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Frontiers in Clinical Drug Research - Anti-Cancer Agents

(Volume 2)

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PREFACE

The present volume of *Frontiers in Clinical Drug Research - Anti-Cancer Agents* presents cutting edge reviews on developments in new and more powerful agents against cancer.

The advantages that dendrimers offer as drug carriers are associated with their unique structure that imparts inner space and multiple terminal groups for drug encapsulation and conjugation. Hossain Sk and Kojima discuss the use of dendrimers as drug delivery vehicles for anticancer drugs.

Cutaneous squamous cell carcinoma (SCC) is the second most common type of non-melanoma skin cancer after basal cell carcinoma, and its incidence is on the rise. In Chapter 2, Nakamura *et al*. highlighted the importance of cytotoxic chemotherapy, immunotherapy and targeted therapy for advanced cutaneous squamous cell carcinoma. This review describes the previously published clinical trials for assessing the potency and efficacy of various approaches used for treating advanced cutaneous SCC. It provides the current evidence-based approaches and highlights the areas for further research.

In Chapter 3, Jackson *et al*. discuss important developments in the field of pharmacodynamic biomarkers that have greatly enhanced the information obtainable from clinical trials and played a vital role in the development of pharmacokinetic/pharmacodynamic (PK-PD) models. The literature on the use of Bayesian systems in oncology (involving prior assumptions being made based on preclinical data and historical precedent) is reviewed. The applications of these models to develop strategies for new drugs, and to develop personalised medicine approaches in oncology are discussed.

In Chapter 4, Ciocca *et al*. discussed the molecular approaches for targeting the Heat Shock proteins for cancer treatment. They discuss HSP90, HSP27, HSP70, and HSP60 as targets for anticancer therapy.

A promising strategy to block inhibitors of apoptosis (IAP) proteins IAPs is with small-molecule IAP antagonists. A number of small molecule inhibitors have been developed that have the potential to bring exciting new treatment options to overcome apoptotic resistance for anticancer treatment. In chapter 5, Arnst and Li have presented the recent advances and clinical challenges of targeting the inhibitor of proteins with some of the recently developed small molecule IAP antagonists. They have highlighted the biological mechanisms of IAPs and provided an update to the clinical challenges, recent advances and potential opportunities for small-molecule IAP inhibitors.

Many substances present in fruits, vegetables and herbal essential oils have been shown to have important antiproliferative activity, inducing cell and genomic changes favorable for cancer prevention and therapy. In Chapter 6, da Silva and Salvadori highlight the importance of natural products as anti-neoplastic medicines. They stress that products that have natural origin are found to be more compatible with the human body and associated with fewer side effects.

In the final chapter contributed by Doug Dix, the chemotherapy and chemotherapeutic paradigms are discussed in the light of modern challenges. The chapter describes the ways for overcoming tumor defenses, preventing treatment resistance, as well as how to preserve and enhance the host anti-cancer responses and lessen the severe side effects.

I hope that the current volume of this popular Series will provide fresh insights into development of recent approaches to anti-cancer therapy for interested researchers and pharmaceutical scientists. I would like to thank the editorial staff, particularly Mr. Mahmood Alam (Director Publication) and Mr. Shehzad Naqvi (Senior Manager Publication) for their hard work and determined efforts.

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CHAPTER 1

Dendrimers for Drug Delivery of Anticancer Drugs

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Abstract: Cancer cells have the potential to proliferate at an abnormal rate and spread to the whole body. To combat cancer, many therapeutic strategies using small drug molecules have been explored, but their therapeutic effects are generally low and they often have harmful side effects. Therefore, to achieve maximum drug activity with minimal side effects, many attempts have been made to delivery anticancer drugs using macromolecular formulations. Recently, dendrimers have been used as drug delivery vehicles for anticancer drugs. A dendrimer is a synthetic macromolecule with a unique structure. Dendrimers have inner space and multiple terminal groups for drug encapsulation and drug conjugation. In addition, imaging probes and targeting ligands can be attached to the dendrimer to prepare a multifunctional nanocarrier. Thus, dendrimers are potent platforms for cancer therapy. In this article, we focused on the application of dendrimers for delivery of anticancer therapeutics. Also, we have discussed the mode of attachment between drug and dendrimer and their anti-cancer activity *in vivo* and *in vitro* on the basis of recent research.

Keywords: Anticancer drug, Conjugation, Dendrimer, Encapsulation, Imaging, Ligand, Linker, pH-sensitive, Polyethylene glycol, Targeting.

INTRODUCTION

The word ‘dendrimer’ is derived from the Greek word ‘dendra’, meaning tree. A dendrimer is a hyper-branched, well-defined, and chemically versatile tree-like molecule. Dendrimers comprise a structure composed of branched monomers (the building blocks) that originate from a central core and radiate outwards, which is

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reminiscent of a tree. Varying the chemical constituents of the core, the building blocks, and the peripheral groups leads to dendrimer variety. Additionally, dendrimer variations derive from the number of repeated branched cycles (defined as the generation (G)). The higher-generation dendrimers are larger and more branched, and have more end groups at their periphery than those of lower generation (Fig. **1**). An exponential increment of the branches and surface groups accompanies each increasing generation. The diameter of dendrimers, which is of the order of nanometers, can be controlled. The relationship between the generation number and the size and number of surface groups in a typical polyamidoamine (PAMAM) dendrimer is shown in Table **1** [1, 2].

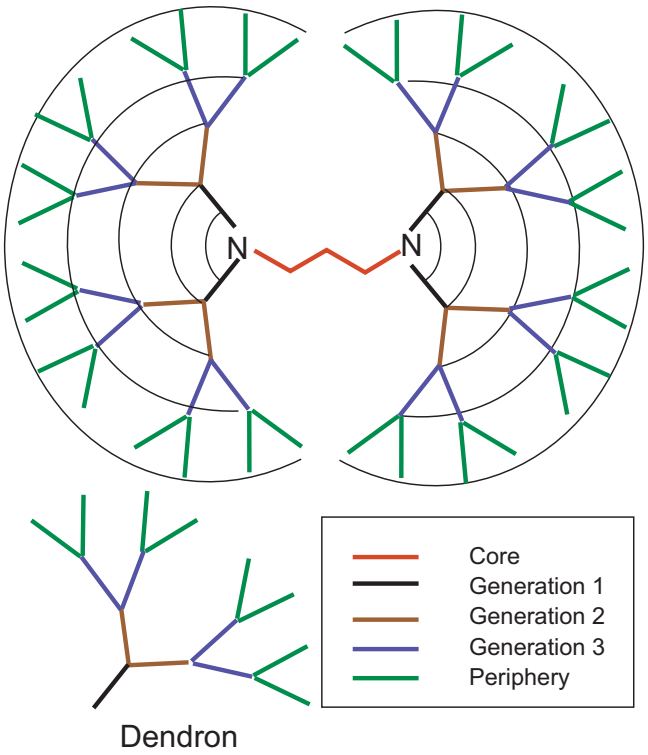

Fig. (1). General structure of dendrimer with 1,3-propanediamine core.

Dendrimer modification at the peripheral functional groups for conjugation and/or complex formation is feasible. Often amino, hydroxyl, and carboxyl groups at the periphery can be used for conjugation. Moreover, owing to the globular structure

of dendrimers, their interior space is of benefit for encapsulation. Several synthetic app-roaches have been used to prepare a large variety of dendrimers with adaptable chemical compositions, which have a range of applications in chemistry, medicine, diagnostics, and biology [1 - 3]. Dendrimers based on PAMAM [1], poly(propylene imine) (PPI) [4], poly(L-lysine) [5], poly(aryl ethers) [6], polyesters [7], carbohydrates [8], and DNA [9] have been studied for biomedical applications (Fig. **2**). Among them, PAMAM dendrimers are frequently used *in vivo* and *in vitro* because they are available commercially and have a wide variety of generations and peripheral functionalities.

Table 1. **Relationship between size, molecular weight, surface group, and generation in PAMAM dendrimers with an ethylenediamine core [2].**

Generation	Surface Group	Molecular Weight (Da)	Diameter (nm)
G0	4	517	1.4
G1	8	1,430	1.9
G2	16	3,256	2.6
G3	32	6,909	3.6
G4	64	14,215	4.4
G5	128	28,826	5.7
G6	256	58,048	7.2
G7	512	116,493	8.8

Nanotechnologies for cancer therapy and cancer diagnosis have been explored extensively in recent decades. Multifunctional polymeric nanoparticles can be designed for cancer therapy and diagnosis. The major objectives in cancer chemotherapy are to control the drug release rate, increase the solubility and stability of the drug, and increase the half-life of the formulated drug. Moreover, to access the target organ, there must be control of cellular entry and intracellular localization with minimal side effects [10, 11]. Dendrimers have potential as unimolecular nanoparticles with low polydispersity that can be used in nano-theragnostic applications in various diseases, including cancer, owing to their unique structural dimensions and the reproducibility of their synthesis. Anticancer therapeutic agents incorporated into dendritic carriers have shown improved activity against cancer cells [2, 3]. Recently, the use of dendrimers in drugs with

CHAPTER 2

An Overview of Cytotoxic Chemotherapy, Immunotherapy, and Targeted Therapy for Advanced Cutaneous Squamous Cell Carcinoma

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Abstract: Cutaneous squamous cell carcinoma (SCC) is the second most common type of non-melanoma skin cancer after basal cell carcinoma, and its incidence is continuously increasing. Although most cutaneous SCCs are localized early-stage tumors, regional lymph node and distant metastases can occasionally develop. The standard treatment of early disease is surgical excision, and shows good prognosis. In contrast, the treatment of advanced disease, such as unresectable or metastatic disease, is difficult, and there are currently no established standard treatment options, despite it being a potentially life-threatening condition. In the past, the clinical outcomes of various regimens have been investigated, including bleomycin, peplomycin, platinum agents, anthracycline agents, fluoropyrimidines, 13-cis-retinoic acid, and interferon-2a. Several clinical trials have shown favorable responses to these agents; however, these were all limited by a lack of randomization, a small number of enrolled patients, and/or heterogeneous patient populations, resulting in a lack of defined treatment strategies for this disease.

Recent studies have elucidated that the epidermal growth factor receptor (EGFR) is highly expressed in many epithelial tumors, including non-cutaneous SCC of the head and neck and cutaneous SCC, and several agents that target human EGFR, such as gefitinib, cetuximab, and erlotinib, have shown preliminary evidence of activity in phase II clinical trials and case series reports.

This review looks mainly at the previously published clinical trials in an attempt to assess the effectiveness of the various modalities used in the treatment of advanced cutaneous SCC, and aims to provide an overview of the current evidence base and to highlight the areas in need of further research. Only appropriate clinical trials that are

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well randomized and include adequate patient numbers with well-defined endpoints may prove the clinical efficacy of these promising treatment options.

Keywords: Chemotherapy, Cutaneous squamous cell carcinoma, Cytotoxic agents, Human epidermal growth factor receptor, Immunotherapy, Interferon-α, Retinoids, Targeted therapy.

INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) is one of the most common types of skin malignant tumors, and occurs mainly in elderly individuals. The incidence of cutaneous SCC has increased 1.5-fold over the past 15 years [1]. Most cutaneous SCCs develop on sun-exposed areas of the skin, particularly in the head and neck region. The standard first-line treatment of cutaneous SCC is complete surgical excision. Most cutaneous SCCs are diagnosed at an early stage, and the overall cure rate of the initial treatment is approximately 95%. In contrast, 4-10% of patients develop local recurrence or regional lymph node or distant metastases, and these cases account for approximately 20% of all skin cancer-related deaths [2 - 4]. In addition, surgery for advanced SCC on the head and neck is challenging, as cosmetic and functional reconstruction after tumor excision is often difficult.

Some of the prognostic factors for recurrence and risk of metastasis are included in the American Joint Committee on Cancer (AJCC) 2010 staging classification [5], namely tumor diameter >2 cm; tumor depth >2 mm; Clark's level ≥IV; location on the ear, lip, and sun-protected sites; presence of perineural invasion; poor degree of differentiation; and presence of lymph node metastasis. Several other risk factors for poor prognosis not included in the AJCC classification include desmoplastic growth [4], chronic dermatosis such as epidermolysis bullosa [6], and immunosuppression such as in human immunodeficiency virus-positive [7] and post-organ transplantation patients [8, 9]. These high-risk cutaneous SCCs have been reported to have a 2-year recurrence or metastasis rate of 20-25% after diagnosis [5, 10].

SYSTEMIC THERAPY FOR ADVANCED CUTANEOUS SCC

Advanced cutaneous SCCs generally include locally advanced unresectable

tumors that are deeply invasive and involve the adjacent structures, with unresectable regional lymph node and/or distant metastases. Such advanced disease is usually treated with systemic therapy. However, studies on systemic therapy for this disease are very limited, and there is currently no standard chemotherapy regimen for advanced cutaneous SCC. Currently, the recommendations for systemic therapy are based on the results of one adjuvant phase III trial, several single-arm phase II prospective studies, and a number of retrospective studies/case series and case reports (Tables **1 - 3**). A number of systemic therapies have been reported for the treatment of advanced cutaneous SCC, including cytotoxic chemotherapy (cisplatin, carboplatin, 5-fluorouracil [5-U], bleomycin, peplomycin, doxorubicin, and S-1), 13-cis-retinoic acid (13cRA), immunotherapy (interferon α2a [IFN-B1;]), and molecular targeted agents (gefitinib, cetuximab, and erlotinib). Some of these previous studies have reported favorable responses in patients with advanced cutaneous SCC, and these agents can be used either as monotherapy or combination therapy.

Table 1. Clinical trial and retrospective study of bleomycin and peplomycin for advanced cutaneous squamous cell carcinoma.

Year	Author(s)	n	Study Design	Population	Treatment	Response Rate	Survival
1976	Medical Research Council Working Party on Bleomycin	70	Phase III prospective randomized study	Advanced SCC	BLM *vs.* physicians choice of chemotherapies	39% (BLM) 39% (another chemotherapies)	Median survival 200 days in both groups
1986	Ikeda, *et al.*	86	Prospective observational study	Advanced locoregional or metastatic SCC	PEP	62% (CR 23%, PR 38%)	-

SCC, squamous cell carcinoma; BLM, bleomycin; PEP, peplomycin; CR, complete response; PR, partial response

CYTOTOXIC AGENTS

Bleomycin and Peplomycin

The initial study of systemic therapy for advanced cutaneous SCC was a non-rigorous randomized trial reported in 1976, which compared bleomycin with other

CHAPTER 3

Bayesian Systems for Optimizing Treatment Protocols in Oncology

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Abstract: The development of new pharmacodynamic biomarkers has greatly increased the information content of clinical trials, and made possible the construction of pharmacokinetic/pharmacodynamic (PK-PD) models. A population PK-PD model, in conjunction with a disease model, can then be used to simulate clinical trials *in silico*. In the case of oncology, the disease model must describe the cancer cell cycle, and such aspects of tumour biology as growth, invasion, metastasis, angiogenesis, and interactions of tumour cells with the immune response. Such models of tumour growth and its response to drug treatment can be used in conjunction with databases of drug PK and PD parameters and with databases of biomarkers, to ask the question: for a tumour with a given biomarker expression profile, what treatment protocol is likely to be most effective? Various treatment options can then be modelled, and the one predicted to be most active selected for clinical evaluation. Since, in practice, many of the tumour growth parameters are still unknown, a Bayesian approach is required: prior assumptions are made, based upon preclinical data and historical precedent. The course of treatment, based upon these prior assumptions, is predicted, compared with the clinical outcome, and the difference fed back to drive model adjustments. The assumptions of the model are thus progressively refined - the system learns from experience. A Bayesian model can be used to devise optimal control strategies for chronic disease. A frequent cause of cancer treatment failure is the rapid development of acquired drug resistance. *In silico* clinical trials that incorporate the techniques of evolutionary dynamics can be used to predict the incidence of drug resistance, including multi-drug resistance, so that emergence of resistant clones can be minimized and delayed. In due course, the actual clinical outcome can then be compared with the predictions. We review the literature on the use of Bayesian systems in oncology, and discuss their application to development strategies for new drugs, and to developing

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personalised medicine approaches in oncology.

Keywords: Bayesian networks, Cyclotherapy, Evolutionary dynamics, Expert systems for chemotherapy, Immune system modelling, *In silico* clinical trials, Optimal control, Pharmacokinetic-pharmacodynamic modelling, Systems pharmacology, Virtual interactive patient, Virtual tumour.

INTRODUCTION: THE TUMOUR-HOST RELATIONSHIP AS A COMPLEX INTERACTIVE SYSTEM

Since the pioneering work of Paul Ehrlich, and his concept of the "magic bullet" [1], the focus of chemotherapy has been a search for selective toxicity. This proved much harder to realise for cancer chemotherapy than for antimicrobial chemotherapy, where the exploitable biochemical differences between the pathogen and the host are much greater than the differences between a tumour and the normal tissues of its host. The first effective anticancer drugs were cytotoxic agents, which, in general act on processes such as DNA synthesis, DNA precursor generation, or mitosis that are common to all replicating cells, whether normal or transformed, so that the margin of selectivity is narrow. Growing understanding of the molecular biology of cancer suggested more selective sites of intervention, so that the current generation of "targeted agents" acts on tumour growth factor receptors, their associated signalling pathways, or cell cycle checkpoints that carry mutations or changes in expression levels not found in normal cells. However, the particular changes targeted by these drugs will usually only be found in a small proportion of tumours of a particular type. As a result, targeted agents achieve much greater selectivity, but do so at the cost of a narrower anti-tumour spectrum.

Cancer is a disease of complexity. Over 300 oncogenes and tumour suppressor genes are known: genes that when mutated, amplified, or partially deleted are associated with malignant transformation. Up to six of these oncogenic mutations may be necessary for full expression of the malignant phenotype. Hanahan and Weinberg [2] described six "hallmarks of cancer": ability to proliferate in the absence of an external growth stimulus; loss of response to negative growth regulation; loss of response to physiological death signals; biochemical changes that make cells potentially immortal, such as expression of telomerase; loss of

dependence on contact signals required for survival of normal cells (resulting in invasiveness and metastasis); and ability to survive and proliferate in conditions of hypoxia [2, 3]. This is an accurate description of the natural history of cancer, but tells us nothing of the dynamics of malignant transformation. The phenotype of an advanced tumour has these features in common, whether it is a lung cancer cell, a brain tumour, or a melanoma cell, but this final state is reached by a number of steps, and the different tumours may have arrived at this full expression of malignancy by different routes. We thus cannot speak of "*the* malignant phenotype".

An alternative view regards malignancy as a *process*, *i.e.* a succession of events in time. This process appears to be driven, or at least triggered, by genetic instability. Duesberg pointed out that all malignant tumours are aneuploid to some degree [4, 5]. Benign tumours, which are abnormal growths that are not invasive or metastatic, are by contrast usually diploid. Normal dividing cells are never aneuploid (though normal differentiated cells, such as brain cells, may be). The aneuploidy of cancer cells is a progressive state, so that with time the karyotype becomes increasingly abnormal and increasingly heterogeneous. Chromosomal instability results in gene duplication, gene deletion, and abnormal gene expression, so that the successive appearance of the various hallmarks of cancer is probably driven by the underlying chromosomal instability. What causes the chromosomal instability in the first place? Random errors can occur in the complex process of chromosomal replication and segregation, but random chromosomal rearrangements are usually lethal. Cells with chromosomal rearrangements that are not lethal normally continue to replicate faithfully, as seen for example in chronic myeloid leukaemia (CML), where the t(9;22) translocation results in a karyotype that, during the chronic phase of the disease, is faithfully replicated [6]. The chromosomal instability of carcinomas appears to be driven by mutations in components of the mitotic spindle assembly checkpoint (SAC). For example, overexpression of the enzyme aurora kinase A causes override of the SAC [7, 8]. This means that cells in metaphase proceed to anaphase before their replicated chromosomes are correctly sorted into two identical sets, resulting either in polyploid cells, or aneuploid cells. A mutation in the SAC cannot, in itself, result in malignant transformation, because aneuploid cells have a higher

CHAPTER 4

Molecular Approaches to Target Heat Shock Proteins for Cancer Treatment

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Abstract: HSP90 was the first molecular target to inhibit the interaction of this heat shock protein (HSP) with client proteins in cancer cells and tissues. The HSP90 inhibition was attempted to liberate from this chaperone the oncogenic fusion proteins, mutated and activated serine/threonine protein kinases, tyrosine kinases, as well as transcription factors with oncogenic activity, in this manner, the free proteins could be recognized by the proteasome system to be degraded. We should remember here that many HSP family members are overexpressed in different kinds of cancer tissues, these molecules act as chaperones of tumorigenesis. In cancer patients, the first generation of HSP90 inhibitors showed elevated levels of toxicity, which was partially solved with the second-generation of inhibitors that could be intravenously delivered. With the arrival of the third-generation drugs that could be orally administrated, anticancer activities were achieved in clinical trials, however, the results were not as successful as expected due to: 1) limited anti-tumor efficacy; 2) acquisition of drug resistance; 3) difficulty to identify the client protein(s) specifically degraded in response to drug administration. The main problem is the redundancy of chaperones that the cancer cells

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have, in fact during HSP90 or HSP70 inhibition the heat shock factor (HSF1) could be liberated increasing the levels of other HSPs and in addition, HSF1 can by itself act as an inducer of the multidrug resistance MDR response and is also implicated in HER2 and hormonal responses. These difficulties, rather than decreasing the interest of having the HSPs as molecular targets, are increasing the exploration of new ways to interfere with several HSPs simultaneously and using HSP inhibitors with more "conventional" anticancer drugs. In this article we review, in addition to HSP90, HSP27, HSP70, and HSP60 as targets for anticancer therapy.

Keywords: Cancer, Drug resistance, Heat shock proteins, HSP27, HSP60, HSP70, HSP90, Molecular targets, New anticancer drugs, Therapy.

INTRODUCTION

Ferruccio Ritossa (1962, Italy) discovered the heat shock proteins (HSPs) genes when fruit fly *Drosophila melanogaster* cells were exposed to heat, the polytene chromosomes revealed heat shocked-DNA puffs (sites of increased transcription) given rise to what latter were named as HSPs (Alfred Tissières, Switzerland). These proteins can be induced not only by heat but also by different physiological and pathological conditions; they are present in all living cells and microorganisms and belong to a subset of molecular chaperones that are rapid and abundantly induced by many stresses. Although there are guidelines for the use of a new nomenclature of the human HSP families [1], the old names based on their molecular weight are still amply used Table **1**. The HSPs participate in protein homeostasis stabilizing and assisting in the correct folding of nascent polypeptides; they contribute in proteome maintenance (assembly of macromolecular-complexes, transport and degradation, and refolding or disaggregation of stress-denatured proteins). Therefore the HSPs are involved in the protein quality control (PQC) system [2]. On the other hand, the HSPs are involved in degradation pathways: ubiquitin-proteasome system, endoplasmic reticulum-associated degradation (ERAD), autophagy, and in the regulation of apoptosis [2, 3]. In addition, the 96 HSP family members display a considerable degree of functional diversity depending on the protein localization and on the diverse molecules with which they interact (these proteins are in general named "client" proteins) [4].

Table 1. Examples of the nomenclature of the main HSPs.

New Name	Old Names
HSPA	**HSP70**
HSPA1A (inducible HSP70)	HSP70-1; HSP72; HSPA1
HSPA2	HSP70-2
HSPA5	BIP;GRP78; MIF2
HSPA6	HSP70-6, HSP70B
HSPA7	HSP70-7
HSPA8	HSC70;HSC71; HSP71; HSP73
HSPB	**Small HSPs**
HSPB1	HSP27;HSP25; CMT2F
HSPB4	Crystalline alpha A; CRYAA
HSPB4	Crystalline alpha B; CRYAB
HSPC	**HSP90**
HSPC1	HSP90; HSP89; HSP90AA1
HSPC2	HSP90-ALPHA; HSP90AA2
HSPC3	HSP90-BETA; HSP90B
HSPC4	GRP94; GP96; TRA1
HSPD1	**HSP60; GroEL**
HSPE1	**HSP10; chaperonin 10; GroES**
HSPH	**HSP110**
HSPH1	HSP105
HSPH2	HSP110; HSPA4; APG-2
DNAJ	**HSP40**
DNAJA1	DJ-2; DjA1; HSDJ

The HSP family members can be induced constitutively (by genes that are transcribed continually compared to facultative genes which are only transcribed as needed), not induced by stress. Another form is constitutively and induced upon stress; and those that are induced only upon stress [5]. Upon stress, HSF1 is the key transcriptional activator of a) chaperones, b) cochaperones (*e.g.*, those forming part of the family of HSP40/DNAJ proteins that have in common a conserved J domain by which they interact with HSP70, stimulating its ATPase activity) and c) ubiquitin (a system of proteins and enzymes that adding different

CHAPTER 5

Targeting the Inhibitor of Apoptosis Proteins with Small Molecules: Recent Advances and Clinical Challenges

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Abstract: Apoptosis is a tightly regulated cellular mechanism that is frequently dysregulated in many human malignancies. Inhibitor of apoptosis (IAP) proteins are preferentially expressed in many cancers and are attractive therapeutic targets. One of the most promising strategies to block IAPs is with small-molecule IAP antagonists. In the past decade, intense research efforts have been dedicated to the development of this novel class of drugs. While currently there are no FDA approved IAP inhibitors, a number of small-molecule inhibitors have moved into clinical trials either as single agents or in combination with existing anticancer drugs. Both monovalent and bivalent IAP inhibitors have been reported. These small-molecule inhibitors have the potential to bring exciting new treatment options to overcome apoptotic resistance for anticancer therapy. However, due to the dynamic nature of IAPs and their involvement in cell signaling, there are still challenges that need to be addressed to optimize their efficacy and incorporate them into eventual clinical regimens. This chapter reviews the biological mechanisms of IAPs as well as provides an update of the recent advances, clinical challenges and potential opportunities for small-molecule IAP inhibitors, particularly SMAC mimetics and survivin antagonists, in anticancer therapeutics.

Keywords: Apoptosis, Cancer therapy, cIAP, IAP antagonists, Inhibitor of apoptosis (IAP) proteins, SMAC, SMAC mimetics, Small-molecule inhibitors, Survivin, XIAP.

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INTRODUCTION

Apoptosis is a critical component of cell regulation, homeostasis, and programmed cell death. While cell death can proceed through several pathways such as autophagy or necroptosis, apoptosis is perhaps the best-understood and primary pathway through which programmed cell death is carried out. Dysregulation of apoptosis is observed in many human diseases and is one of the hallmarks of cancers [1, 2]. In principle, evasion of programmed cell death is the result of failure to propagate apoptosis and caspase activation pathways [3]. Inhibitor of apoptosis (IAP) proteins are up-regulated in many types of cancer and contribute to tumor progression, treatment resistance, and poor prognosis. They suppress apoptosis induced by an array of stimuli, including death receptor activation, growth factor withdrawal, ionizing radiation, viral infection, endoplasmic reticulum stress, and genotoxic damage [4, 5]. IAPs also promote cell survival through regulation of signaling pathways. While many traditional treatment approaches such as radiation and chemotherapy seek to treat cancer by inducing apoptosis, cancer cells often develop resistance to these treatment strategies, particularly when IAPs are up-regulated. Targeting these apoptotic regulators and suppressing their inhibitory function to promote cell death is an attractive anticancer strategy [2, 6 - 8]. Substantial progress has been made in the development small molecules that are capable of penetrating the cell membrane and potent enough to restore apoptotic function *via* IAP suppression. IAP inhibitors may induce cell death and tumor regression as single agents by direct IAP interaction or synergize with additional cytotoxic agents to sensitize cancer cells to apoptosis and overcome drug resistance. Increased knowledge and greater insight of the biological mechanisms and structure of IAPs have laid the groundwork for the targeting strategy of small-molecule IAP inhibitors and have greatly contributed toward their translation and incorporation into clinical practice.

INHIBITOR OF APOPTOSIS PROTEINS

Structure of IAP Proteins

IAP proteins are a family of endogenous anti-apoptotic proteins that hinder

apoptosis by interfering with caspase activation. In addition to their roles in apoptosis, they can also influence non-apoptotic processes such as cell differentiation, invasion, migration, and metastasis [9 - 11]. The first IAP family member was identified during a genetic screening of SF21 baculoviruses, where a 1.6kB gene encoding a 31kDa anti-apoptotic protein with a zinc finger-like motif was discovered [12]. To date, there are eight mammalian baculoviral IAP repeat-containing (BIRC) protein family members: neuronal IAP (NIAP, BIRC1), cellular IAP1 (cIAP1, BIRC2), cellular IAP2 (cIAP2, BIRC3), X chromosome-linked IAP (XIAP, BIRC4), survivin (BIRC5), apollon (BRUCE, BIRC6), melanoma IAP (ML-IAP, livin, BIRC7), and IAP-like protein 2 (ILP-2, BIRC8) [13] (Fig. **1**). Among these, XIAP, cIAP1, cIAP2, and ML-IAP are known to participate in the inhibition of apoptosis through caspase inhibition and cell signaling [14, 15].

Proteins in this family are characterized by at least one (but up to three) baculoviral IAP repeat (BIR) domains in the N-terminal portion of the protein. The BIR domains are highly conserved, comprised of ~80 amino acids, and contain histidine and cysteine residues that coordinate a zinc ion. In the C-terminus, they may also contain a Really Interesting New Gene (RING) domain with E3 ligase activity, a caspase activation recruitment domain (CARD), a ubiquitin-conjugating (UBC) domain, or a ubiquitin-associated (UBA) domain [14] (Fig. **1**). Only X-linked IAP has been shown to potently inhibit apoptosis through caspase interaction and suppression. The BIR domains are largely responsible for binding to caspases, whereas RING domain-containing IAPs can regulate apoptosis through their E3 ligase activity [16, 17]. Dimerization of the RING domain potentiates their E3 ubiquitin ligase activity, which induces IAP-mediated ubiquitylation by recruiting E2 ubiquitin-conjugating enzymes and facilitating the transfer of ubiquitin to target proteins and binding partners [18, 19]. The function of the CARD domain in cIAP1 and cIAP2 is largely unknown, though it has been indicated to play a regulatory role in auto-inhibition of E3 ligase activation by preventing RING dimerization [20]. The UBA domain enables IAP proteins to bind to mono-ubiquitin as well as Lys 63- and Lys 48-linked poly-ubiquitin chains and is implicated in cell survival and oncogenesis [21]. Survivin is the smallest member of the IAP family, containing a single BIR

CHAPTER 6

Some Natural Products May Represent a Future Alternative to Anti-Neoplastic Medicine

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Abstract: Currently, the main treatments available for cancer include surgery, biological therapy, radiation and chemotherapy. However, these treatments have strong secondary effects on patients, which can prohibit their use. Therefore, the search for alternative treatments is a current challenge for scientists. Several studies have identified compounds from plants that exhibit biological properties compatible with the desired activity of anti-neoplastic drugs. Natural products are thought to be more compatible with the human body and cause fewer side effects. Furthermore, substances present in fruits, vegetables and herbal essential oils have demonstrated important anti-proliferative activity, inducing cell and genomic changes favorable for cancer prevention and therapy. Taking into account that the molecular mechanisms by which natural compounds function to prevent cancer are not fully understood and that molecular targets can be important tools for evaluating their effectiveness, this chapter aims to present and discuss potential active compounds as possible anti-cancer agents.

Keywords: Apoptosis, Cancer, Cell cycle, Natural products.

INTRODUCTION

Cancer is the second most common cause of death worldwide, causing 8.2 million deaths in 2012 according to the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO) [1]. Different types of treatment for cancer are available, including surgery, biological therapy, immunotherapy, gene therapy, photodynamic therapy, radiation therapy and

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chemotherapy, and the selection of therapy depends on the tumor type, tumor staging and approaches for organ preservation [2].

Tumors are made up of billions of cells; these cells originate from a progenitor cell that has eluded apoptosis, accumulated genetic alterations and multiplied clonally. External factors include lifestyle, such as excessive alcohol consumption, an unhealthy diet, exposure to excessive sunlight and chemical carcinogens, lack of exercise and smoking, while internal factors include gene mutations, changes in the hormonal and immune systems, and metabolic abnormalities [3].

Carcinogenesis is a multistep process that involves initiation, promotion and progression. Initiation is characterized by the formation of a preneoplastic cell resulting from an irreversible genotoxic event [3]. This mutation usually occurs in genes that control cell cycle, cell differentiation, apoptosis and DNA repair, leading to the survival of cells with genetic alterations. The promotion stage involves the selective clonal expansion of the initiated cell through an increase in cell growth or decreased apoptosis. The third step, progression, involves genetic events such as changes in ploidy and chromosome integrity and results in a change from the preneoplastic state to the neoplastic state, producing cells with a high degree of anaplasia, an imbalance between cell proliferation and apoptosis and self-sufficiency [3, 4].

Chemotherapy is currently used to treat several types of tumors [5, 6]. However, despite improvements in chemotherapeutic protocols, patient outcomes have only improved slightly in recent decades [7, 8], mainly because of the high systemic toxicity, lack of selectivity and tumor resistance after prolonged treatment [9]. Therefore, to improve the quality of life of cancer patients, interest in alternative treatments has increased. Some authors have shown that in addition to helping prevent cancer, diet-associated factors and nutritional interventions may also confer therapeutic effects [10 - 12]. Based on these hypotheses and considering the profusion of biological properties, many compounds derived from fruits, vegetables and other plants have been investigated regarding their potential to be used as anti-tumor agents [13 - 15]. For example, Arora *et al.* [15] reported that compounds derived from medicinal plants present advantages, such as better

compatibility with the human organism and lower costs. Furthermore, other authors have shown that these compounds possess anti-proliferative activities and an ability to preferentially destroy malignant cells with low levels of toxicity to non-neoplastic cells [7, 13]. These anti-tumor drugs, which interfere with the cell cycle, generally act by three different mechanisms: blocking DNA synthesis, causing DNA damage and disrupting mitotic processes. One example of a drug that blocks the syntheses of DNA is mimosine (Leucenol®), an alkaloid–β--hydroxy-4 pyridone amino acid–from the leguminous tree *Leucaena leucocephala*. Etoposide (VePesid®) and teniposide (VM-26), which are derived from *Podophyllum peltatum,* are drugs that can damage DNA and/or RNA. Examples of substances that can disrupt the formation of spindles are the vinca alkaloids vinblastine (Velban®) and vincristine (Oncovin®) and paclitaxel, which is extracted from *Taxus baccata* (Taxol®) [16].

The use of natural products for treating diseases represents the oldest and most widespread form of medication [17]. Indeed, many reports have shown that compounds derived from plants have chemopreventive and/or therapeutic effects on various cancers, including the induction or suppression of specific cellular inflammatory activities, alteration of molecular signaling pathways [18], induction of apoptosis and anti-proliferative activity [7, 13]. Cruciferous vegetables have demonstrated activities against lung, breast, prostate, pancreas and bladder cancer cells, most likely due to their high concentrations of isothiocyanates (ITCs) [19]. However, limited knowledge regarding the effectiveness of these natural derivatives, combined with a lack of understanding of the molecular mechanisms and lack of scientific evidence to prove their beneficial effects, have detained the incorporation of these products into medical care [20, 21]. Nevertheless, what is known is that these compounds are pleiotropic, *i.e.*, have the advantage of acting on multiple targets, and thus are promising therapeutic agents [21]. The use of complementary and alternative medicine for children for cancer treatment ranges between 6% and 91% worldwide [22].

The choice of complementary and alternative medicine varies from country to country. In the United Kingdom, the most commonly reported complementary and alternative medicines are aromatherapy, massage and multivitamins, whilst herbal remedies are more common in the United States [22]. One study reported that

CHAPTER 7

Chemical Control of Cancer: The Best Way Forward

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Abstract: Ehrlich invented chemotherapy in 1909 with a simple rationale: Chemicals could cure infection by hitting targets in microbes that didn't exist in hosts. Arsenicals, sulfa drugs, and antibiotics lent credibility to the notion. But now we know it's oversimplified. Immune and inflammatory responses are essential to curing infection, and continued treatment with any single chemical leads inevitably to resistance. Cancer is more challenging than infection. Host and cancer cells are similar, host responses to cancer are less vigorous than those to microbes, and drugs that inhibit cell division tend not only to suppress inflammation and immunity, but also to erode gastrointestinal mucosa causing nausea, vomiting, and malnutrition. Together these side-effects predispose to infection, and a desperate dilemma: Should the patient die of cancer or it's treatment? Despite long odds, chemicals remain the only hope for control of disseminated cancer. To realize this hope, however, we must enact a sea-change in our thinking. Rather than searching for new magic bullets, we must focus on overcoming tumor defenses, precluding resistance to treatment, preserving and enhancing host anti-cancer responses, minimizing toxic side effects, and inspiring patients and their physicians to engage in realistic dialogue about life and death. Combining effective drugs and drug combinations with nutritional manipulations, metabolic modifications, mind-body interventions, and philosophic contemplations holds the most promise for realizing this goal.

Keywords: Aging, Alternative and complementary medicine, Cachexia, Chemotherapy, Conventional medicine, Death, Diagnosis, Drug resistance, Essential amino acids, Etiology, Folate deficiency, Ketogenic, Life, Metabolic modification, Nutritional withdrawal, Oncologists, Pathology, Selective toxicity, Suffering, Terminal, Triage.

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INTRODUCTION

The history of chemotherapy stretches back more than a century to Ehrlich's invention of selective toxicity and his demonstration that Salvarsan could cure syphilis. Cancer chemotherapy reaches back almost as far to Gilman's application of Ehrlich's concept to cancer and his demonstration that nitrogen mustard could achieve partial remission against lymphoma [1]. This initial lucky success was quickly followed by reasoned success, *i.e.*, induction of partial remission in acute lymphoblastic leukemia (ALL) with folic acid antimetabolites. This lead to a rationale: Isosteric analogs of critical metabolites, *e.g.*, 6-mercaptopurine and 5-fluorouracil, would fool enzymes involved in cell division. A modified rationale defeated drug-resistant relapse: Combine individually-effective drugs with differing toxicities at full dose. In 1965, this rationale produced complete remission in ALL. Intrathecal injection of methotrexate converted these complete remissions to cures by destroying leukemic blasts in the protected site. Long-term toxicity in cured children and lack of success with solid tumors inspired research for new drugs and new protocols. Targeted therapies were heralded as "magic bullets" but they're vulnerable to resistance and don't penetrate solid tumor defenses. Chemistry, currently, doesn't control much cancer.

In 2014 almost 1,666,000 Americans will be diagnosed with cancer and almost 586,000 will die from it [2]. Unlike heart attack, that can kill quickly, cancer tends to kill slowly, and those who die of it tend to suffer. Part of the suffering is from symptoms such as pain, nausea, fatigue, and weakness. Another part is from helplessness and hopelessness. Once a patient is declared terminal, physicians quit fighting and leave the patient with no weapons or strategy. For patients who can embrace death, hospice offers comfort. But for those who want to continue the fight, there is, at present, nothing. This chapter is for them, and for those who want to help them. It offers weapons and strategies that are inexpensive and relatively safe. And it offers a perspective on how to change cancer medicine to make it more responsive to the people with cancer and more considerate of the people with other diseases.

Cancer has two kinds of victims: the individuals who contract it, and the society that funds the fight against it. And the two suffer from the same cause, *i.e.*, the

enormous profit that comes from fighting cancer. Patients suffer from abandonment once they become unprofitable. Society suffers from expert misappropriation of priority. Intellectual and financial resources are commandeered for cancer when they would yield better public health (although less profit) by being spent on other diseases.

The greatest barrier to the cancer care we want is the distinction between conventional and alternative or complementary medicine. Conventional medicine is dominated by objective thinking as epitomized by the double-blind, controlled clinical trial. Objective physicians stay out of the way so that their chemicals can express themselves. Alternative or complementary medicine is dominated by subjective thinking as epitomized by the anecdotal case study. Subjective therapists actively urge patients toward recovery. We need both forms of medicine. When Food and Drug Administration (FDA) – approved medicines lose efficacy, we want our therapists to use whatever is available to urge us toward recovery, at least until such time as we are ready to embrace death. This chapter provides weapons and strategies for urging "terminal" cancer patients toward recovery. Ideally, physicians will recommend these treatments to their patients. But few of the interventions require physician supervision. Patients can cook the remedies up in their own kitchens and self-medicate. But without physician-endorsement, the interventions lose much of their potential placebo effect.

In all of medicine, nothing is more powerful or mysterious than the placebo. When a physician assures a patient that a remedy will work, it tends to work. Physicians shun placebos because they typically require dishonesty. The remedies described below require no such dishonesty. Physicians can endorse them because they are consistent with textbook biochemistry, and are inexpensive and relatively safe. "Terminal" patients have little to lose by trying them. But the remedies described below are untested, and, therefore, unconventional or alternative or complementary. I advocate against distinguishing conventional from other forms of medicine as such distinction can diminish the placebo effect. To control cancer with chemicals, we'll need every advantage we can find.

All patients are not equally disposed to placebo therapy [3]. "Terminal" patients who want to continue to fight are likely to rank among those most able to benefit.

SUBJECT INDEX

PROF. DR. ATTA-UR-RAHMAN, *FRS*

Prof. Atta-ur-Rahman obtained his Ph.D. in organic chemistry from Cambridge University (1968). He has 974 publications in several fields of organic chemistry including 718 research publications, 37 international patents, 151 books and 68 chapters in books published largely by major U.S. and European presses. He is the Editor-in-Chief of several European Chemistry journals and the Editor of "Studies in Natural Product Chemistry" 43 volumes of which have been published by Elsevier Science Publishers (Netherlands) under his Editorship during the last two decades. Eighty students have completed their Ph.D. degrees under his supervision.

Prof. Rahman was elected Fellow of Royal Society (London) (2006) and won the UNESCO Science Prize (1999). He has been conferred honorary doctorate degrees by Cambridge University and many other universities. He was elected Honorary Life Fellow of Kings College, Cambridge University (2007).