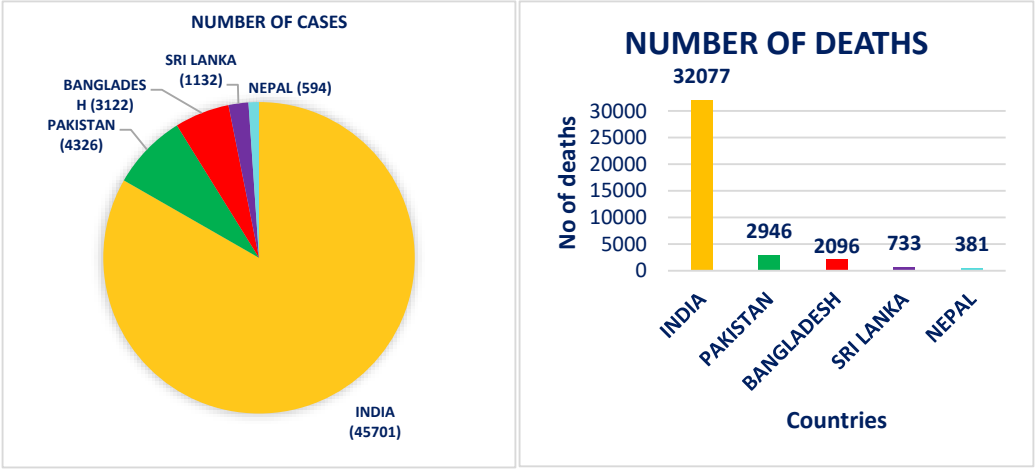

Fig. (1). Ovarian cancer cases statistics in India and its neighboring countries in the year 2020.

Ovarian cancer emanates from a single or both ovaries in its primary stage and dissipates through the fallopian tube to the uterine tract towards distant organs. Ovarian malignancies are of three types: the first is an epithelial tumor covering the ovarian membrane, which is categorized as serous epithelial cancer found in younger people (low grade) with altered KRAS and BRAF genes as well as in older age (high grade) populations with altered p53 and BRCA1/2 genes in the majority of cases. Mucinous epithelial cancer comprises solid tumor masses with mutated KRAS and HER2 genes' higher reoccurrence rate, and endometrial cancer results from mutations of PI3KCA, PTEN gene, and Clear-Cell Carcinomas, which are unusually early age conditions that give rise to solid tumor formation in the abdominal region and increased calcium content in the blood, which weakens the bones due to the alteration of ARID1A and PI3KCA gene expression [2]. The second type is Stromal Cell ovarian cancer regulated by hormone-producing granulosa cells and theca cells, resulting in anomalous vaginal bleeding, abdominal distress, and growth of facial hair at the juvenile age expressing a polycystic mass [3]. Genetic modifications of DICER1 at its RNase IIIb domain and of FOXL2 at its c.402C> G (p.C134W) site result in Sertoli-Leydig cell ovarian tumors [4]. The third is germ-cell ovarian malignancy originating from reproductive cells reported at the age of 10 to 30 years, with a higher expression of alpha-fetoprotein, b-hCG, and lactic dehydrogenase isoenzyme-1, which were examined in the majority of patients. Unilateral nodules with necrosis and hemorrhage were confirmed by computed tomography and could be eliminated through Surgery, Hysterectomy, and bilateral salpingo-oophorectomy in the second and third stages. Furthermore, surgery along with platinum-based chemotherapy or adjuvant chemotherapy is recommended for the

fourth stage of cancer [5]. Therefore, typical tumor germ cells exhibiting increased telomerase activity and aggressive growth caused by a certain set of genes typically expressed in progenitor cells were found to be overexpressed in tumor germ cells, resulting in genomic instability and DNA impairment [6].

Advancing ovarian tumor cells by means of ascetic fluid communicate with specific cell types, including stromal cells, fibroblasts, and adipocyte cells, which activate certain metabolic pathways that promote tumor growth. Ovarian cancer ascitic fluid is composed of lysophosphatidic acid, interleukin-6, VEGF, TNF-alpha, and TGF, which enables new blood vessel formation, chemoresistance, and epithelial-mesenchymal transition, and prevents cell death [7].

Cancer stem cells are young masses of uncontrolled growing cells with specialized competency for regeneration and dynamic division and possess oncogenic characteristics for their survival (Fig. **2**). They can reform themselves into a heterogeneous variety of cells and have significant variation in their gene expression compared to normal embryonic stem cells (ESCs) and adult stem cells. The foremost breakthrough in the discipline of stem cells was the transmission of human acute myeloid leukemia stem cells to severely immune-deficient mice with a higher expression of CD34 [8]. Notably, ovarian high-grade serous adenocarcinoma cells develop clones acquiring cancer stem cell characteristics and exhibit anchorage-independent growth by upregulating vimentin, slug, snail, and metastatic behavior by dispersing to the omentum, stomach, liver, pancreas, intestines, and heart [9]. Ovarian cancer stem cells (OCSC) were identified using biological markers, particularly CD133, CD44, CD117, CD24, and aldehyde dehydrogenase (ALDH), which trigger the NF-κB signaling mechanism for cellular proliferation [10].

Exosomes are cup-shaped double-layer nanovesicles that are constitutively released from all cells for intercellular communication. Their structure measures around 40-150 nm in diameter with zeta potential, and cargo varying from exosome sources exhibiting diversification; therefore, this variegation in exosomes helps simplify the identification of distinct types of cancer in comparison with the exosome-derived healthy population. Exosomes transport their conventional constituents, namely, lipids, nucleic acids, proteins, carbohydrates, and certain metabolites that are either present in their lumen or embedded in a lipid bilayer with the intention of delivering to the target cells for development [11]. Exosome biosynthesis is eventuated by the endosomal sorting complex required for transport (ESCRT) complexes, beginning from endosomes forming in the cytoplasm followed by the stepwise incorporation of specific molecules in the intraluminal vesicles (ILVs) through the Vps27–Hse1 complex assembled together in the multivesicular body (MVB) that is combined with the

CHAPTER 6

Sphingosine Kinase as a Target to Treat Gastrointestinal Cancers

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Abstract: Gastrointestinal cancer is a malignant condition of the gastrointestinal tract including the esophagus, stomach, small and large intestine, rectum, and anus. About 4.8 million new cases of gastrointestinal cancer were recorded in 2020. Current treatment options of gastrointestinal cancers have failed to treat the disease condition and newer approaches are under investigation. One such approach includes targeting the sphingosine kinase, a critical enzyme in sphingolipid metabolism. Known as structural molecules of the cellular membrane, sphingolipids, and their metabolism have emerged as important components of cellular functions like cell proliferation, cell survival, and cell apoptosis. Over the last few years, most of the enzymes involved in the metabolism of sphingolipids have been extensively studied, which has enlightened the primary roles of these metabolic enzymes in the sphingolipid metabolic pathway. Ceramide and sphingosine are synthesized mainly by oxidative stress, and chemotherapy/radiation which mediates apoptosis, and cell cycle arrest, while sphingosine-1-phosphate (S1P) converted from ceramide, has proliferation and anti-apoptotic properties. Findings regarding the nature of ceramide and/or S1P lead to evaluating the potential target enzymes, which are involved in the metabolism of ceramide and S1P. Sphingosine kinase HK1 (SPHK1) and sphingosine kinase HK2 (SPHK2) are diacylglycerol kinase family which converts ceramide into S1P. The overexpression of SPHK1 and SPHK2 has been documented in various cancers. Many *in vitro* and *in vivo* studies have been carried out to evaluate the role of sphingosine kinase in cancer. Based on the findings, few pharmacological interventions are under clinical study. This chapter includes sphingolipid metabolism and its essential enzymes, the role of sphingolipids and metabolic enzymes in cancer, potential enzyme targets for the treatment of cancer, and molecules under investigation.

Keywords: Ceramide, Ceramidase, Gastrointestinal tract, Gastrointestinal cancer, Sphingosine kinase.

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INTRODUCTION

Gastrointestinal cancer is a broad term that includes cancer of the upper gastrointestinal (GI) tract and lower GI tract. Upper GI tract cancer mainly includes esophagus cancer, stomach cancer, pancreatic cancer, gallbladder, and small intestine cancer while lower GI tract cancer includes colon cancer, rectal cancer, and gastrointestinal carcinoid cancer. Out of all types of cancer, colon, stomach, rectum, and esophageal cancer accounts for 6.1%, 5.7%, 3.9%, and 3.2% respectively. In 2018, over 1.8 million new colorectal cancer cases were registered and 881,000 deaths were estimated around the world. Colorectal cancer lines are second regarding mortality and third regarding incidence. The incidence of colorectal cancer is higher in developed countries compared to developing countries although the scenario is changing dramatically. For stomach cancer, over 1,000,000 new cases in 2018 were reported with an estimated number of deaths of 783,000 persons, making it the fifth most frequently diagnosed cancer and third in mortality of all cancer deaths. Esophageal cancer accounted for 5,72,000 new cases and 5,09,000 deaths in 2018. Esophageal cancer lines are ranked seventh in terms of incidence and sixth in overall cancer-related death [1].

Currently, cancer treatment involves multiple approaches using targeted drug therapy, chemotherapy, radiotherapy, hormonal therapy, and surgery. Albeit, all the current therapieshave some problems like they fail to destroy tumor cells without any side-effects on healthy cells of the body. Radiotherapy does not differentiate between healthy cells and cancerous cells and causes extensive damage to healthy ones. Chemotherapy resistance is one of the prime problems when used for long-term treatment. Thus, mono-drug therapy is not a viable option to treat cancer cells. Many cancer types have a higher recurrence rate after chemotherapy. For example, breast cancer has a 30% recurrence rate, melanoma has an 87% recurrence rate in the metastatic state, and non-small cell lung cancer has a 27% recurrence rate. Chemotherapy also causes different kinds of toxicities. 5-fluorouracil, a widely used chemotherapeutic drug, is known to cause cardiotoxicity and myelosuppression. Doxorubicin is a commonly used anthracycline drug that causes cardiotoxicity and renal toxicity. Bleomycin is also known to cause pulmonary toxicity. Cyclophosphamide has been shown to have bladder toxicity and immunosuppression. Other unwanted effects of current anticancer drugs are anemia, GIT disturbance, inflammation, alopecia, immunosuppression, and heart and nerve disorders. Surgery in cancer is mainly used for the removal of the tumor and surrounding tissues if required. Although some complications are associated with cancer surgery like blood loss, wound complications like delayed healing and wound infection, other infections like pneumonia, unbearable pain, and blood clots.

Newer targets and treatments are required to tackle the disease, particularly in the GI tract cancer.

In this chapter, we will discuss the sphingolipid metabolic pathway and the role of its enzymes and metabolites in cancer. Further, we will discuss existing knowledge regarding the role of sphingolipid metabolism in GI tract cancer.

Currently Available Therapies to Treat Gastrointestinal Cancer

Systemic chemotherapy treatment is one of the most common and widely used strategies to combat GI tract cancer [2]. The metastasis of GI tract tumors generally involves the overexpression of p21 proteins and mutated Ras proteins [3]. The most commonly used chemotherapeutic agents in GI tract cancers are alkylating agents mainly cyclophosphamide, melphalan, ifosfamide, and busulfan, antimetabolites with first preference to 5-Fluorouracil followed by gemcitabine, and methotrexate, antibiotics such as doxorubicin daunorubicin and epirubicin, platinum-based agents (cisplatin, carboplatin, oxaliplatin) and topoisomerase inhibitors (topotecan, irinotecan, etoposide, teniposide) [4]. Asirinotecan and docetaxel are not commonly used and are considered as a treatment only during drug-resistance scenarios. The most common challenges regarding these drugs are anorexia, diarrhea, rash, and skin problems. Platinum-based drugs are considered first-line therapy for advanced gastric cancer while treatment for advanced gastric cancer includes platinum, taxanes, anthracyclines, doxorubicin, fluoropyrimidines, and irinotecan. Neurotoxicity (central and peripheral) produced as a by-product of anti-cancer drugs can affect the body for many years even after the completion of chemotherapy and can affect functional ability and quality of life in cancer patients. Chemotherapy-induced peripheral neuropathy (CIPN) is another major problem caused by anti-cancer agents including angiogenesis inhibitors, vinca alkaloids, platinum-based agents, taxanes, and proteasome inhibitors. Lifelong CIPN is linked with a complication like insomnia, anxiety, and depression [5].

Sphingolipid Metabolism

In the past 2 decades, research on the role of ‘bioactive lipids’ has extensively emerged. Before the last 2 decades, the role of lipids in the body is thought to be involved only in energy metabolism and cellular structure. In the 1950s, Hokin and Hokin identified that the amount of inositol phospholipids drastically increased in pancreatic cells that were treated with acetylcholine [6]. Only years later, the role of diacylglycerol (DAG) and inositol1,4,5-trisphosphate was identified in the regulation of protein kinase C (PKC) and calcium release, respectively [7]. Over many years, different bioactive lipids like eicosanoid [8], phospholipids, sphingolipids, phosphatidic acid, monoacylglycerols, anandamide,

CHAPTER 7

Hippo Signaling and its Regulation in Liver Cancer

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Abstract: Globally, liver cancer is a severe health problem, which affects both men and women. A large number of scientific studies have suggested dysregulation of signaling cascades as a major characteristic feature in cancer. Hippo is one of the key pathways, which is dysregulated in several human cancers including liver cancer. Therefore, targeting such dysregulated signaling pathways with small molecules and phytochemicals offers significance for liver cancer therapeutics. Numerous phytochemicals were tested for their effect against the dysregulated hippo pathway. This chapter will focus on the phytochemicals that were reported in regulating the hippo pathway in experimental liver cancer.

Keywords: Anti-cancer, Dysregulated signaling, Hippo pathway, Liver cancer, Phytochemicals, Small molecules.

INTRODUCTION

Coordination of fundamental biological processes such as proliferation, differentiation, and cell death is important for development, tissue homeostasis, and tumorigenesis [1, 2]. During the development process, cell number is increased to enhance organ size. During wound healing and organ regeneration, cell division and differentiation of tissue-specific progenitor cells are upregulated to compensate for the lost cells [3]. However, the coordination and integration of cellular proliferation, cell death, and cell differentiation are poorly understood. In very recent years, hippo signaling has been shown to possess coordination of the

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cellular processes, including the inhibition of cell proliferation, promotion of cell death, and cellular differentiation [3 - 5].

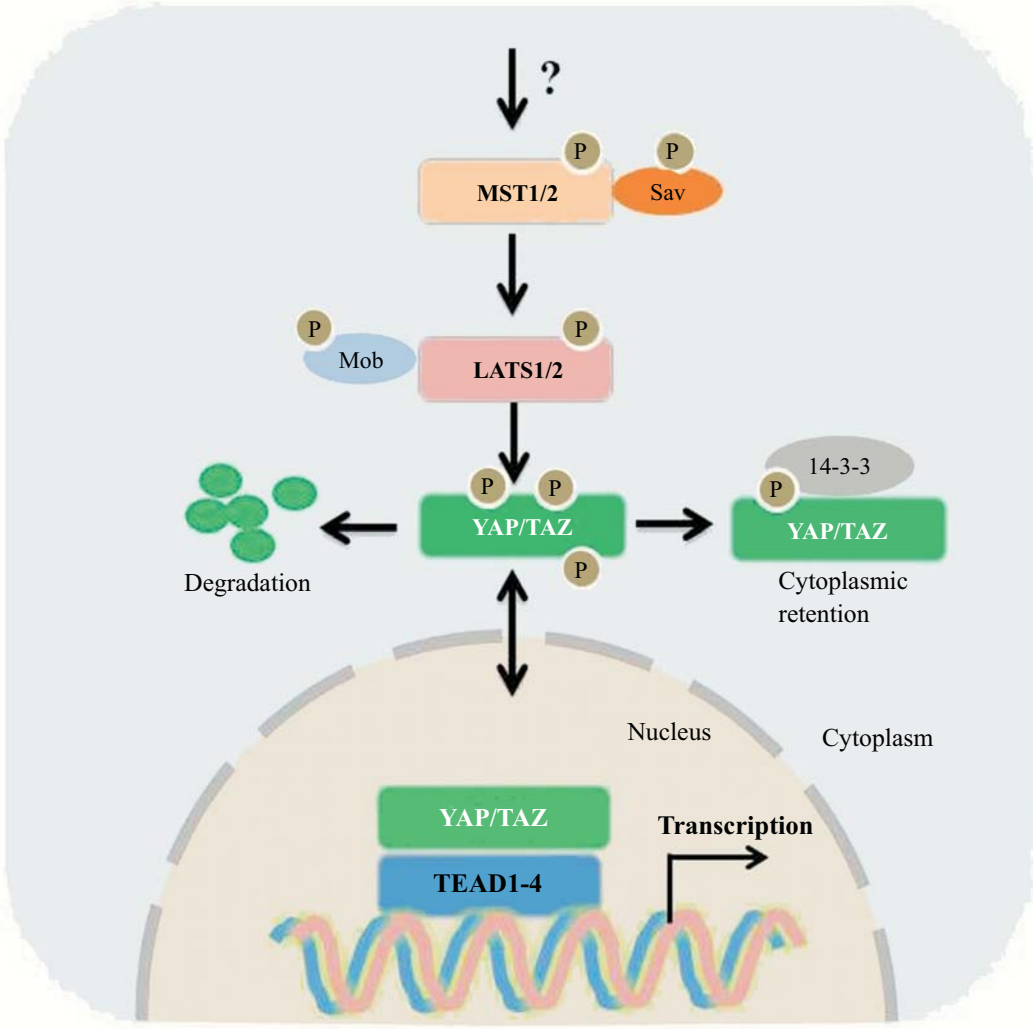
Hippo Pathway

The hippo pathway was first identified by genetic mosaic screens for tumor suppressor genes in Drosophila. The major hippo components include hippo (hpo), warts (wts) and yorkie (Yki) [6]. Hpo interacts directly with Sav (WW domain-containing protein) and promotes Sav and Wts phosphorylation [7]. The Mats protein interacts with Wts as an activating subunit [8, 9]. Mats is also phosphorylated by Hpo, resulting in increased interaction with Wts, and forms the core components of the Drosophila hippo pathway. On attenuation of hippo signaling, Yki phosphorylation is reduced, leading to its nuclear localization, binding to the sequence-specific DNA-binding protein scalloped (Sd), and regulation of target genes promoting proliferation and survival [10, 11].

The Mammalian Hippo Pathway

In mammals, Msts, Lats, YAP, and TAZ are human homologues of the Drosophila Hpo, Wts, and Yki respectively [11, 12]. Mst1/2 belongs to the STE20 family protein kinases and phosphorylate Sav1, Lats1/2, and Mob1 [7, 13 - 15]. The kinase activity of Mst1/2 is enhanced through interaction with Sav1, which is mediated by SARAH (Sav/Rassf/Hpo) domains present in both Mst1/2 and Sav1 [14]. Mst1/2 directly phosphorylates Lats1/2 at the hydrophobic motif (Lats1 T1079 and Lats2 T1041), and this phosphorylation is required for Lats1/2 activation [13]. Mob1, when phosphorylated by Mst1/2, binds to the auto-inhibitory motif in Lats1/2, which in turn leads to the phosphorylation of the Lats activation loop (Lats1 S909 and Lats2 S872) and thereby increases the Lats1/2 kinase activity [13, 15]. Also, the protein levels of Lats1/2 kinases are controlled by Itch E3 ubiquitin ligase-mediated degradation [16].

Lats1/2 directly interacts and phosphorylates YAP/TAZ [6, 17, 18]. The phosphorylated YAP (Ser127) is sequestered in the cytoplasm *via* a 14-3-3 interaction [19]. In contrast, when upstream kinases are inactive, YAP/TAZ will be hypophosphorylated and translocated into the nucleus [6, 18 - 21]. Phosphorylation of YAP (S381) and TAZ (S311) by Lats1/2 primes subsequent phosphorylation events by casein kinase 1; this sequential phosphorylation results in the recruitment of b-transducin repeat-containing proteins (b-TRCP) and consequently leads to the degradation of YAP/TAZ (Scheme **1**) [22, 23]. Hypophosphorylated YAP/TAZ in the nucleus binds to TEAD1-4 to regulate key genes [10, 11, 24 - 26]. Besides TEADs, YAP/TAZ may also interact with other transcription factors, such as Smad1 [27], smad2/3 [28], Smad7 [29], RUNX1/2 [30], p63/p73 [31], and ErbB4 [32].



Scheme (1). Central components of mammalian hippo pathway.

Hippo Pathway in Cancer

Mutations of Sav1 and Mob1 have been observed in a human renal carcinoma cell line [33] and colorectal cancer [34]. Downregulation of Lats1/2 has been reported in human cancer including ovarian, breast, retinoblastomas, and acute lymphoblastic leukemia [35 - 37]. In some cases, attenuated Lats1/2 expression with promoter hypermethylation has also been reported [38, 39]. Differential expression of Mst1/2 has been observed in human colorectal and soft tissue sarcomas [40, 41]. The germline $Mst1^{-/-}$ $Mst2^{+/-}$ mice mainly developed hepatocellular carcinoma (HCC) due to Mst2 loss of heterozygosity [42].

CHAPTER 8

Immunotoxin: A New Generation Agent for Cancer Treatment

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Abstract: According to WHO/ Pan American Health Organization, 10 million global cancer deaths have been estimated in 2023. The International Agency for Research on Cancer (IARC) declares that over the ensuing two decades, the burden of cancer will augment by about 60%. For several years, the main treatment modalities for cancer were entailing chemotherapy, radiotherapy, and surgery. Conventional chemotherapies were not tumor-tissue specific and presented a large toll of toxicities for normal cells. But in the last two decades, the idea of targeted therapy, where drug or protein molecules are delivered to specific cells, is a captivating approach to treating malignancy. Immunotoxins comprising a toxin together with an antibody or growth factor hinder the growth and progression of cancer by disrupting specific genes that employ tumor growth and development. With further advances, it is expected that immunotoxins will exhibit a brilliant role and will bring a new era in the treatment of malignancy.

Keywords: Antibodies, Cancer, Immunotoxin, Malignancy, Toxins.

INTRODUCTION

According to the World Health Organization (WHO) estimate, there were over 18 million new cases of cancer and around 10 million deaths from cancer-related causes in 2018 [1]. It is predicted that by 2040, the rate of cancer mortality will get nearly doubled due to the increasing pace of industrialization [2]. Radiotherapy, chemotherapy, and surgical excrescence excision are conventional treatment modalities for cancer and these not only eradicate malignant cells, but also disrupt healthy cells leading to numerous uninvited health hazards, like loss of appetite, anemia, internal bleeding, and fatigue [3].

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Early in the 1980s, when monoclonal antibodies that responded to cancer cells were widely accessible, the first immunotoxins were created. Numerous bacterium and protein toxins from different sources were investigated [4]. The production of immunotoxins using *Pseudomonas exotoxin* A (PE) has drawn the attention of numerous researchers. Immunotoxins directed against CD22 have the potential to induce complete remissions in individuals with refractory hairy cell leukemia (HCL) [2]. In several instances of advanced chemotherapy-resistant mesothelioma, recombinant immunotoxins directed against the mesothelin protein resulted in significant excrescence retrogressions [3].

One of the key medications to fight against cancer is monoclonal antibodies (mAbs) [4-6]. Generally speaking, the mAbs bind to cell face receptors and invade through their signal transduction pathways, inducing cell death and apoptosis [7, 8]. Because of their big size (150 kDa), tumor penetration and mAb dispersion are limited [9, 10]. As an example, antigen-list scrap (Fab), single-chain variable scrap (scFv), and disulphide stabilised Fv (dsFv) are used to generate mAbs fractions in order to overcome the problem [11 - 13].

According to mAbs resistance and the need into cancer treatment, immunotoxins (ITs), a novel class of anticancer drugs, are produced [14, 15]. ITs are anticancer medications made up of two distinct pathways: the cytotoxic half and the targeted half. The receptor binding sphere of native poison replaces the targeting half in the formation of ITs, guiding the IT to the target cell [16, 17]. Usually, mAbs (or antibody fractions) make up the targeted halves. Targeting peptides like affibody [22], growth factors [20, 21], protein ligands resembling interleukins (ILs) [18, 19], and designed ankyrin repeat proteins (DARPins) [23] have all been employed. Generally, the cytotoxic half causes both cell death and suppression of growth. The source of the cytotoxic portion is bacteria that are found in insects, plants, and invertebrates.

After processing, the cytotoxic half enters the cytosol and generally inhibits protein coalescence, and induces apoptosis [2, 24]. Antibody-medicine conjugates (ADCs) are other vehicles for the delivery of cytotoxic half [25, 26]. The cytotoxic halves of ADCs are small patch composites that conjugate to the targeted half by a chemical or enzymatic response [27]. Due to the non-specific nature of chemotherapy medications and the resistance that the solid dosage forms induce, additional poisons may result. Immunotherapy snappily came as one of the smart styles of cancer treatment, along with chemotherapy and radiation [28]. In the end, despite clinical aspirations centered around the creation of innovative cancer therapies, a great deal has been learned about intracellular pathways and toxin action. As a result, poisons are viewed as both diagnostic tools for cellular function and medications for treating fatal ailments.

Mechanism of Action

In immunotoxins, plant and bacterial poisons are employed to stop cellular protein coalescence and kill cells. For anticancer activity, intracellular transport to the cytosol is required. The patch is internalized to the endocytic cube when the immunotoxin targeting half binds to the face of the cancer cell. As these specks are processed and transported in a target- and poison-specific manner, an enzymatically active part of the poison is eventually delivered to the cytosol.

Diphtheria toxin (DT) and PE cause irreversible modification and inactivation of eukaryotic extension factor 2 (eEF2), an essential part of the protein synthesis machinery [29, 30]. Plant poisons that are similar to ricin and gelonin also stop proteins from fusing together, but they accomplish this by blocking the ribosomal enzyme instead of eEF2 [31, 32]. Variations mediated by poison activate the apoptotic pathway, resulting in cell death.

Diptheria Toxin (DT)

The prototype for the class of ADP-ribosylating poisons is DT, a single-chain 58 kD protein produced by the bacterial disease of *Corynebacterium diphtheria*. Diphtheria toxin consists of two subunits connected by disulfide bridges, recognized as an A-B toxin. It comprises a B subunit (amino acids 482–535) and an enzymatic A subunit (amino acids 1–193, catalytic C domain). Subunit B controls cell entrance while subunit A intoxicates the cell *via* its class of enzymatic action. A third domain, called the translocation or trans-membrane (T) domain, is located in the center of the patch. It is sometimes referred to as the part of the B subunit. The C domain blocks protein synthesis through the transfer of ADP-ribose (from NAD) to a diphthamide residue (of eukaryotic elongation factor 2, eEF-2). The T domain or TM domain is assumed to perform the cytoplasmic transfer of the C domain. The C-terminal receptor-binding R domain allows the toxin to get entry into the cell through the process of receptor-mediated endocytosis.

In order to destroy the cells, DT goes through the following processes, which are supported by the 3-D structure of the DTs in reality and the absence of NAD [33 - 35]:

• Cell-face furin or furin-like proteases intracellularly disrupt native DT between residues Arg193 and Ser194, located within a disulfide circle formed by Cys186 and Cys201. This results in a complex of CD9 *via* its residues 482 to 535 on the receptor list sphere and heparin-binding EGF precursor on the cell membrane.

CHAPTER 9

Multifactorial Drug - A Revolution in the Treatment of Cancer by Inhibiting Hedgehog Pathway

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Abstract: In the human body, Hedgehog (Hh) signaling is an essential pathway and plays a major role in embryo development, tumorigenesis, distant metastasis, poor prognosis, and tissue patterning. The Hh pathway has three ligands in mammals: Sonic Hedgehog (SHh), Desert Hedgehog (DHh), and Indian Hedgehog (IHh). Malfunctions of this pathway are associated with diseases that include cancer. Cancer is one of the leading causes of death worldwide and factors like dietary habits, family history, obesity, environmental conditions, tobacco, and genetic factors affect the likelihood of developing cancer. The Hh signaling pathway through sporadic mutations is explicitly associated with cancer development and progression in various solid malignancies. Abnormal expression of the Hh signaling cascade has been reported in the development of basal cell carcinoma, breast, liver, prostate, colon, pancreas, and stomach cancer. Most researchers target the inhibition of the Hh signaling pathway and therefore it has emerged as a popular and validated therapeutic for the treatment of a wide range of cancers. A novel class of drugs such as sonidegib and vismodegib inhibits the Hedgehog pathway. There has been significant progress regarding the development of multifactorial drugs blocking Hh signaling. The discovery of multifactorial drugs to block the pathway has led to a new treatment that may significantly improve clinical outcomes in cancer patients. Several of these molecules have been included in the clinical testing stage. Yet finding a sustainable multifactorial inhibitor is still a challenge. This book chapter describes the Hh signaling pathway as a vital and multifactorial therapeutic target for cancer.

Keywords: Cancer therapy, Hedgehog pathway, Multifactorial drug, Sonidegib, Vismodigeb.

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INTRODUCTION

Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body, cancer is one of the leading causes of mortality worldwide, in both developed and developing nations due to changes in lifestyle and eating habits. Around 7.6 million people die from cancer each year, according to current estimates [1, 2]. The Hedgehog (Hh) pathway is a signalling mechanism that drives patterning and is required for appropriate development. At the molecular level, Hh ligands cause cell proliferation in some cell types while inducing differentiation in others. It is most active during embryogenesis, and its aberrant reactivation in adult tissue has been linked to the development of cancer [1]. Hedgehog gets its name from a polypeptide ligand identified in the *Drosophila* genus named Hedgehog (Hh). Christiane Nusslein-Volhard and Eric F. Weischaus found the Hh gene in 1980 [3]. The Hh signalling pathway's key target genes are PTCH1, PTCH2, and GLI1. Deregulation of the Hh signalling pathway has been linked to sporadic malignancies such as basal cell carcinoma, medulloblastoma, pancreatic, breast, colon, ovarian, and small-cell lung carcinomas, as well as developmental defects and cancers like Gorlin syndrome [4]. In humans inflicted with cancer, the Hh pathway boosts stem cell DNA synthesis. Many signalling pathways involved in the developmental process, including Hedgehog, Wnt, and Notch, have a critical role in carcinogenesis as well as resistance to various anticancer medicines. Understanding how cancer uses these developmental pathways to resist multi-therapeutic approaches can lead to new insights into anti-therapy resistance mechanisms that can be investigated for the creation of a new therapeutic method [5].

According to some evidence, Hh ligand binding to PTCH1 regulates the cell cycle by facilitating the transition from Gap 2 to mitosis by binding to a cyclin B1 and CDK-1 complex. PTCH1 functions as a tumour suppressor. The pathophysiology of cancers such as breast, lung, pancreatic, prostate, and haematological malignancies is linked to abnormal activation of Hh signalling [6]. The first Hh pathway inhibitor is cyclopamine, a naturally occurring plant alkaloid. The active cyclopamine chemical found in corn lilies was later discovered to block the Hh pathway by binding to and inactivating the Smoothened (SMO) transmembrane receptor protein [3]. Hedgehog pathway inhibitors were found by researchers, and the Vismodegib advance medication was authorised by the FDA for use in basal cell carcinomas [7].

Cancer resistance is influenced by the Hedgehog signalling system. Different cancer treatment options include immunotherapy, chemotherapy, molecular targeted therapy, and radiation [5]. As a result, Hh signalling has become a therapeutic target for cancer treatment. The topic of Hh signalling and the

principal molecular actors engaged in suppressing the Hh pathway modulator, as well as a current description of what natural and synthetic chemicals affect Hh signalling in cancer treatment, will be discussed in the framework of this chapter.

CANCER AND Hh PATHWAY

Hedgehog (Hh) is a short- or long-range morphogen that affects a variety of tissue types. Sonic Hh, Indian Hh, and Desert Hh are the three Hh proteins found in mammals. Newly produced Hh enters the secretory system and undergoes auto-processing and lipid modifications resulting in the addition of a palmitoyl group to the NH_2 terminus and cholesterol to the COOH terminus in cells to produce Hh [8]. The Hh protein is involved in various developmental processes in Drosophila, including gonadal formation and function [9]. The Hedgehog (Hh) signaling pathway, also known as Hedgehog-Patched (Hh-PTCH), Hedgehog-GLI (Hh-GLI), or Hedgehog-Patched-Smoothened (Hh-Patch-Smo), is an evolutionarily conserved signaling pathway that transmits from the cell membrane to the nucleus [10]. This pathway involves inhibition of the twelve transmembrane protein Pathed1 (PTCH1) by binding Hh protein, activation of the seven-transmembrane protein Smoothened (SMO), the release of the five-zinc finger transcription factor GLI forms a large protein complex, and is involved in the nuclear translocation of GLI, and transcription of target genes. GLI makes a large protein complex with Costal2, Fused, and suppressor fused in the absence of sonic Hh (SHh) and are sequestered in the cytoplasm. A full-length GLI3 produced from the big protein complex is transported into the nucleus in the presence of SHh to activate Hh target genes. GLI1 is one of the GLI3's target genes. As a result, GLI1 is a marker for the activation of the Hh pathway [11]. The role of Hedgehog signaling is to control cell proliferation and differentiation in the embryonic development stage and when it is altered or misregulated, it can lead to cancer [10].

Hh signalling has been implicated in various stages of carcinogenesis in various cancers, according to several research. The activation of this signalling system is seen in the early stages of pancreatic and oesophageal cancers, as well as in metastatic tumors. The activation of the Hh signalling system has been linked to tissue invasion and enhanced metastatic potential in various cancers, such as gastric cancer and prostate cancer. Inhibition of the Hh signalling pathway suppresses tumour cell proliferation in prostate and gastric cancer, according to research studies [4]. In cancer, abnormal Hh pathway activation is caused by both ligand-dependent and ligand-independent pathways. Loss-of-function PTCH or SUFU mutations (Fig. **1**), as well as gain-of-function SMO mutations, promote ligand-independent Hh signalling and drive the development of basal cell carcinoma (BCC), medulloblastoma (MB), rhabdomyosarcoma, and meningioma tumors [12]. Studies on Gorlin syndrome, an autosomal dominant illness

CHAPTER 10

Promising Natural Agents for Targeting Micro-RNAs in Cancer

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Abstract: Micro-RNAs, a family of small non-coding RNAs of 20-22 nucleotides, are evolutionarily preserved, and regulatory RNAs that negatively control gene expression also play an important role in all biological pathways in multicellular organisms by inducing feedback mechanisms that safeguard key biological processes including cell proliferation, differentiation, and apoptosis. The 3′ UTR of the target mRNAs is the binding site of micro-mRNAs, to induce translational repression by mRNA degradation or inhibition of protein synthesis from m-RNA while miRNA interaction with promoter region has been reported to induce transcription. Many natural products and dietary phytochemicals possess anti-cancer properties along with their tested antioxidant, anti-inflammatory, and anti-proliferative effects. Natural agents including (-)-resveratrol, curcumin, indole-3-carbinol, isoflavone, epigallocatechin-3-gallate, and 3,3'-diindolylmethane could modify miRNA expression, therefore reverse the epithelial-mesenchymal transition, causing the induction of apoptosis as well as the inhibition of cancer cell growth leading towards the advances of the efficacy of conventional cancer therapeutics. This review paper focuses on the precise targeting of mi-RNAs by natural agents that could open a newer line of attack for the complete eradication of tumors by killing drug-resistant cells to improve survival outcomes in patients with malignancy. In this chapter, we have paid attention to the use of natural products for mi-RN--mediated chemo-preventive and therapeutic approaches in various cancers, with the aim to extensively identify their pharmacological prospective.

Keywords: Chemo-preventive, Cancer therapeutics, Gene expression, Induction of Apoptosis, Micro-RNA, Natural Products.

INTRODUCTION

Despite the advances in different cancer therapies, cancer is still the second leading cause of death worldwide. About 1,898,160 new cancer cases and 608,570

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cancer deaths were expected to occur in 2021 in the United States. Among all incident cases in men, 46% constitute prostate, lung, bronchus, and colorectal cancers whereas prostate cancer alone accounts for 26%. In women, breast cancer, lung cancer, and CRCs account for 50% of all new diagnoses, while breast cancer alone accounts for 30% of female cancers [1]. The primary treatment of cancer includes surgery, chemotherapy, radiotherapy, and palliative care along with immunotherapy, stem cell therapy, hormonal therapy, and gene therapy. The treatment should be provided depending on the size, type, and location of the tumor, and also metastasis diagnosis depending on the health of the patient. Different approaches have been used for targeting cancer in three ways, one is by expressing a gene to encourage apoptosis or enhance tumor sensitivity to conservative drug-radiation therapy, the second one is by inserting a wild-type tumor suppressor gene to compensate for its damage and the third one is by blocking the expression of an oncogene by using antisense by RNA or DNA for enhancing the immunogenicity of the tumor to stimulate immune cell recognition [2].

Micro-RNAs are a highly conserved family of small non-coding RNAs of 20-22 nucleotides that can regulate a wide array of biological processes including cell proliferation, differentiation, apoptosis, and others [3]. Normally miRNAs belong to the heterogeneous class of non-coding RNAs, that can reduce translation by binding to the 3'- untranslated regions (UTRs) of target mRNA, thus triggering mRNA degradation and causing inhibition of protein translation [4]. They regulate gene expression both at the posttranslational and posttranscriptional levels [5]. Up to now, in humans, more than 2500 miRNAs have been isolated, and miRNA-conserved targets control around 1/3rd of all human genes [4]. Individual miRNA plays a specific function in cells. miRNAs have been found to be severely dysregulated in cancer cells compared to normal healthy cells. miRNAs have different targets on genes by inhibiting or overexpressing the specific gene and miRNAs show a potential effect by inhibiting cancer [6]. Natural products could sensitize cancer cells to therapeutic agents by altering miRNA expression or function, therefore benefiting cancer patients [7]. As natural agents exercise their antineoplastic effects by targeting multiple signaling pathways, and miRNAs regulate various biological processes comprising cell proliferation and apoptosis or programmed cell death, it is assumed that miRNAs could take a key role in governing response towards natural agents. Hence, In the last few decades in cancer therapy, natural agents have gained attention for their applications in the modulation of miRNAs expression.

miRNA Synthesis

It is well known that microRNAs (miRNAs), short non-coding regulatory RNAs are found to be dysregulated in almost all types of cancers and play significant roles in cancer growth and progression [8]. RNA interference (RNAi) has come into the limelight in the antisense world in the last few years in the therapeutic market. There has been a significant effort to investigate miRNAs' processing in animals and plants. The synthesis of miRNAs starts from DNA sequences, called miRNA genes, or the clusters, genes, or polycistronic transcripts, respectively. Alternatively, the miRNAs can be restricted within an intron or untranslated region (UTR) of a protein-coding gene [9]. From the miRNA gene, miRNAs are transcribed to a primary miRNA (pri-miRNA) by RNA pol-II that also possesses one or more hairpin structures within the miRNA [8]. In animal cells, the biogenesis of miRNA is Drosha and DGCR8 dependent, those are not found in plant cells. Drosha and Dicer, two RNase III enzymes can form mature miRNA in an evolutionary conserved process (Fig. **1**). Pri-miRNA is the substrate of DROSHA. The miRNA hairpins are acknowledged and cleaved by a heterotrimeric complex of DROSHA and two molecules of DGCR8 (DiGeorge syndrome critical region 8), a double-stranded RNA binding protein that releases precursor miRNAs (pre-miRNAs). Then exportin-5 (EXP-5) transports the pre-miRNA, connected with Ran-GTP into the cytoplasm where they are further processed by Dicer, an RNase III type protein to develop mature miRNAs and loaded onto the Argonaute (ago) protein to form the effector RNA-induced silencing complex (RISC) [10, 11]. Dicer, Argonaute2, and TRBP are vital components in the formation of the RISC-loading complex (RLC), thus contributing to the formation of short RNAs [12]. Another alternative pathway for miRNA biosynthesis is Dicer-independent. After the transcription and cleavage by Drosha, the precursor binds to Ago2. As it is a dicer-independent, the Ago2 splits the star strand [13]. Fig. (**1**) represents the overview of biosynthesis of microRNAs.

MicroRNA (miRNAs) in the Development of Tumorigenesis and Carcinogenesis

Several research articles have been reported that are associated with the process of tumorigenesis and carcinogenesis (Fig. **2**). The exact role of miRNAs in the molecular mechanism of initiation, promotion, progression, and metastasis of some cancers was recognized previously. They employ a critical role in the mechanism of programmed cell death as well as cellular differentiation by regulating tumor suppressors and oncogenes. With the ability to regulate the expression of a lot of genes, miRNAs have the ability to modulate many cellular pathways. Different investigators have reported that about half of the miRNAs are

CHAPTER 11

Understanding the Mechanism of Targeted Therapy- The Next Generation for Cancer Treatment

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Abstract: In recent years, there has been significant progress in understanding the cellular, molecular, and systemic factors that contribute to the development and spread of cancer. This has been made possible by advancements in sequencing methods and data analysis, which have allowed for the identification of various genomic alterations in tumors. While there are currently several specific therapies available, there is a growing focus on target-specific treatments that show better results in cancer treatment. Cancer is widely recognized as the second deadliest disease in the world. For many years, the main forms of treatment for cancer have been chemotherapy and radiotherapy for advanced stages. However, recent advancements in science and technology have led to the discovery of new chemotherapeutic drugs. Additionally, repurposing existing drugs has proven to be a cost-effective strategy for discovering new treatments that target specific cancer regimens and inhibit the growth of cancer cells. The next generation of cancer treatment is largely focused on targeting specific factors that contribute to the development and spread of cancer. This includes therapies that target hypoxia, p53, ERK, and specific proteins through the use of monoclonal antibodies. These treatments have shown promising results in inhibiting the growth of cancer cells and have been effective against various types of cancer. In this article, we will primarily focus on the mechanisms of next-generation therapies and the significance of repurposing drugs. We will also discuss the biology behind targeted cancer treatments and how they work to inhibit the growth of cancer cells.

Keywords: Cancer, Chemotherapy, Next-generation therapy, Radiotherapy, Targeted therapy.

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INTRODUCTION

The most common maladies are cancer and regarded as a chief communal health issue worldwide. In accordance with GLOBOCAN estimates, approximately several million new cancer cases as well as deaths happened worldwide. Cancer is regarded as a deadly disease and one of the primary reasons for death globally [1, 2]. Discovery of new drugs with support of advancing technology helps in the mitigation of cancerous cell growth [3, 4]. However, new drug introduction requires clinical trials before releasing into the market. Approximately 13 years of research and clinical testing are necessary before the entry of drugs into the market [5, 6].

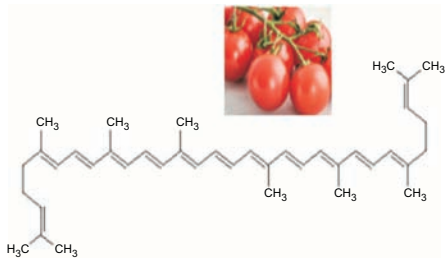
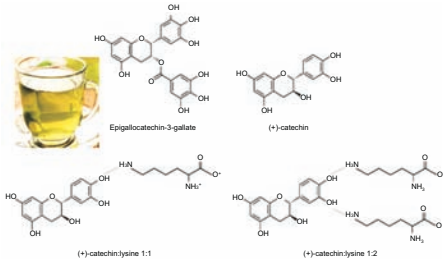
At present, understanding the molecular mechanism of the progression of cancerous cells to metastatic state needs to be analyzed for the identification of genomic modifications within tumor cells [7 - 11]. For decades, chemotherapy has been used to prevent the progression and intensification of tumor cells. The major drawback of chemotherapy is the incapability to differentiate between cancerous and regular cells. Nonetheless, with the progression of recent advancements, remarkable alteration has been seen in tumor therapy from a wide-continuum of cytotoxic agents to targeted drugs [12]. In contrast to conventional chemotherapeutic drugs, targeted drugs can particularly target cancerous cells and spare normal cells. In 2001, the Food and Drug Administration (FDA) [13] have permitted the expansion of targeted agents for cancer therapy. For precise comprehension of targeted therapy, recognition of tumor immunology is essential [14]. Therefore, our current article provides a clear understanding of targeted drug treatment for cancer disease and prognosis of patients [15]. In this article, our primary focus is on the mechanism of action of anticancer drugs on tumor resistance along with the mechanism of targeted therapy on proliferating cells and how further tumor resistance can be improved. Further, we also focusedon the drawbacks of chemotherapy as well as radiotherapy and diverse classes of targeted therapies as recent advancements. Thus, for an effective understanding of targeted treatment, *in-silico* approaches play a key role in exploiting potentially effective drugs with higher efficacy, and further, those oncological drugs after clinical trials might significantly reduce mortality in the populace suffering from cancer diseases.

ROLE OF NATURAL PRODUCTS IN CHEMOTHERAPY

Although, for decades natural products have been playing a prominent role in the treatment of several diseases. The bioactive compounds present in plant parts provide relief to many. However, approximately 60 percent of present anticancer agents were obtained in one way or another from natural resources [16]. Table **1**

shows the latest chemotherapeutic agents obtained from natural products such as fruits and vegetables [17] and the Mediterranean diet [18, 19]. However, several literature studies have reported on the significance of nutritional substances such as beta carotene from carrots, the bioactive agent lycopene present in tomatoes, catechins from green tea, anthocyanins from blueberries, and curcumin from turmeric. Nonetheless, with the help of *in-silico* approaches, it is possible to screen the drugs binding to receptors [20, 21] and regarded as a mainstay for chemotherapy.

Table 1. Natural products used as chemotherapeutic compounds against proliferating cancerous cells.

Structure of Bioactive Compound	Mechanism of Action	Study Type	Target Gene	References
 **Lycopene**	Through oxidative and non-oxidative mechanisms, it reduces chronic maladies like cancer.	*In-vitro*	Bax & Bcl2	[22]
 **β-Carotenoid**	The chief anti-oxidant alleviates oxidative stress and oxidative damage to DNA.	*In-vitro*	The epidermal growth factor (EPGF) receptor and NF-kB	[23, 24]
	Mitochondria within cancer cells control metastasis by altering reactive oxygen species (ROS) production.	*In-vitro*	transforming growth factor β (TGF-β) signaling.	[25, 26]

CHAPTER 12

Cell Death Apoptotic Pathways and Targeted Therapeutic Research in Cancer

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Abstract: Apoptosis or programmed cell death refers to a form of death in cells critical to physiological homeostasis occurring in almost every organ system and is characterized by distinct morphological features and a cascade of energy-dependent biochemical processes. This modulation ability of cells is recognised for its immense therapeutic potential. Cancer being the outcome of a spectrum of genetic alterations transforms a healthy body into a cancerous one. Oncologists have been targeting newer therapies for the elimination of cancer cells by apoptosis. Understanding the underlying mechanism of the ordered and orchestrated cellular mechanism plays a pivotal role in disease pathogenesis. There are two major pathways for the induction of apoptosis in malignant cells: Intrinsic and Extrinsic pathways. In this chapter, we summarise the various treatment strategies and therapeutic classes for curbing the different tumor types. This chapter also highlights the utilization of plants and their bioactive compounds in medicine for the treatment of various types of cancer.

Keywords: Apoptotic pathways, Cancer, Tumours, Therapies.

INTRODUCTION

Cell death is an inevitable fate or contrived consequence of cellular life. It is a condition in which biological cells lose their activity or cease to perform their functions. Numerous research over the past decades have revealed the involvement of a broad spectrum of genetically encrypted mechanisms for targeted elimination of excessive, irreversibly damaged, infected, and/or potentially harmful cells [1]. The phenomenon of cell death is crucial during the development, homeostasis, and immune regulation of multicellular organisms and is associated with morphological alterations, deregulation of which might lead to numerous pathologies. Morphologically cell death can be broadly classified as

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apoptosis, necrosis, autophagy, oncosis and pyroptosis. Apoptosis is associated with cell content shrinkage including the nuclei, mitochondria, and cytoplasm and the cell becomes encased in 'apoptotic bodies', which are surrounded by plasma membrane followed by cytomorphological events including membrane blebbing and chromatin condensation. The apoptotic bodies are engulfed by nearby phagocytic cells and get digested in the lysosomes. The apoptotic mechanisms are highly complex and involve a cascade of energy-dependent molecular events. This process is biochemically characterised by the involvement of cysteinyl-aspartate-specific proteases called caspases followed by internucleosomal fragmentation of DNA and phosphatidylserine externalization. This brings about alterations in the mitochondrial membrane permeability and this type of cell death is regulated by B-cell lymphoma 2 (Bcl-2) family proteins. Apoptotic pathways are majorly of three types namely intrinsic, extrinsic, and perforin/granzyme pathways that trigger a series of molecular events. Intrinsic pathway involves the activation of stimuli including DNA damage, oxidative stress, and lack of growth factor, and is directed by permeabilization of the outer membrane of mitochondria [2]. This permits the release of Cytochrome-C that induces Apaf-1. Apaf-1 is a protease-activating factor that stimulates caspase-9 activation to assemble the apoptosome. This apoptosome is involved in activating executioner caspases. At the same time, the extrinsic apoptotic pathway is associated with the involvement of external signals of death ligands including tumor necrosis factor (TNF) superfamily and TNF-related apoptosis-induced ligands (TRAIL) that activate membrane receptors [3]. This leads to the stimulation of death-inducing signalling complex (DISC) that activates caspase-8. Caspase-8 then activates executioner caspase-3, -6, or -7 performing the process of apoptosis. However, the functioning of Granzyme A is caspase-independent [4].

Necrosis is regarded as 'passive' cell death since it encompasses nonapoptotic, accidental cell death. This uncontrolled cell death mechanism occurs due to severe insult resulting in the spillage of cellular contents into surrounding or nearby tissues. Regardless of the pre-lethal process, necrosis is the sum total of all changes that occur within a cell after its death [5]. Oncosis refers to a prelethal pathway that leads to cell death followed by swelling, organelle swelling, blebbing, and elevated membrane permeability [6]. Oncosis might occur due to the interference of toxic agents with ATP generation or might also occur due to conditions that cause uncontrolled consumption of cellular energy. Ultimately cellular energy stores get depleted and ionic pumps fail in the plasma membrane. Pyroptosis cell death is induced by infection with *Salmonella* and *Shigella* species [7]. This inherently pro-inflammatory cell death pathway relies on caspase-1. Caspase-1, which is not involved in apoptosis, processes the pro-forms of inflammatory cytokines, IL-1beta, and IL-18 to their activated form. Hence, this is an inflammatory and programmed cell death mechanism that is likely to be

involved in antimicrobial response [8]. Autophagy is regarded as an evolutionarily conserved cellular process that involves the engulfing of cytoplasm by autophagic vesicles or lysosomal degradation of intracellular macromolecular components. Three major types of autophagy are microautophagy, macroautophagy, and chaperone-mediated autophagy. The autophagic cellular machinery is encoded by Autophagy-related genes (ATG), which contribute to the activation of various signalling complexes *via* 19 core Atg proteins. It involves the engulfing of the cytoplasm by autophagic vesicles [9].

For over three decades, clinical oncologists have aimed at the development of therapies for the effective elimination of cancer cells by apoptosis. Cancer biology and cancer genetics involve dynamic interactions between cancer cells and their tissue microenvironments. Bypassing the apoptotic pathway to instigate cancer cell death is considered to be a potential approach to overcoming this deadly complication. This is because the programmed cell death mechanism acts as a natural blockade that defends against cancer development [10]. Research has suggested that certain oncogenic alterations promote apoptosis instead of suppressing it and that anticancer agents induce apoptosis. Induction of apoptotic cell death by anticancer agents hints upon cellular responses after drug-target interaction could potentially affect drug-induced cell death. In the early days, viral and cellular oncogenes, cell proliferation, and transformation were the main parameters for anticancer therapeutic approaches. However, in the 1980s, the advent of apoptosis as a realistic anticancer therapeutic approach came to the forefront. BCL2 [11] and Bu2L1 [12] were anti-apoptotic oncogenes that exhibited powerful mechanisms for tumor growth [13] and drug resistance [14].

Cancer is a serious metabolic syndrome that is one of the principal causes of mortality and morbidity across the world [15]. Despite the advancements in tools for diagnosing, treating, and preventing this frightful disease, the number of cases is elevating constantly and it is estimated to reach 21 million by 2030 [16]. Cancer is a critical condition in which genetic instabilities and alterations occur within a cell caused by the uncontrolled proliferation of normal cells leading to the transformation of the normal cells into cancerous ones. Malignancy can occur due to various external factors including smoking, tobacco, radiation, intake of contaminated substances (water, food, air, chemicals), and infectious agents as well as internal factors including gene mutation, improper immunity, and hormonal disorder [17]. Around 60% of the drugs useful for treating cancer have been obtained from natural products with plant kingdom as the major source. Plants and their bioactive compounds have been utilized in medicine for ages and these have served as nature's blessing to mankind to help them pursue improved health. Although the plant kingdom embodies 250,000 plants, only 10% of these have been studied for medical practices. Phytochemicals and their derivatives

CHAPTER 13

Apoptosis Defects in Cancer and its Therapeutic Implications

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Abstract: Apoptosis is the programmed cell death that regulates the cell survival or cell death balance in animals. Defects in apoptosis can cause cancer or autoimmunity, while enhanced apoptosis may cause degenerative diseases. The apoptotic signals mostly contribute to protecting the genomic integrity whereas defective apoptosis might lead to carcinogenesis. The signals of carcinogenesis alter the central points of the apoptotic pathways, which include the FLICE-inhibitory protein (c-FLIP) and the inhibitor of apoptosis (IAP) proteins. The tumor cells trigger the expression of antiapoptotic proteins such as Bcl-2 or downregulate the proapoptotic proteins like BAX. Most of these changes lead to intrinsic resistance to the most common anticancer therapy, chemotherapy. Apoptosis-resistant cells and transduction pathways that inhibit apoptosis can stimulate non-apoptotic mechanisms of cell death and senescence; this preserves the antitumor effect of several anticancer agents. The development of some promising cancer treatment strategies has been discussed below, which target apoptotic inhibitors including Bcl-2 family proteins, IAPs, and c-FLIP for the induction of apoptosis.

Keywords: Apoptosis, Cell death, Cancer, Carcinogenesis, Therapies.

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INTRODUCTION

Programmed cell death is a central component of many biological processes in animals. It plays a crucial role in the development of immunity, embryogenesis, and integrity of eukaryotic organisms [1]. This firmly coordinated event when subjected to dysregulation leads to an array of diseases such as immunodeficiency, autoimmune disease, developmental disorders, neurodegeneration, and cancer [2]. Programmed cell death can be characterized into apoptotic and non-apoptotic cell death, conventionally called necrosis. Indisputably, apoptosis is the best-described and most evolutionary conserved form of programmed cell death. It not only involves homeostatic mechanisms of cell suicide for controlling the cell populations in tissues but also the defense mechanisms in immune reactions and disease pathogenesis [3]. Apoptosis is modulated by complex molecular signaling pathways and can be initiated by both external and internal stimuli. The stimuli can result from various DNA-damaging agents like chemotherapeutic agents and UV radiations giving rise to intracellular stresses such as oxidative stress, DNA damage, or oncogene activation. Extracellular signals include the death-inducing signaling complex (DISC), which comprises Fas ligand, TNF-α, FADD, TRADD, caspase-8 and -10 [4, 5]. On the contrary to apoptosis, non-apoptotic cell death or necrosis is an uncontrolled form of cell death mediated by different mechanisms from apoptosis leading to accidental cell death. Pathologists often use the term necrosis to classify the presence of dead cells or tissues. Irrespective of the processes occurring before cell death, it includes the overall changes that take place after cell death [6]. Necrotic cells are the dying cells that neither showed morphological traits of apoptotic nor any sign of autophagic cell death. Even though pathological traumas like ischemia and infection generally initiate necrosis, both death receptors as well as DNA damage can lead to necrosis [7].

APOPTOTIC DEFECTS AND CANCER

There is a massive amount of different biochemical components in the various apoptotic pathways that still have ongoing research [8]. The normal functioning of a pathway is often deranged resulting in a compromise to normal apoptosis thus leading to disastrous effects such as disorders or diseases. Apoptotic defects are the genetic and epigenetic modifications that directly affect the expression of the specific machinery of the intrinsic and extrinsic apoptosis pathways. These modifications have been chiefly observed in primary adenocarcinoma.

Defects in Caspase Signaling

Alterations in the gene encoding caspase proteases affect the expression of caspases in human tumors. These generally include mutation of initiator caspase-

8, caspase-9, and caspase-10, along with executioner caspase-3 and caspase-7. A mutant form of caspase-8 was observed in head and neck carcinoma as well as gastric and colorectal carcinoma specimens [9]. It leads to the decreased ability of the stimulation of apoptosis due to a frameshift mutation in the caspase-8 gene. Hyper methylation of this gene has been observed to have a loss of caspase-8 expression in neuroblastoma patients [10, 11]. It has also been observed in small-cell lung cancer (SCLC), hepatocellular carcinoma (HCC), and bladder cancer [12, 13]. Caspase-10 mutations have not only been observed in tumors but also in autoimmune disorders. Inactivating caspase-10 point mutations are the principal causes of the autoimmune lymphoproliferative syndrome (ALPS). Frameshift mutations give rise to the termination of premature caspase-10 in systemic juvenile idiopathic arthritis [14]. Multiple myeloma, hematopoietic carcinoma, and T-acute lymphoblastic leukemia also have been detected to have caspase-10 mutations. There is not much information on the mutation of caspase-3, caspase-7, and caspase-9.

The inhibitor of apoptosis (IAP) family of proteins, on the other hand, usually gets activated resulting in dysregulation of the intracellular activities of caspase-3, caspase-7, and caspase-9 [15]. X-linked IAP or XIAP acts directly to potentially inhibit these caspases, while cIAP or cellular IAP (cIAP1 and cIAP2) indirectly act upon the caspases to inhibit their activities. XIAP possesses baculovirus IAP repeat (BIR) domains, which have a high affinity for binding to caspase-3 and caspase-7. When the BIR1 and BIR2 domains are potentially bound to the active site of the caspases, access to the caspase substrate protein is prevented. The BIR3 domain binds to the monomeric form of caspase-9, thus inhibiting dimerization and enzyme activation [16, 17]. cIAP1 and cIAP2 involve two separate mechanisms, firstly, they can bind to the second mitochondria-derived activator of caspases (SMAC) and inhibit the action of SMAC protein by hindering XIAP from moving away from the bound caspases. Secondly, cIAP1 and cIAP2 subject the executioner caspases to ubiquitination leading to a gradual disintegration by the proteasome [18, 19]. Hematopoietic carcinoma and many other solid tumors have been detected to have an overexpression of IAPs, particularly XIAP. High levels of XIAP correlate with poor prognosis in adult acute myeloid leukemia (AML), childhood T-cell acute lymphoblastic leukemia, and diffuse large B-cell lymphomas (DLBCL) [Ibrahim AM *et al.* 2012, Hussain AR *et al.* 2010]. Both cIAP1 and cIAP2 including survivin have been observed to have reduced expression in various tumors with poor clinical outcomes. Overexpression of cIAP2 has been frequently detected in MALT lymphomas [20].

Defects in Intrinsic Pathways

The intrinsic apoptosis pathway is highly coordinated by the members of the Bcl-

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