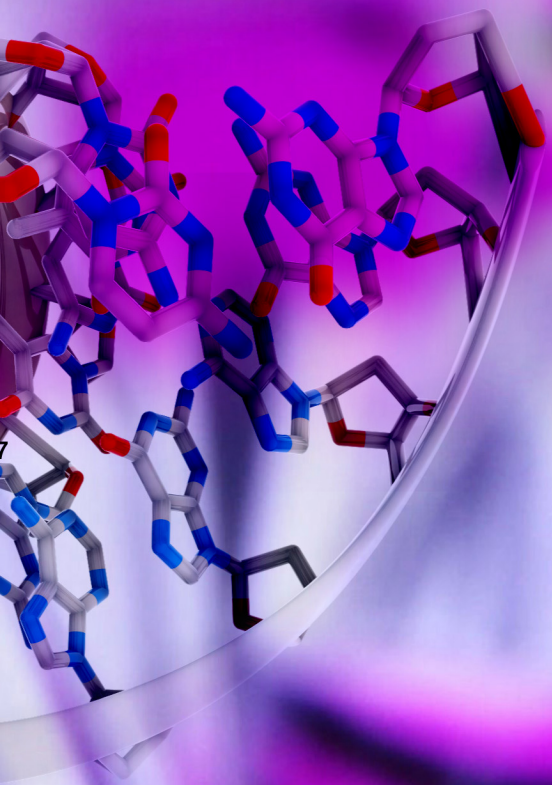
Topics in Anti-Cancer Research



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PREFACE

The ninth volume of **Topics in Anti-Cancer Research** covers new developments in the field of cancer. It comprises six comprehensive chapters which are exciting contributions in frontier areas of anti-cancer research.

Karaosmanoğlu presents a discussion on recent patents on exosome-derived therapeutic agents in the first chapter of the volume. The chapter by Koyuncuer deals with serrated lesions of the colon and rectum; he discusses serrated polyps, nomenclature, the particularly associated risk of cancer, terminology and classifications, molecular features and colonoscopic follow-up in this chapter.

Rezaei *et al.* have presented new information on the development of radioactive materials for brachytherapy plaques and selected 188W/188Re and 144Ce/144Pr plaques for eye cancers brachytherapy.

In the next chapter of the book Mir *et al.* focus on the structure of ShcA proteins and their role in promoting metastasis and progression of various cancers. Understanding the role of ShcA proteins may provide new tools for therapeutic interventions in cancer therapy. Aljafary *et al.* discuss the cellular and molecular role of different types of hormones in treating various kinds of cancers. Other topics related to their impact on stem cell functionality and cancer management are also presented.

Al-Khater, in last chapter of the book, presents an account of the anti-cancer effects of melatonin, focusing on mechanisms of action. Cancers of the lung, prostate, breast, and colon, as well as ovarian cancer are discussed in this context.

I am thankful to the authors for their excellent contributions and to the reviewers for their in-depth comprehensive comments for the improvement of chapters. I am also grateful to Mr. Mahmood Alam (Director Publications), Mr. Obaid Sadiq (Incharge Books Department), Ms. Asma Ahmed (Senior Manager Publications) and other colleagues for their support and assistance in the finalization of this volume.

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CHAPTER 1

Recent Patents on Exosome-Derived Therapeutic Agents

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Abstract: Exosomes are extracellular vesicles that are 30-150 nm in diameter. Exosomes have recently emerged as critical mediators of cell-cell communication by the transfer of DNA, RNA, and protein structured macromolecules between cells and tissues. With the advantage of the distant endocrine signalling, cancer cells use exosomes to suppress the immune system, next contribute to the formation of pre-metastatic niches and angiogenesis. On the other hand, researchers have been benefited from the immunosuppressive, natural carrier, and tissue regenerating roles of exosomes and disclosed patents that are claiming the utilities of exosomes for treating chronic inflammation, autoimmunity related diseases, targeted drug delivery vehicles, and tissue regenerating agents. Moreover, the use of exosomes as vaccine components to prevent cancer, therapeutic molecules for cancer treatment, and the host of biomarkers for the diagnosis and prognosis of cancer are among the issues that are protected by recent patents. The most inspiring one among them could be the incorporation of a therapeutic siRNA that is complementary to oncogenic $KRAS^{G12D}$ into $CD47^{+}$ exosomes for the treatment of pancreatic cancer. The other one could be the demonstration of the utility of exosomes secreted from dendritic as a cancer vaccine component in phase II clinical trial. It is clear that we have started to understand the fundamentals of exosomes. However, more studies are needed to develop exosome-based cancer vaccines, drug delivery vehicles, immune-stimulating agents that evoke immune cells to kill the cancer cells, and diagnostic and prognostic markers for monitoring cancer in the next years.

Keywords: Cancer Vaccines, Chemoresistance, Cancer Diagnosis, Drug Delivery Vehicles, Dexosomes, Exosomes, Genetically Engineered Exosomes, Intercellular Communication, Immune Stimulation, Immune Supp-ression, Immune Tolerance, Multivesicular Bodies, MiRNA, Nucleic Acid Delivery, Pre-metastatic Niche, SiRNA, ShRNA, Tissue Regeneration, Tumour Microenvironment, Viruses.

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INTRODUCTION

Extracellular secretory vesicles that are released from various cells can be termed as apoptotic bodies, argosomes, archeosomes, epididimosomes, dexosomes, exosomes, exosome-like vesicles, microvesicles, oncosomes, and prominin-osomes but mainly divided into three categories that are apoptotic bodies, microvesicles, and exosomes. Differential centrifugation is used to distinguish the subtypes of secretory vesicles. While microvesicles that are of the 200-1000 nm diameter can be precipitated at 10,000-20,000 × g, exosomes that are of the 30-150 nm diameter can be precipitated at 100,000 × g [1]. Besides, exosomes are secreted by the fusion of multivesicular bodies (MVBs) with the plasma membrane [2]. However, microvesicles are released by direct budding of the plasma membrane to outward extracellular milieu [3]. The process of exosome secretion was related to waste disposal mechanism until a study suggesting the exosomes as mediators of intercellular communications in cancer in the 2000s [4]. Upon this initial study, it was demonstrated that exosomes are implicated in both physiological and pathological conditions. In physiology, exosomes involve in coagulation, inflammation, cellular homeostasis [5], immune surveillance [6], fetal survival in pregnancy [7], and neuroprotection [8]. Exosomes contribute to pathological progression of autoimmune diseases [9], cardiovascular diseases [10], neurodegenerative diseases [11], and metastasis [12 - 14]. Beyond this, exosomes are considered as a source of biomarkers that is useful for both diagnostic and prognostic purposes from cancer [15] to Alzheimer [16] with the ability of simply accessible from various body fluids.

Exosomes are produced continuously by nearly all types of cells in the human body [17]. Exosomes can specifically bind to the recipient cells through adhesion molecules like integrin and tetraspanin web complexes [18] then uptaken by the recipient cells with the endocytic pathways such as caveolin-mediated endocytosis, clathrin-mediated endocytosis, lipid raft-mediated endocytosis, macropinocytosis, and phagocytosis [19]. Upon the uptaken, exosomes release the macromolecular contents including, DNA (single-stranded DNA, double-stranded DNA, mtDNA), RNA (mRNA, miRNA, lncRNA and other RNAs), proteins (adhesion molecules (integrins), cell skeleton proteins (actin, tubulin), enzymes, heat shock proteins (Hsp70, Hsp90), receptors (MHC-II, MHC-I, CD86), tetraspanin proteins (CD9, CD63, CD81), and vesicle traffic proteins (Anneksin, TSG01, Alix)) and lipids (ceramide, cholesterol, and sphingolipids) to the cytoplasm of the recipient cells [20 - 22]. Then these molecules modulate recipient cell function and gene expression. With these modulatory effects in the recipient cell, the utilities of exosomes for discovering new treatment methods for cancer have been growing exponentially.

In this chapter, more than thirty of recent patents protecting the use of exosomes as vaccine components, immune suppressors, drug delivery vehicles, mediators of tissue regeneration, and therapeutic molecules for cancer treatment are discussed.

EXOSOMES AS VACCINE COMPONENTS

With the benefits of circulating in various body fluids and reaching to the distal organs, exosomes can improve the distribution of antigens through the whole body. In addition, exosomes provide stable conditions for maintaining protein structure of the vaccine. Moreover, since exosomes express the adhesion molecules on their surface, the binding and uptake of exosomes by antigen-presenting cells are increased [23]. Therefore, exosomes are newly emerging alternative tools for developing new vaccines.

Exosome biology resembles retroviruses in many details. Both exosomes and retroviruses are about 150 nm in diameter [24]. Both are coated with a lipid membrane, carry genetic material, originate from endosomal pathways, bind to the plasma membranes of recipient cells, uptaken by common mechanisms, and initiate specific reactions by their macromolecular contents in the recipient cells [25]. Moreover, the spread of viral infections to the new cells is facilitated by exosomes. For example, in hepatitis C infected patients, exosomes released from infected cells can transmit infections to new target cells [26]. Thereby exosomes hide viral particles and mediate new infections, like a Trojan horse, by avoiding immune recognition. On the other hand, researchers are making efforts to produce DNA vaccines by using the ability of exosomes to transport viral particles. In a recent patent, the inventors discovered that an exosome expressing a fusion antigen protein has excellent cytotoxic T-cell inducibility [27]. After this patent coverage, there is an attempt to produce vaccines by using DNA vectors that are expressing viral proteins on the exosomes [28]. This approach is found useful for the development of vaccines against viral diseases such as Ebola Virus VP24, VP40, and NP, Influenza Virus NP, Crimean-Congo Hemorrhagic Fever NP, West Nile Virus NS3, and Hepatitis C Virus NS3 [29]. However, this exosome-based vaccination procedure is not examined with clinical trials.

There is accumulating data for the utility of exosome-based vaccines in the management of non-viral infectious diseases caused by pathogenic microorganisms such as *Corynebacterium diphtheriae* [30], *Eimeria tenella* [31], *Leishmania major* [32], *Mycobacteria tuberculosis* [33], and *Streptococcus pneumoniae* [34]. These vaccination procedures are not examined with clinical trials. Therefore, the clinical utility of these vaccines is remained unclear for now.

When it comes to cancer, one might suggest that if I educate immune cells with cancer cell-derived exosomes, then these exosomes would mediate the elevated

CHAPTER 2

Serrated Lesions of the Colon and Rectum: An Overview of Pathology and Emphasis on a New Classification

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Abstract: The most common malignancy in the gastrointestinal tract is colorectal carcinomas (CRC), which is the second most common cancer in women and the third most in men worldwide. Adenomas are the most frequently observed precursor lesions for CRC. Two basic pathways have been defined for CRCs: the classical adenoma-carcinoma sequence and serrated pathway developing from sessile serrated lesions or adenomas. In the previously reported literature, there is no potential for malignancy, but now the serrated neoplasia pathway is observed in approximately 30% of all CRCs. In large colonoscopic series studies, the prevalence of serrated polyp is approximately 20%. Colorectal serrated lesions are characterized by sawtooth or stellate morphological features of the epithelium. For sessile serrated lesion (SSL) definition, according to the World Health Organization (WHO) Classification of Tumors of the Digestive System 2019, the presence of at least 1unequivocal distorted crypt is considered sufficient for diagnosis. There is major variability in the morphology of colorectal serrated lesions or polyps, and as a consequence, a number of pathological subtypes have been described and 3 significant types have been defined; hyperplastic polyp (HP), sessile serrated lesion (SSL), and traditional serrated adenoma (TSA). HP is the most common lesion among all serrated polyps, and the potential for colorectal cancer development is very low. Improving the detection of SSLs reduces both the incidence and mortality of CRCs and reduces the risk of developing cancer of interval cancers. In this article, we will discuss serrated polyps, nomenclature, the particularly associated risk of cancer, terminology and classifications, molecular features and colonoscopic follow-up with the current designation.

Keywords: Cancer, Colonoscopy, Colorectal, Distorted, Dysplasia, Epidemiology, Gastrointestinal Tract, Histopathology, Hyperplastic, Immunohistochemistry, Localization, Macroscopic Appearance, Molecular, Polyps, Prognosis, Sessile, Serrated, Traditional, Unequivocal, WHO.

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INTRODUCTION

Adenocarcinoma is the most common malignant epithelial tumors of the colon, rectum. In 2018, 1 849 518 new cases (about 10.2% of all cancers) were reported worldwide, which is the second most common cancer in women and the third in men [1, 2]. In 2018, 880 792 deaths (approximately 9.2% of deaths reported from all cancers) were reported due to colorectal cancer. In Europe, the incidence of colorectal cancer is very high in some countries, while in Asia and some Africa regions, the incidence is very low [2]. Incidence and mortality are 25% less in women than in men. Especially in developing countries, it is estimated that colorectal cancers will reach new cases between 2-5 million years old in 2035. An important reason for this is thought to be the result of the increase or development of colonoscopy screening [3]. Recent studies have been published over the past twenty years regarding serrated polyps or lesions, and evidence on clearly, defined classifications are available. Detection of precursor lesions of colorectal carcinomas is one of the main targets of colonoscopy screening and surveillance programs today [4]. It was known that serrated lesions had no potential for malignancy for a long time. However, an increasing number of molecular studies have yielded clear conclusions about colorectal carcinoma pathogenesis. Almost all CRCs are believed to develop from a precursor adenoma, and many studies have been shown when detecting the classic adenoma-to-carcinoma sequence, while other carcinoma pathways are present [5]. This process, defined as a serrated neoplastic pathway, has been shown to develop colorectal cancer from serrated polyp or adenomas. In the past few decades, all serrated polyps were considered to be hyperplastic, but thanks to new developments, it was shown to have the malignant potential of hyperplastic polyps [6]. The most important reason for insufficient diagnosis of SSL can be related to the fact that clinicians and pathologists lack awareness of these lesions. This demonstrated the importance of pathologists or colonoscopists in recognizing these lesions, especially in colorectal cancer screening programs.

CLASSIFICATION AND TERMINOLOGY

Polyps with different growth, differentiation patterns and combined morphological features, hyperplastic and adenomatous epithelium, were previously defined as a mixed hyperplastic adenomatous polyp. For the first time in 1990, potentially different lesions were evaluated in the category of serrated adenoma by Longacre and Fenoglio-Preiser [7]. Classical criteria of hyperplastic polyps (HPs) include a serrated epithelium on the surface and limited proliferative zone, narrow straight crypts in uniform spaced crypts. Serrated adenomas (SAs)

were defined as dilatation in T and L shaped crypt bases, serration in crypt bases, abnormal proliferation and also in crypt bases determination of goblet or foveolar cells [8]. Today, the WHO-2019 reported that 1 or more unequivocal architecturally distorted serrated crypt would be sufficient for SSL diagnosis. Serrated lesions of the colorectum are subdivided into four categories by WHO-2019 (5th edition): Hyperplastic polyp, sessile serrated lesion (SSL, formerly known as sessile serrated adenoma/polyp), traditional serrated adenoma (TSA) and unclassified serrated adenoma. SSL terminology, which is one of the most important changes in the fifth edition, has been defined according to the opinion that not all lesions have a polypoid appearance [4].

LOCALIZATION

Hyperplastic polyps are more frequently showed in the distal colon and rectum. SSLs predominantly occur in the proximal colon; about 25% are detected distal to the splenic flexure [9]. Approximately 70% of TSAs are detected in the distal colon-rectum or left colon [9, 10].

Table 1. Classification of colorectal serrated lesions or polyps.

Histologic Subtypes
Hyperplastic Polyp Microvesicular HPs (MVHPs) Goblet Cell-Rich HPs (GCHPs)
Sessile Serrated Lesion
Sessile Serrated Lesion with Dysplasia Intestinal Dysplasia Serrated Dysplasia
Traditional Serrated Adenoma
Unclassified Serrated Adenoma

CLINICAL, ENDOSCOPIC FEATURES AND RISK FACTORS FOR SERRATED POLYPS OR LESIONS OF THE COLONRECTUM

HPs are defined as small and innocuous lesions observed in the adult colon. They increase with age, especially one-third of the increase in asymptomatic individuals after age 50. These lesions detected incidentally during colonoscopic examination are generally asymptomatic and associated with smoking, alcohol and obesity. It is sometimes difficult to distinguish from classical adenomas clinically [11]. A diet rich in fats creates risk, and it has been reported that the use of NSAID and aspirin has protective properties [12]. On the other hand, age, female sex, diabetes

CHAPTER 3

Introducing the $^{188}W/^{188}Re$ and $^{144}Ce/^{144}Pr$ Plaques for Eye Cancers Brachytherapy

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Abstract:

Background:
Plaque brachytherapy has been introduced as a treatment for ocular melanoma, an intraocular tumor, and is an available alternative to eye enucleation. Brachytherapy is one of the radiotherapy methods, which uses radioactive sources near or on the tumor.

Introduction:
So far, various plaques have been used to treat eye tumors. The aim of this research is the development of radioactive material for brachytherapy plaques.

Method:
In order to introduce and produce new brachytherapy plaques, all the isotopes of the periodic table of elements have been identified, and the mother and daughter of elements whose mother had long half-life beta decay and its daughter had a short half-life have been identified and the method of mother production has been examined.

Result:
After reviewing, two new ^{188}W / ^{188}Re and ^{144}Ce /^{144}Pr plaques have been selected for use in brachytherapy.

Conclusion:

Each of the new plaques has a special advantage in comparison with old plaques. The 2D dose distribution of $^{188}W/^{188}Re$ and ^{144}Ce /^{144}Pr plaques in eye and tumor was obtained and was compared with old plaques.

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Keywords: ^{188}W / ^{188}Re Plaque, ^{144}Ce, ^{144}Pr Plaque, Brachytherapy, Beta Radiation, Eye Cancer, Elements, Half Life, MCNPX Code, Melanoma, Reactor, Serum-144, Tumor, Tangsen-188.

INTRODUCTION

Eye cancer is a rare but debilitating disorder. This cancer can affect the outer and inner parts of the eye. The most common cancers in adults are melanoma and lymphoma, while in children, retinoblastoma may be outside or inside the eye [1]. A large percentage of the cells in this tumor is retinoblasts in terms of retinal tissue [2]. At a stage of evolution, cells prevent division, and they become adult retinal cells. Typically, this process is controlled by normal RB1 genes. Some cells grow out of control and cause cancer. This resemblance prompted Verhoeff to coin the term retinoblastoma, which was adopted by the American Ophthalmological Society in 1926 as a general term for this eye cancer [3]. Retinoblastoma usually occurs in children under 5 years of age [2]. In some patients, the tumor may start in one or both eyes. If retinoblastoma is not detected in time, it may involve a significant portion of the eyeball [2]. Melanoma is a relatively rare tumor that results from melanocytes in various anatomical sites, including the skin, mucous membranes, eye area, and rarely from unknown primary sites. Melanoma are special cells that makeup melanin, and because of its origin in melanocytes, it is called melanoma. Most UMs are returned depending on where they are located; *i.e.*, UMs are often referred to by their location; *i.e.*, the origin of iris melanoma is elsewhere, but it attacks the iris. Although iris melanoma is derived from uveal, it is more common with cutaneous melanoma [4, 5]. Mutations in the BAP1 gene are strongly associated with two options: metastatic spread and patient survival [6]. The incidence of ocular tumors varies according to the age and race of the patient. UM affects people with fair skin, light eye color, and European descent [2, 7 - 9]. A New York City study found that the annual incidence of UM in black patients is 0.31 per million [2]. UM's propensity for lightly pigmented persons and the posterior part of the uveal tract suggests that UV light may play a role in pathogenesis, but studies are inconclusive [10, 11]. Retinoblastoma is the most common cancer worldwide, and UM is the most common cancer in Europe and the United States [4]. From 84836 of the National Cancer Database between 1985 and 1994, the percentage of melanoma in the skin, eyes, mucosa, and primary unknown was 9%, 5%, 1%, and 2%, respectively. Melanoma of the ocular structures accounts for approximately 5% of all melanomas. Most (95%) are UV allele melanomas. Men have a higher rate of melanoma than women. The causes of melanoma are ambiguous. However, several host and environmental factors have been studied. Clinical, epidemiological, physiological, and genetic data suggest that ultraviolet radiation an important parameter in UVL melanoma development. Melanoma is not an

inherited disease. The lesions may be associated with pigmented spots in the iris, cataracts, blurred vision, blinking, gradual weakness in the visual field, or severe eye pain. The consequences of vascular melanoma can be served and dangerous. Such as the risk of metastasis and the development of a malignant secondary tumor in areas far from the main tumor, which usually develops in the liver, is the leading cause of death among metastatic ocular melanoma patients [12]. The most common sign of melanoma inside the eye is vision loss, and another symptom is pupillary whiteness [2, 8, 9]; worsening vision over weeks to months; blurred vision or sudden loss of vision; floaters or flashes of light; loss of part of the visual field; a growing dark spot on the iris; change in pupil size or shape; bulging of the eye; and change in how the eye moves [7, 8, 13]. Oncogenic mutations in GNAQ or GNA11 (genes encoding for widely expressed G protein alpha subunits), which are observed in >80% of primary UMs, activate signaling pathways, including the mitogen-activated protein kinase pathway. Most intraocular melanoma originates in the iris and is easily seen. A small percentage of these spread to other parts of the body.About 50% of UMs harbor mutations in the GNAQ or GNA11 genes that encode G protein–coupled receptors in the RAF/MEK/ERK pathway, also found in benign lesions. Congenital ocular melanocytosis GNAQ mutations are thought to be an early or initiating event in the pathogenesis of UM [2, 14 - 16]. The National Cancer Institute's Surveillance, Epidemiology, and end Results data on about 1,500 patients diagnosed with eye melanoma between 1988 and 2001 show that, overall, about 3 out of 4 people with eye melanoma survive for at least 5 years [17]. Survival rates are higher in the early stages of diagnosis, but the exact survival rate of ocular melanoma is difficult because it is rare cancer [9, 17, 18]. When the cancer is confined to the eye, the 5-year relative survival rate is about 80% [17]. For people with eye melanomas that have spread to distant parts of the body, the 5-year relative survival rate is about 15%. If there is spread outside the eye, a stage is assigned [18]. About half of patients with melanoma develop metastases between 10 and 15 years later, which is very fatal [2, 9]. Methods of diagnosing melanoma include: indirect ophthalmology, deep eye photography, fluorescent angiography, ultrasound, MRI, CT, complete biopsy [12]. There are several treatments for eye cancer, the most common of which are radiation therapy and eye drainage. Radiation therapy includes external radiotherapy (proton therapy, hadron therapy and gamma knife) and brachytherapy (using radioactive plaque) [19, 20].

ENUCLEATION

Enucleation is used for advanced and large melanoma, which occupies most of the structures inside the eye and has no hope of healing. It is used for those who have developed secondary gradual blindness and involves removing the entire visual

CHAPTER 4

ShcA Family of Adaptor Proteins: Dual Role in Cell Growth

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Abstract: ShcA proteins are the family of adaptor proteins that mediate biological responses by transducing extracellular signals into intracellular signals. ShcA family consists of three different alternatively spliced or alternative translational initiated isoforms known as p66Shc, p52Shc and p46Shc. The p52and p46Shc isoforms are usually involved in promoting cell growth, mediating their action by activating mitogen-activated protein kinases (MAPK) and phosphoinositide-3-kinase/Akt signalling pathways. However, the p66Shc isoform acts as a dual player in cell development and is involved in stimulating both cell proliferative and apoptotic pathways. Any deregulation in the expression of ShcA proteins and pathways regulated by ShcA proteins results in the occurrence of different types of cancerous diseases, including breast cancer, thyroid cancer, prostate cancer and lung cancer. Aberrations in the expression of ShcA proteins have been demonstrated to promote key elements of cancer progression, including cell migration, cell proliferation, metabolic reprogramming, angiogenesis and tumorigenesis. Based on all these studies, the present chapter focuses on the structure of ShcA proteins and their role in promoting metastasis and progression of various cancers. Understanding the role of ShcA proteins may provide new tools for therapeutic interventions in dreadful cancer disease.

Keywords: Adaptor proteins, Apoptosis, Aging, Cell proliferation, Cell differentiation, Cell signalling, Cell survival, Metabolism, Modular domains, Neoplasms, Oxidative stress, Reactive oxygen species, Vascularization.

INTRODUCTION

ShcA proteins are one of the subtypes of the Shc family of adapter proteins, which

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act as transducers of extracellular signals to intracellular in different signal transduction pathways [1]. ShcA family consists of three different proteins p46, p52 and p66Shc, which arise from the same gene locus [2].

However, different isoforms of ShcA are generated from two mRNAs *via* RNA splicing and alternative translational initiation [3]. The p46shc/p52shc isoforms are formed by the assembly of the non-coding exon 1 with the 3' portion of exon 2 (exon 2a), and with exons 3-13 while the p66shc transcript is formed by the assembly of exons 2-13 [4]. Apart from this, the translation process is also involved in the formation of these three isoforms, while the two shorter isoforms p52/p46Shc use two translational in-frame ATG start codons, the longest p66Shc isoform product formation utilizes three ATGs in-frame start codons [4]. Structurally, all isoforms of the ShcA family have a distinctive modular character, containing phosphotyrosine binding (PTB) domain at N-terminal end, which is linked to C-terminal Src homology 2 (SH2) domain by Collagen homology (CH1) linker domain [5]. A cytochrome C binding domain is also present in p66Shc and P52Shc isoform. Nevertheless, 66kda isoform contains an extra glycine/proline rich fragment linked to N-terminus of PTB domain known as collagen homology (CH2) domain, which makes it the longest and the most different from the other two isoforms. Moreover, p52Shc and p46Sh are ubiquitously expressed while p66Shc displays a constrained pattern of expression [5]. P52/46Shc proteins have been implicated in the regulation of diverse cellular functions like cell survival, cell proliferation, cell-cell adhesion and cell migration, whereas p66Shc is mainly involved in reactive oxygen species (ROS) production, apoptosis, aging and cell metabolism, *etc*. ShcA proteins have also been implicated in the progression of many cancers including colon cancer, pancreatic cancer and breast cancer, *etc* [6 - 8]. The ability of ShcA proteins to activate different signalling pathways and mediate different biological responses is endorsed to its multi-domain organization which enables these proteins to interact with the number of other proteins, thereby regulating different biological processes.

ShcA Expression and Localization

ShcA isoforms are expressed differentially both at the cellular level and tissue level; while the longest isoform p66Shc is specifically expressed in most of the cells except hematopoietic lineage and in tissues including heart, kidney, lungs, liver and spleen, the two shorter isoforms show ubiquitous pattern of cellular and tissue expression [9]. Epigenetic modifications also play a crucial role in the regulation of ShcA expression [10]. Demethylating agents and histone deacetylase inhibitors have been reported to positively regulate p66Shc protein expression in a dose-dependent manner [11]. A class III histone deacetylase enzyme SIRT1 was

observed to bind p66Shc promoter directly and represses its transcription by deacetylating Lys9 in histoneH3. Moreover, the exogenous introduction of SIRT1 in mice showed alle*via*tions in mRNA and protein levels of p66Shc. Similarly, a significant enhancement in p66Shc expression was found in response to low-density lipoproteins induced methylation of p66Shc promoter [12].

Besides variances in expression pattern, ShcA proteins also show differences in their localization pattern. P66Shc is mainly located in the cytoplasm, mitochondria and endoplasmic reticulum [13]. P52Shc is found on membranes of endoplasmic reticulum, while p46Shc is directed to mitochondrial matrix by mitochondrial specific signals [14, 15] (Table **1**).

Table 1. Characterization of ShcA family.

S. No.	Character	P66Shc	P52Shc	P46Shc
1.	Number of amino acids	583	473	428
2.	Molecular weight	66 kDa	52 kDa	46 kDa
3.	Structural Domains	CH2-CB-PTB-CH1-SH2	CB-PTB-CH1-SH2	PTB-CH1-SH2
4.	Localization	Cytoplasm, mitochondria and endoplasmic reticulum	Endoplasmic reticulum	Mitochondrial matrix
5.	Expression pattern	constrained	ubiquitous	ubiquitous
6.	Functions	Apoptosis, ROS production, Rac1 activation and ageing	Ras regulation, cell survival, cell growth, Cytoskeleton Organization.	Ras regulation, cell proliferation, Cytoskeleton Organization
7.	Occurrence	Vertebrates	Amphibians, nematodes, insects, fishes and mammals	Amphibians, nematodes, yeasts, insects, fishes and mammals

Modular Domains of ShcA

ShcA-PTB Domain

ShcA phosphotyrosine binding domain (PTB), made of around 195 amino is also known as the phosphotyrosine interaction domain (PID). This domain consists of 3 alpha-helices and 7 beta-sheets [14]. ShcA-PTB domain shares some structural similarity with the pleckstrin homology (PH) domain possessing a β-sandwich

CHAPTER 5

Melatonin as an Anti-cancer Agent

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Abstract: Cancer is a disease that causes a huge health burden for communities. Despite the great progress made in diagnostic tools for cancer and the advancement of treatment strategies, cancer is still one of the commonest causes of death in the world. Melatonin, a hormone produced mainly by the pineal gland, possesses an anti-cancer property. The discovery of this effect of melatonin on cancer cells was a breakthrough in the field of cancer research. Several lines of evidence support this property of melatonin, including *in vitro* and *in vivo* studies and clinical trials. This effect of melatonin was examined in various types of cancer, and a consensus has been reached with regard to its oncostatic/anti-cancer effect. Multiple mechanisms have been proposed for this effect of melatonin, among which are the anti-oxidant, anti-inflammatory, anti-estrogen/androgen, anti-angiogenic, and pro-apoptotic actions of melatonin. This chapter presents an account on the anti-cancer effect of melatonin, focusing on mechanisms of action by presenting examples of cancer types, including the most common types of cancer in the world: cancers of the lung, prostate, breast, and colon, as well as ovarian cancer.

Keywords: Breast cancer, Cancer, Colorectal cancer, Lung cancer, Melatonin, Oncostatic effect, Pineal gland, Prostate cancer.

INTRODUCTION

Melatonin is a naturally occurring hormone secreted by various types of tissues in the body, mainly by the pineal gland. The pineal gland is a small endocrine gland that forms part of the diencephalon of the brain. It is attached to the posterior aspect of the third ventricle by a stalk. The pineal gland is a highly vascular structure and has two types of cells: pinealocytes and neuroglial cells. The pinealocytes are the cells that synthesize and secrete melatonin.

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The secretion of melatonin is regulated by the circadian rhythm of the body, being higher at night [1]. Serum melatonin level during darkness (night-time) is higher than that during daytime. The regulation of melatonin secretion is achieved by input from the circadian pacemaker, the suprachiasmatic nucleus (SCN), one of the hypothalamic nuclei [1, 2]. The SCN receives information about time of the day from the retina through the retino-hypothalamic pathway. The neural connection between the SCN and the pinealocytes of the pineal gland is an indirect one. This connection descends through the reticular formation of the brainstem to reach the sympathetic neurons in the upper thoracic part of the spinal cord. From there, the preganglionic fibers synapse with postganglionic neurons in the superior cervical ganglion, whose axons reach the pinealocytes and make synaptic contact with them. Noradrenaline (norepinephrine) is the neurotransmitter secreted by the sympathetic fibers to cause the secretion of melatonin from the pinealocytes. This pathway is activated by darkness and deactivated by light. Therefore, melatonin production is primarily under sympathetic control, and other hormones do not play any known role in its control.

Melatonin was first discovered in the late 1950s after the work of Lerner and co-workers, who isolated this hormone from bovine pineal gland [3]. Starting in the 1970s, studies demonstrated that melatonin is also secreted by extra-pineal sites, such as the retina, gastrointestinal tract, skin, thymus, and bone marrow [4, 5]. Moreover, it has recently been reported that melatonin is secreted by any cell with a nucleus [6].

Initially, the role of melatonin was thought to be limited to the control of the circadian rhythm, but further studies have shown that it is implicated in many physiological functions of the body. Now, it is believed that the control of the circadian rhythm is mainly performed by pineal melatonin, whereas extra-pineal melatonin is implicated in the other physiological functions elaborated below [6].

Some scientists argue that melatonin possesses several properties beyond those of classical hormones [7]. This is because it acts like an autocoid (used by the cells of the source, such as the retina), paracoid [used by the cells in the vicinity of the source, such as neural tissue from the cerebrospinal fluid (CSF)], and as a free radical scavenger (anti-oxidant). In addition, the pineal gland, unlike other endocrine glands, lacks storage machinery for melatonin and the regulatory feedback mechanisms known for hormonal function. This is in addition to the fact that melatonin is secreted by extra-pineal sources not recognized as endocrine glands. Food is also a known source of melatonin; thus, it can be regarded as a vitamin [7].

Several basic and clinical studies have reported a beneficial effect of melatonin administration in the treatment of a number of organic or psychological diseases [8, 9]. One of the organic diseases that showed a positive response to melatonin was cancer [10 - 12]. Melatonin has well-documented anti-cancer properties that have attracted the attention of researchers since the last century. It has been found that the cancer inhibition properties of melatonin are present at various levels of cancer development, including the early and late stages [13, 14]. The recent literature in the field of cancer therapy is advocating the use of melatonin as an adjuvant therapy with other treatment modalities [15]. This recommendation is based on the evidence obtained from a few clinical trials that showed improved survival and outcomes among cancer patients treated with melatonin, in addition to chemo- or radiotherapy, as compared to patients who received only traditional therapy [16]. Lissoni's research group was active in addressing the issue of melatonin treatment for cancer patients [10, 11, 17 - 20]. Mills *et al.* [16] conducted a meta-analysis of Lissoni's group studies and found a significant difference between patients who used melatonin as an adjuvant to chemotherapy and patients who used chemotherapy only. Following these studies, more interest has been directed toward melatonin as an anti-cancer agent. Currently, researchers focus on investigating the underlying mechanisms of this anti-cancer effect of melatonin. This chapter highlights the current views on the role of melatonin in the prevention and treatment of cancer.

The History of the Anti-Cancer Effect of Melatonin

The notion that melatonin has an anti-cancer effect is not recent. Rather, it arose around the middle of the last century. More attention was paid to this relationship between melatonin and cancer after the observations of Cohen and co-workers, who presented a hypothesis, in 1978, that referred to a potential relationship between pineal gland dysfunction (for example, pineal calcification) and the increased incidence of breast cancer in women [21]. They suggested an inhibitory effect of melatonin on the production of estrogen; therefore, the reduction of melatonin leads to an increase in estrogen level and, thus, increases the risk of the development of breast cancer. Their study published in 1981 provided evidence for this relationship [22]. In that study, they performed pinealectomies in rats and observed that this procedure stimulated the development of 9,10-dimethyl-1-2-benzanthracene (DMBA)-induced mammary tumors, whereas rats that received melatonin were protected from developing such tumors.

Recent research work has documented this oncostatic effect of melatonin on various types of cancers, including cancer of the breast [23, 24], lung [25], gut [26 - 29], liver [30], pancreas [31], prostate [32], ovary [33], uterus and cervix [34],

CHAPTER 6

Hormones Management as Anticancer Treatment and Protection: Functions and Mechanism of Action

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Abstract: The available therapy for cancers mostly revolves around chemotherapy, radiation, immunotherapy, and surgery, but these treatment modalities are not satisfactorily treating the patients and are associated with various side effects, pain, immune reduction, trauma, and also induce drug resistance in some patients. Besides, these treatments do not treat the disease's origin but eliminate the tumor itself somewhat without confirmation of avoiding its metastasis. Therefore, there is a need to develop a new effective therapy to treat cancer patients successfully. Hormones naturally present in the human body for controlling various biological and physiological functions also possess potential capabilities to treat different types of cancers. Both preclinical and clinical data show that hormones include anticancer abilities, are controlled by hormonal managing. This chapter has discussed the cellular and molecular role of different types of hormones in treating various kinds of cancers and other pertinent topics related to their impact on stem cell functionality and cancer management.

Keywords: Anticancer Treatment, Cardiac hormones, Functions, Hormones, Management of endogenous hormones, Mechanism of Action, Oxytocin hormones, Sex hormones, Stem cell functionality.

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GENERAL INTRODUCTION

Cancers pose severe global health challenges, and millions of patients are currently present in different parts of the world. One of the challenges of the different types of cancer is early diagnosis and treatment. The cancers' available therapy mostly revolves around chemotherapy, radiation, immunotherapy, and surgical interventions. Unfortunately, all of these treatments fail to provide a complete cure to patients and come with various side effects; pain and trauma also induce drug resistance in some patients. Therefore, there is a need to develop effective therapy management, which can successfully be investigated and used to treat cancer patients. Hormones usually produced in the human body for regulating various biological and physiological functions also possess potential capabilities to treat different types of cancers. Both preclinical and clinical studies show that hormones possess anti-cancer potential. In the present chapter, we have discussed the roles of different hormones, such as sex hormones, cardiac hormones, and oxytocin hormones, as anti-cancer agents. We have also discussed the topics, such as the impact of hormones on cancer therapy and their implications on stem cell functionality and the management of endogenous hormones as promising therapeutic candidates for treating cancers.

Sex Hormones in Anti-Cancer Management

Cancer causes severe health problems, and it is estimated to be responsible for millions of deaths by 2030. Breast cancer is one of the significant cancers causing many lives due to the lack of proper protection, diagnosis, and treatment availabilities. The role of estrogen receptor-positive [ER+] on breast cancer is a significant target for anticancer therapy as [ER+] represents 75% of all breast cancers. The female estrogen hormones initiate and progress breast malignancy; hence estrogen receptors have been targeted at breast cancer treatment. Estrogen alpha receptors have been targeted by therapies to suppress the estrogen effect [1, 2].

Dehydroepiandrosterone [DHEA] is an inactive steroidal hormone, secreted by the adrenal cortex [zona reticularus] with age-related secretion patterns; it declines 2% per year. DHEA transformed in peripheral target tissues into active sex steroids, responsible for most body functions, involving the endocrine system. Besides, to serve as an indirect precursor to other steroid hormones [estrogen and testosterone], DHEA is used as an anticancer, anti-allergic treatment, and treatments for obesity and cardiovascular problems. DHEA is also known as an anti-aging hormone in dementia and osteoporosis [3]. New approaches focus on preserving the brain as it controls homeostasis's primary role in the body [4]. With age progression, all tissues noticeably observed to decline in physiological

functions and are increasingly susceptible to disease. Sex- steroids are associated with many human diseases, including hormone-dependent tumors. Women with premenopausal show fluctuating estradiol concentrations [E2] and progesterone [P4] levels in their blood circulation. After menopause, blood circulating hormones reduce, but they are still present in high peripheral tissue concentrations. There is a strong link between the amount of circulating hormone levels and female reproductive cancers, including breast cancer; the hormones bind to estrogen receptors [ERs] [ERα, ERα36, ERβ], or progesterone receptors [PRs] activating specific signaling pathways. Endocrine therapy uses after identifying ER or PR positive tumors [5]. The influence of sex hormones on many physiological functions is shown in Fig. **(1)**.

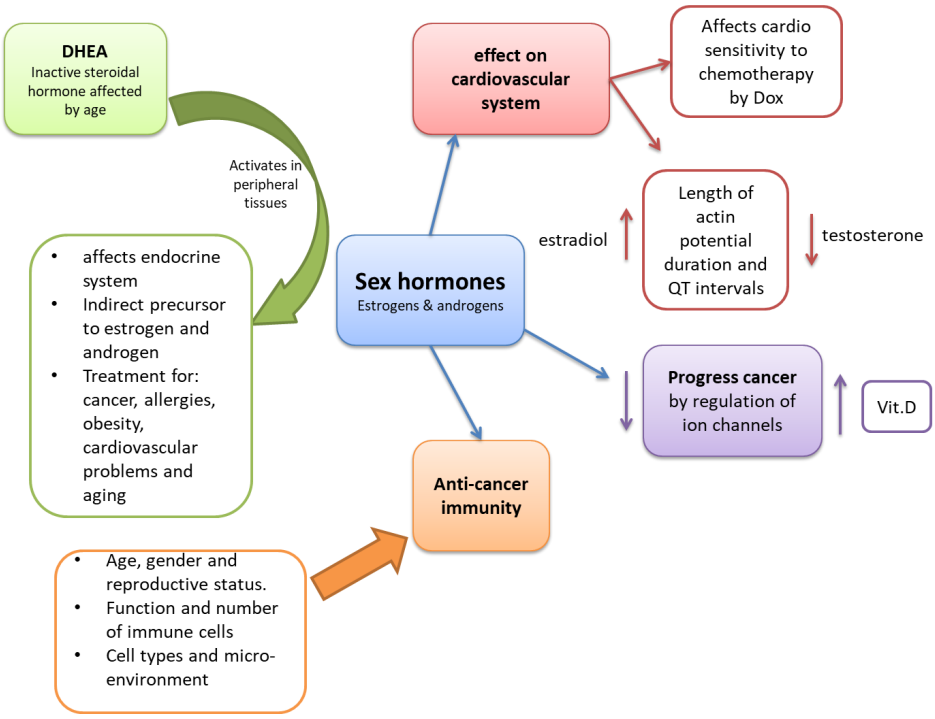

Fig. (1). Sex hormones influence many physiological functions: cancer progression, anticancer immunity, and cardiovascular system.

Estrogen is essential for the average growth and development of breast tissues, but high estrogen levels are major risk factors for breast cancer. One mechanism by which estrogen could contribute to breast cancer is through the induction of DNA damage. The estrogen alters the DNA damage response (DDR) and DNA repair by regulating essential effector proteins, including ATM, ATR, CHK1, BRCA1, and p53. There is a possibility that estrogen receptor signaling converges to

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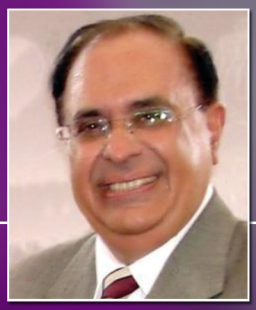

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