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Atta-ur-Rahman, *FRS*

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Edited By

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PREFACE

The third volume of ***Frontiers in Clinical Drug Research - Anti-Cancer Agents*** presents seven cutting edge reviews on recent developments in various therapeutic approaches against different types of cancer.

Studies have revealed that the Epidermal Growth Factor Receptor (EGFR) is involved in the pathogenesis and progression of different types of carcinoma. Tumor resistance to agents targeting the Epidermal Growth Factor Receptor (EGFR) is common, and is well recognized as a major challenge. In first two consecutive chapters, Rodney B. Luwor provides an overview of the progress in targeting the EGFR that will lead to overall refractory outcomes to anti-EGFR therapies. In Chapter 1 he discusses on the resistance mechanisms driven by alterations in ligand and receptors of the EGFR family as well as on the cross-talk between EGFR receptors and non-EGFR family members. In Chapter 2 the same author describes the current understanding regarding the resistance mechanisms mediated by alterations in substrates downstream of the EGFR. Luwor has also reviewed the other intracellular mechanisms that mediate both sensitivity and resistance outcomes to anti-EGFR agents in this chapter.

Melanoma is the most dangerous form of skin cancer that develops when unrepaired DNA damage to skin cells triggers mutations, which lead to the formation malignant tumors. In Chapter 3 Shukla *et al.*, present a comprehensive review on the chemotherapeutic, immunologic, and molecularly targeted therapy approaches to the treatment of advanced melanoma.

In various tumor cells, there is increased aerobic glycolysis that represents a major biochemical alteration associated with malignant transformation. This phenomenon is known as the Warburg effect. 18F-deoxyglucose positron emission tomography (18FDG–PET), a metabolic imaging technique, is based on the avidity of cancer cells for glucose; currently, it represents the only successful exploitation of the Warburg effect for medical purposes. In Chapter 4, Abreu and Urbano focus on past and current efforts to target the Warburg effect for selective anti-cancer therapeutics.

Follicular lymphoma (FL) is a B-cell lymphoma and the most common slow-growing form of non-Hodgkin lymphoma (NHL). Studies suggest that immunotherapy, radioimmunotherapy and vaccines result in high response rates and survival in FL patients. Chapter 5 by Panizo *et al.*, briefly describes the biology and conventional treatment of follicular lymphoma with immunochemotherapy. They also discuss novel immunotherapy strategies (active and passive) for the treatment of follicular lymphoma.

The progression of cancer involves epigenetic abnormalities along with genetic alterations. The manipulation of epigenetic alterations holds great promise for the prevention, detection, and therapy of cancer. Evidence indicates that the activities of key epigenetic regulators including DNA methyltransferases and histone modification enzymes are sensitive to cellular metabolism. Wong and Yu in Chapter 6 discuss that the cross-talk between epigenetics and cancer cell metabolism may reveal novel therapeutic opportunities. They also highlight their implications in oncogenesis, and potential therapeutic approaches to target these cancer specific abnormities.

Apoptosis is a programmed cell death, which involves various biochemical events that lead to characteristic cell changes and death. Dysfunctions of apoptosis pathways promote oncogenesis as well as confer resistance of cancer cells to most conventional therapies. In Chapter 7 by Moorthy *et al.* focus their discussion small molecular anticancer drugs, especially target proteins, responsible for apoptosis.

I hope that the current volume of this book series will provide fresh insights into development of new 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 Publications) and Mr. Shehzad Naqvi (Senior Manager Publications) for their hard work and dedicated efforts.

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CHAPTER 1

Tumor Resistance Mechanisms to Inhibitors Targeting the Epidermal Growth Factor Receptor– Part I: Extracellular Molecules

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Abstract: Since its discovery several decades ago, the Epidermal Growth Factor Receptor (EGFR) has become one of the most extensively studies receptor tyrosine kinases. However, despite continued insight into the cancer promoting properties of the EGFR and its downstream signalling substrates, clinical use of agents targeting the EGFR continue to yield modest outcomes. Clinically, approved anti-EGFR therapeutics can successfully inhibit receptor activation. However major tumour regression is observed in only 10-30% of advanced unselected cancer patients, with most patients showing no therapeutic benefit. Furthermore, those who initially respond commonly relapse presenting with reoccurrence of tumours that are frequently resistant to the original therapy. In addition, the standard course of treatment of such agents is estimated to cost between "US $15,000-80,000/patient" for an improved overall survival of only 1-2 months. Therefore, it is both medically and financially critical to determine the true molecular mechanisms of tumour resistance, and how it can be overcome. In these 2 back-to-back chapters, we will provide an overview of the progress made in targeting the EGFR and discuss the challenges presented by the numerous molecular mechanisms currently identified, leading to overall refractory outcomes to anti-EGFR therapeutics. In this chapter (Part I) we will specifically focus on the resistance mechanisms driven by alterations in ligand and receptors of the EGFR family and cross-talk between EGFR receptors and non-EGFR family members.

Keywords: Afatinib, Cancer, Cetuximab, Epidermal Growth Factor Receptor,

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Atta-ur-Rahman (Ed.)

Erlotinib, Gefitinib, Lapatinib, Panitumumab, Resistance, Signaling, Therapeutics, Tumor.

1. INTRODUCTION

Since the discovery of the Epidermal Growth Factor (EGF) in 1962 by Stanley Cohen and colleagues [1] tremendous advances in our understanding of the sophisticated interactions between growth factors and their accompanying cell surface receptors have been made. One of the most intensely studied classes of receptors is the HER or ErbB family [2]. This family consists of four members, the Epidermal Growth Factor Receptor (EGFR) (also referred to as ErbB1 or HER1) [3], HER2 ($p185^{Neu}$ or ErbB2) [4], HER3 (ErbB3) [5] and HER4 (ErbB4) [6]. All 4 family members share a similar overall structure consisting of an extracellular domain with 2 cysteine-rich regions, a single membrane-spanning region and a cytoplasmic domain containing multiple tyrosine residues that are phosphorylated upon receptor activation [7, 8].

The *EGFR* gene is located on the short arm of chromosome 7 [9, 10], and encodes an 1186 amino acid long, 140 KDa polypeptide chain [3, 11], which contains approximately 30 – 40 KDa of N-linked oligosaccharides [12, 13]. A single 23 amino acid long hydrophobic sequence transverses the cell membrane. The extracellular N-terminal end (amino acids 1 - 621) can be divided into four domains (I-IV) [14, 15]. The intracellular C-terminal region (amino acids 645 - 1186) is responsible for tyrosine kinase activity and regulatory functions [16].

Currently eight ligands have been identified to bind the EGFR with varying affinity and potentially differential downstream function. They include EGF [1], transforming growth factor alpha (TGF() [17], amphiregulin (AR) [18], heparin-binding EGF-like growth factor (HB-EGF) [19], betacellulin [20], epiregulin [21], neuregulin-2-beta (NRG2β) [22] and the most recently discovered Epigen [23]. These peptide ligands are produced as trans-membrane precursors that are then processed by metalloproteases and released in their soluble form [24] (Fig. **1**).

Ligand induced ATP binding to the EGFR lysine-721 residue is a critical step in tyrosine kinase activation and auto-phosphorylation in the intracellular region of the receptor [11, 25 - 28]. In turn, this auto-phosphorylation results in a more open

conformation allowing access to several cellular substrates to the tyrosine kinase domain of the EGFR [25, 29] and subsequent triggering of downstream signaling cascades including the RAS-RAF-MAPK-Erk1/2 pathway, the PTEN regulated phosphatidylinositol 3-kinase (PI3-K)-Akt-mTOR pathway, Src-Signal transducer and activator of transcription (STAT) family members and the Phospholipase C gamma (PLCγ) signaling pathway [30]. These signaling networks and the evidence for alterations or hyper-activity of each of these downstream molecules in providing resistance mechanisms to anti-EGFR therapy will be covered thoroughly in Part II of our series of reviews.

Due to the EGFR's many associations at the cell membrane and the diverse network of signaling, its activation is intimately associated with many cellular activities in both development and in the adult organism including proliferation, survival, differentiation, adhesion, migration and invasion and tumor metastasis. The importance of the EGFR in development is provided from the analysis of genetically altered mice. EGFR knockout mice display impaired epithelial development resulting in either embryonic or perinatal lethality or in mice suffered from abnormalities in multiple organs including the brain, skin, lung and gastrointestinal tract, depending on the genetic background [31 - 34]. Among the functions attributed to the EGFR are the proliferation and development of specific epithelial regions in the embryo, including branch point morphogenesis, maturation of early embryonic lung tissue, skin development and promoting survival of early progenitor cells in the cleft palate [35, 36]. The EGFR is also expressed throughout the brain during development primarily in the early postnatal astrocytes and purkinje cells [37, 38]. The EGFR also plays an important role in the adult organism where it is essential for the differentiation of normal mammary glands and the induction of uterine and vaginal growth [39, 40]. It is also required in the adult neurones of the cerebral cortex where it acts to promote terminal differentiation [41].

In summary these data clearly show the essential role of the EGFR during normal development and homeostasis. Not surprisingly, genetic alterations leading to EGFR over-expression or gain-of-function mutation are frequently observed in cancer [42 - 44]. These findings led to the vigorous pursuit that continues today to develop agents targeting the EGFR (and downstream substrates) in the hope that

CHAPTER 2

Tumor Resistance Mechanisms to Inhibitors Targeting the Epidermal Growth Factor Receptor – Part II: Intracellular Molecules

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Department of Surgery, The Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria 3050, Australia

Abstract: Tumor resistance to agents targeting the Epidermal Growth Factor Receptor (EGFR) is common, and well recognised as a major challenge to successful clinical outcome, because patients often present with tumors that contain pre-existing intrinsic resistance mechanisms to current EGFR inhibitors, which ultimately has no therapeutic benefit. Furthermore, patients who initially respond to these therapies commonly relapse, presenting with new tumors that have acquired resistance to the original therapy. Substantial translational and clinical research has been undertaken in order to understand, and more importantly overcome, the molecular initiators of both intrinsic and acquired tumor resistance. However, despite a multitude of cost and effort in gaining greater understanding of the molecular mechanisms that drive tumor resistance, very little has translated into clinical practice and management of patients. In these 2 back-to-back chapters, we will provide an overview of the progress made in targeting the EGFR and discuss the challenges presented by the numerous molecular mechanisms currently identified, leading to overall refractory outcomes to anti-EGFR therapeutics. In this chapter (Part II) we will specifically focus on the resistance mechanisms mediated by alterations in substrates downstream of the EGFR and review other intracellular mechanisms that mediate both sensitivity and resistance outcomes to anti-EGFR agents.

Keywords: Afatinib, Cancer, Cetuximab, Epidermal Growth Factor Receptor,

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1. INTRODUCTION

The HER or ErbB family consists of four members, the Epidermal Growth Factor Receptor (EGFR) (also referred to as ErbB1 or HER1) [1], HER2 ($p185^{Neu}$ or ErbB2) [2], HER3 (ErbB3) [3] and HER4 (ErbB4) [4] and is one of the most intensely studied, and targeted, receptor tyrosine kinase families. Inactive EGFR exists mainly in a "tethered" confirmation where extracellular domains II and IV associate intra-molecularly leading to an auto-inhibitory favoured state. This confirmation occludes the accessibility of the dimerization arm of the receptor (in domain II) and separates two regions in domain I and III involved in ligand binding. Upon ligand binding, the ligand binding regions of domain I and III are brought closer together and the EGFR converts into an extended confirmation resulting in a dis-association of the auto-inhibitory interaction of domain II and IV and exposure of the dimerization arm facilitating dimerization of the extracellular region [5 - 7].

In addition, the ligand induced extended confirmation of the EGFR instigates ATP binding to a lysine residue, (Lys-721), within the EGFR kinase domain [8]. This binding is a critical event required for rapid intrinsic tyrosine kinase activation and auto-phosphorylation of specific tyrosine residues in the intracellular domain of EGFR [9 - 12]. This auto-phosphorylation in turn results in a more open conformation permitting the access of cellular substrates to the tyrosine kinase domain [8, 13]. The phosphorylated tyrosines of the EGFR serve as high affinity docking sites for Src homology 2 (SH2) and phospho-tyrosine binding (PTB) domain containing signalling proteins [14, 15]. Mutational analysis has shown that the removal of the auto-phosphorylation sites has a severe effect on substrate binding if all five tyrosine sites are removed. However, when only one site is altered, the remaining auto-phosphorylated sites appear to be able to compensate for the loss of the tyrosine site [16]. Adding to the diversity of EGFR downstream signaling is the presence of other ligands including the neuregulin family that activate the EGFR indirectly by binding HER3 and HER4 and resulting in EGFR trans-phosphorylation by EGFR-HER3 or EGFR-HER4 dimerization [17, 18].

Furthermore, the EGFR can co-operate with many other non-ErbB family members receptors leading to increased diversity of signaling pathway activation downstream [19 - 30]. It is thought that each ligand within the ErbB family illicit a subtly distinct conformation between the two dimerizing receptors in the intracellular region, resulting in differential tyrosine phosphorylation profiles and unique sets of docking substrates, ultimately leading to distinct biological outcomes [31]. Proteins that directly bind the phosphorylated tyrosines of the EGFR through their SH2 domain include PLC-(, GAP, Grb2, and Crk [15, 32 - 34] whiles others such as Shc interact *via* their PTB domain [32]. HER2, HER3 and HER4 also contain areas in their intracellular region for SH2 domain containing proteins to bind [34]. However, each HER receptor displays a distinct set of C-terminal auto-phosphorylation sites resulting in the recruitment of a different set of substrates. The recruitment and activation of these molecules to the receptor in turn selectively activates downstream signaling networks which include the RAS-RAF-MAPK-ERK1/2 pathway, the PTEN regulated phosphatidylinositol 3-kinase (PI3-K)-Akt-mTOR pathway, Src-Signal transducer and activator of transcription (STAT) family members and the Phospholipase C gamma (PLCγ) signaling pathway [35] (Fig. **1**). In turn these signalling molecules interact with nuclear transcription factors and cytoskeletal proteins triggering gene transcription of many proteins involved in regulating a variety of cellular functions and changes in cell polarity and morphology [36, 37].

Furthermore, despite being originally recognised as a mechanism in which cells inactivate signalling by internalisation and degradation of activated receptors, EGFR signalling is sustained or initiated following receptor endocytosis and subsequent trafficking through early and late endosomes [38 - 40]. In addition, the EGFR (and the other HER family members) translocate into the nucleus where they are involved in direct gene transcription [41 - 47]. Finally, the presence of EGFR ligands, full length EGFR and the truncated variant EGFRvIII, that are all signaling competent have been discovered in secreted exosomes suggesting an inter-cellular role of EGFR signaling [48 - 50].

Not surprisingly, due to the EGFR's many associations at the cell membrane and the diverse network of signaling, and as outlined in our previous review (Part I of this series), EGFR activation is intimately associated with many cellular activities

CHAPTER 3

Chemotherapeutic, Immunologic, and Molecularly Targeted Therapy for the Treatment of Advanced Melanoma

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Abstract: Over the past several decades, the incidence of melanoma has increased. Although surgery remains the primary treatment modality for localized early-stage lesions, melanoma is often diagnosed following locoregional and distant disease spread. Prognosis for advanced stage disease is dismal as one would expect; however, nowadays, the myriad of systemic therapies have allowed for improvements in disease free and overall survival. Such systemic treatment approaches include chemotherapy, immunotherapy, and molecularly targeted agents. Since the time of the approval of dacarbazine by the Food and Drug Administration for the treatment of metastatic melanoma in 1975, other agents have gained approval including interleukin-2, immune checkpoint inhibitors such as ipilimumab (anti-CTLA-4), and others. More recently, studies suggest that combination regimens of the aforementioned approaches may further improve outcomes when compared to monotherapy. Herein, the authors provide an up-to-date comprehensive review on the chemotherapeutic, immunologic, and molecularly targeted therapy approaches to the treatment of advanced melanoma.

Keywords: Advanced Stage, Anti-PD-1, Anti-CTLA-4, Anti-PD-L1, Chemotherapy, Dacarbazine, Immune Checkpoint, Immunotherapy, Interleukin-2,

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Melanoma, Metastatic, Systemic, Targeted Therapy, Vaccine.

INTRODUCTION

Over the past several decades, the incidence of melanoma has markedly increased [1 - 3]. Worldwide, approximately 50,000 deaths can be attributed to melanoma each year [4]. Melanomas originate from melanocytes, which reside in the basal layer of the epidermis and produce melanin. Several mechanisms are thought to underlie the malignant transformation of normal melanocytes in melanoma development. Perhaps one of the most well studied risk factors for melanoma development is ultraviolet radiation [5]. Under normal circumstances, melanin helps protect the skin from ultraviolet light. Overtime, excessive sun exposure, results in excessive DNA damage to proliferating melanocytes, thereby over-whelming the normal DNA repair mechanisms. Occasionally in the process, a cell will undergo malignant transformation [5]. Furthermore, several genes, such as *BRAF*, *PTEN,c-Kit, p53, CDKN2A/p16* are implicated in the development by mutation, deletion, or amplification. Mutations in these genes may be induced by UV radiation or are inherited and ultimately result in the dysregulation of the normal cell cycle checkpoints. Understanding the complex interplay of genetic and environmental factors in melanoma pathogenesis is an ongoing area of investigation.

Surgery is the primary treatment modality for localized early stage lesions, with estimated 5 and 10-year survival rates approximating 97% and 93% for patients with Stage 1a, T1aN0M0 melanomas (≤ 1mm, without ulceration and mitosis ≤ 1/mm^2) [6]. Metastatic melanoma carries an overall median survival of 4-12 months, depending on the site of distant disease [7]. The current melanoma TNM staging system was recently updated using data from an expanded American Joint Committee on Cancer (AJCC) Melanoma Staging Database [4]. For metastatic melanoma (stage IV), elevated serum levels of LDH and site(s) of metastases define the M1 stage into three categories: M1a - only distant skin, subcutaneous or nodal metastases and normal LDH, M1b - lung metastases is present with a normal LDH, or M1c - metastases to any other visceral site and elevated LDH [4]. As one would expect, prognosis worsens as disease progresses from M1a to M1c disease.

While the prognosis after surgical resection in patients with early stage disease is favorable, the median overall survival for patients with distant metastases (stage IV) treated with chemotherapy is less than a year, and 5-year survival approximates 10% [3]. When considering metastatic disease, surgery may improve outcomes, and complete resection has been shown to improve survival when compared to incomplete resection [8, 9]. Melanoma is generally considered to be a relatively radio-resistant tumor; however, radiation therapy (*e.g.*, whole brain irradiation or stereotactic radiosurgery) has been used in adjuvant and palliative settings, such as in cases of metastasis to the brain [10 - 12].

Table 1. Select agents approved by the US Food and Drug Administration (FDA) for the treatment of advanced melanoma.

Class	Agent	Year FDA Approved	Indication
Chemotherapy	Dacarbazine	1975	Stage IV melanoma
Immunotherapy	High-Dose Interferon alfa-2b (IFN-α)	1996	Adjuvant treatment of intermediate and high-risk melanoma (Stage IIB/C, Stage III)
	High-Dose Interleukin-2 (IL-2)	1998	Stage IV melanoma
	Ipilimumab	2011	Unresectable Stage III or Stage IV melanoma
	Nivolumab	2014	Unresectable Stage III or Stage IV melanoma
	Pembrolizumab	2014	Unresectable Stage III or Stage IV melanoma
Molecularly Targeted Therapy	Vemurafenib	2011	Patients with BRAF V600E mutation with unresectable Stage III or Stage IV melanoma
	Trametinib	2013	Patients with BRAF V600E/V600K mutation who have unresectable Stage III or Stage IV melanoma
	Dabrafenib	2013	Patients with BRAF V600E mutation with unresectable Stage III or Stage IV melanoma
	Trametinib/ Dabrafenib Combination	2014	Patients with BRAF V600E/V600K mutation who have unresectable Stage III or Stage IV melanoma

Systemic therapy remains the primary treatment modality for stage IV disease [13]. Prior to 2011, high dose interleukin-2 (IL-2) and an alkylating agent,

CHAPTER 4

Targeting the Warburg Effect for Cancer Therapy: A Long and Winding Road

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Abstract: In the 1920s, Otto Warburg, one of the leading biochemists of the 20th century, uncovered a striking phenotype of cancer cells: their increased dependence on lactic acid fermentation for energy production compared to that of the normal cells from which they derived. Warburg viewed this metabolic particularity of cancer cells, which came to be known as the Warburg effect, as a driving force in carcinogenesis. This perception suggested a novel path for cancer therapy, a strategy that Warburg himself proposed and defended with passion to his death. However, for many decades, both his metabolic theory of cancer and suggested therapeutic approach were essentially ignored by cancer researchers, who were mostly focused on the genetic basis of the disease and on the intricacies of the pathways known to promote cellular proliferation, differentiation and death. Still, thanks to the combined efforts of those who chose to pursue Warburg's line of research, experimental evidence supporting and extending Warburg´s findings on the metabolism of cancer cells accumulated. In the 1980s, ^{18}F-deoxyglucose positron emission tomography (^{18}FDG–PET) was implemented in the clinic. This metabolic imaging technique, which is based on the avidity of cancer cells for glucose, represents, to this day, the only successful exploitation of the Warburg effect for medical purposes. The wide success of ^{18}FDG–PET in the diagnosis and staging of tumors is among the factors most responsible for renewing interest in the central carbon metabolism of cancer cells. This renewed interest was further boosted by the discovery of multiple links between central carbon metabolism and cellular proliferation, differentiation and death and culminated

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in the recent classification, by Weinberg and Hanahan, of tumor metabolism as an emerging cancer hallmark. Tremendous research effort is now being devoted into a more detailed and comprehensive elucidation of the metabolic rewiring that accompanies neoplastic transformation and, unsurprisingly, targeting the metabolic peculiarities of tumors has become a hot topic in drug discovery. This chapter summarizes past and current efforts at targeting the Warburg effect for selective cancer therapies.

Keywords: Aerobic glycolysis, Central carbon metabolism, Clinical trials, Diabetes, Emerging cancer hallmark, ^{18}F-Deoxyglucose positron emission tomography (^{18}FDG–PET), Hypoxia, Ketogenic diet, Metabolic cancer therapies, Metformin, Pasteur effect, Targeted cancer therapies, Warburg effect.

1. THERAPEUTICAL APPROACHES TO CANCER: FROM CHEMOTHERAPY TO TARGETED THERAPIES

The oldest written description of cancer known to exist can be found in the Edwin Smith Papyrus, which is based on what was known in surgery and medicine up to 3000 BC [1, 2]. But humans must have, in all likelihood, been fighting against cancer throughout their existence. Although this papyrus describes the treatment of tumors with cauterization, it also acknowledges the absence of a cure for the disease. By 400 BC, Hippocrates, the "Father of Medicine", advised against the treatment of deep-seated tumors, as this would shorten the lives of patients [2]. Fortunately, this perception of cancer as an incurable disease did not prevent significant advances in cancer therapy, mostly during the last century. Some milestones in cancer therapy will be briefly discussed in this section.

The first successful inductions of tumor regression *via* systemic administration of chemical substances can be traced back to the 1940s. At that time, our understanding of human cancer biology was very limited and the discovery of the anticancer activity of the first cancer drugs stemmed from chance observations. Namely, from the post-mortem observation of severe myelosuppression and lymphoid hypoplasia in First World War soldiers dying of mustard gas exposure, which suggested the use of nitrogen mustards for the treatment of lymphomas [3, 4], and the observation of increased proliferation of acute lymphoblastic leukemia (ALL) cells upon administration of folic acid to children with ALL [5],

which suggested the use of two folate analogues (aminopterin and amethopterin (methotrexate; brand names Abitrexate™ and Brimexate™)[1]) to treat this neoplasy [6]. Although brief, due to development of tumor resistance to the drugs, these remissions stimulated further research on cancer therapy [7].

By this time, attempts were also being made at the rational design of compounds capable of interrupting cell proliferation. These early attempts led to the development of several purine analogs, designed to interfere with the natural production of DNA. The two most promising analogs, 6-mercaptopurine (Purinethol™, Alti-Mercaptopurine™) and thioguanine (Tabloid™, Lanvis™), were introduced in the clinic in the 1950s, establishing a novel class of cancer drugs [8, 9]. Notwithstanding these attempts at rational drug design, serendipity continued to play a role in the discovery of novel classes of cancer drugs. That was the case with vinca alkaloids, whose anticancer potential emerged in a screen for antidiabetic activity [10]. Other discoveries were the result of systematic screenings, most notably that conducted on thousands of natural products by the National Cancer Institute, which led to the discovery of the anticancer activity of taxanes and camptothecins [11].

Once the mechanisms of action of these cancer drugs became known, new compounds with similar actions, but with refined structures, could be synthesized. It was hoped that these novel structures would improve their pharmacological properties, namely in terms of stability and efficacy. However, gains achieved using this approach were rather modest [7]. Those achieved through further systematic screenings were, likewise, modest, as most of the new cancer drugs thus discovered belonged to the classes already in clinical use [12].

It is worth noting that, in spite of exhibiting distinct mechanisms of action, all cancer drug classes used in the clinic up to the mid 1970s acted by directly interfering with cellular proliferation: nitrogen mustards are non-specific DNA alkylating agents [13]; the antimetabolite methotrexate inhibits the enzyme dihydrofolate reductase (DHFR), thereby compromising the synthesis of thymidine and purines and, ultimately, DNA synthesis [14]; vinca alkaloids and taxanes are both antimitotic agents [15]; camptothecin is an inhibitor of topoisomerase I [16], an enzyme essential for DNA unwinding during replication

CHAPTER 5

Immunotherapy Strategies in Follicular Lymphoma: Antibodies, Vaccines and Cells

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Abstract: Follicular lymphoma (FL) is the most frequent indolent non-Hodgkin lymphoma. Therapeutic strategies vary from withholding treatment to aggressive chemoimmunotherapy regimes, and stem cell transplantation, depending on the stage and risk stratification at diagnosis. A prominent role of the microenvironment in FL-cell survival and lymphomagenesis has been brought to light and consequently the manipulation of the FL-cell niche is progressively becoming an important therapeutic tool in FL. Chemotherapy agents are no longer under the spotlight, leaving the main role to immunotherapeutic strategies and targeted therapy that aim towards disease control with minimal side-effects and sequelae. Immunotherapy with monoclonal antibodies, radioimmunotherapy and vaccines, has resulted in increased response rates and survival in FL patients.

Adoptive immunotherapy is an emerging strategy for FL treatment, aiming to exploit the immune system's natural tendency to attack tumoral cells. AntiCD20 monoclonal antibodies have become the backbone of first line and relapse treatments combined with chemotherapy regimens. Anti-idiotype vaccines are the best developed active immunotherapy strategy, with proven efficacy in patients with FL on first relapse. The other vaccine types (Dentritic cells, proteoliposomal or DNA) are still in preclinical development. Adoptive cell transfer (NK cells, LAK and effector T-lymphocytes), chimeric-antigen receptor (CAR) engineered T-cells and Bi-specific T-cell engaging

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antibodies (BiTE) for passive immunotherapy remain also experimental approaches, although promising pre-clinical results have recently become available.

The following chapter will summarize FL biology and conventional treatment with immunochemotherapy, with a final section focusing specifically on novel immunotherapy strategies (active and passive) for the treatment of FL.

Keywords: Adoptive cell-therapy, Anti-idiotype vaccines, Dentritic-cell vaccines, Follicular lymphoma, Immunotherapy, LAK cells, Monoclonal antibodies, NK cells, Radioimmunotherapy, Vaccines.

1. INTRODUCTION

Follicular lymphoma (FL) is the most frequent indolent non-Hodgkin's lymphoma (NHL), it is known to arise from the follicular B lymphocytes and typically features an indolent clinical course consisting of relapses followed by prolonged remissions. FL was originally named Brill-Symmers disease, it was first described in 1925 as a benign adenopatic disorder, typical of the elder [1]. FL is the second most common NHL in United States and Eastern Europe, representing 20-40% of all NHL and 70% of indolent lymphomas, with a yearly incidence of 3/100.000 [2, 3]. Definitive cure of FL seems to occur rarely [4], although patient survival continues to improve with a current average above 10 years [5 - 8].

Improvements in the outcome of FL have been driven by the appearance of novel biologic agents [9] together with a better risk assessment at diagnosis, which combines the traditional FLIPI (Follicular Lymphoma International Prognostic Index) [10] with genetic and molecular biomarkers [11]. These tools have helped clinicians to individualize treatment intensity, reduce unnecessary treatment-related toxicity and ultimately achieve durable complete remissions [12, 13]. Immunotherapy (*e.g.* anti CD20 antibodies, radioimmunotherapy or idiotypic vaccination) have probably been the greatest advance in FL treatment over the past 50 years, contributing to the extension of disease free intervals and challenging some of the oldest paradigms about FL treatment, such as incurability or the use of front-line aggressive treatment to extend survival [14].

2. BIOLOGY OF FOLLICULAR LYMPHOMA

2.1. Histopathology of FL

FL is a neoplasm composed of germinal center B cells (also known as follicle center cells), typically both centrocytes and centroblasts, maintaining at least partially the follicular histologic pattern. FL is characterized by the t(14;18)(q32;q21) translocation resulting in overexpression of anti-apoptotic BCL2 protein [15 - 17]. The World Health Organization (WHO) classification of malignant lymphomas defines three histologic grades of FL (1, 2 and 3), based on the number of centroblasts per high power field, using the cell counting method developed by Mann and Bernard [18]. More than 15 centroblasts per high power field defines grade 3 which is subsequently classified into grades 3a and 3b (3a representing an admixture of centrocytes and centroblasts and 3b predominant sheets of centroblasts). Grade 3 FL is heterogeneous, with increasing aggressiveness and less survival correlating with increasing centroblast counts [19]. In fact, clinical course of grade 3b FL overlaps with that of aggressive NHL and therefore should be treated as such [15]. FL tumor cells express surface immunglobulin (SIg+: IgM, IgD, IgG or rarely IgA) and also express typical B cell associated antigens (CD19, CD20, CD22, CD79a). Other phenotypic features include BCL2+, BCL6+, CD10+, CD5-, CD43+/- [20, 21]. Some cases, especially grade 3b, may lack CD10 but retain BCL6 expression. CD43 is a common marker of grade 3 FL [22, 23].

2.2. Follicular Lymphoma-cell Origin

The t(14;18)(q32;q21) translocation involves BCL2 and IGH genes, the breakpoint is located at the 5′ end of J heavy-chain (JH) gene, suggesting that the event occurs at the DH to JH rearrangement stage; such event occurs in bone marrow lymphoid progenitors or B cell precursors (pro-B and pre-B cells) [24 - 28]. Furthermore, FL-cells occasionally display class-switch recombination (CSR), suggesting altogether an origin between lymphoid progenitors in bone marrow and late germinal center follicular cells [29, 30].

After the immortalization event, FL-cells are thought to continue their normal differentiation path through the germinal center in spite of the BCL2-IGH

CHAPTER 6

Epigenetics and Cancer Cell Metabolism: Cross-talk and Therapeutic Opportunities

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Abstract: Epigenetics is increasingly recognized to play an important role in tumorigenesis. The epigenome encompasses a multitude of elements that regulate gene expression, including DNA methylation, histone modification, microRNA, and more recently, non-coding RNA. Aberrant regulation of the epigenome has been implicated in altered gene expression and function, which contribute to cancer development and progression *via* the promotion of cellular transformation, metastatic spread, and drug resistance. Emerging evidence indicates that the activities of key epigenetic regulators including DNA methyltransferases and histone modification enzymes are sensitive to cellular metabolism. The efficiency of these metabolic enzymes depends on the availability of substrates and/or co-factors that can be profoundly altered in cancer. Mutations in metabolic enzymes in cancer also generate oncometabolites that can lead to the dysfunction of DNA and histone demethylases. Conversely, through mediating aberrant expression of genes that are involved in cellular metabolism, epigenetic mechanisms could contribute to metabolic rewiring in cancer to confer a growth advantage to cancer cells. Understanding this cross-talk between epigenetics and cancer cell metabolism may unravel novel therapeutic opportunities. In this chapter, we will review recent discoveries linking epigenetics and cancer cell metabolism, their implications in oncogenesis, and highlight potential approaches to target these cancer-specific abnormities therapeutically.

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Keywords: Acetyl-coenzyme A, Cancer, Cancer metabolism, DNA methylation, Epigenetics, Fumarate hydratase, Gene expression, Glutaminolysis, Glycolysis, Histone acetylation, Histone demethylase, Histone methylation, Isocitrate dehydrogenase, MicroRNA, Mitochondrial succinate dehydrogenase, Non-coding RNA, S-adenosylmethionine, TET methyl-cytosine dioxygenase, Tricarboxylic acid cycle, Warburg hypothesis.

INTRODUCTION

Epigenetics is defined as heritable changes in gene expression that are not resulted from change(s) in the underlying DNA sequence. Epigenetic regulation of gene expression can be highly dynamic and of a transient nature, or can be relatively stable and be passed to offspring through the germline. Given its role in the regulation of gene expression, it is increasingly recognized that epigenetics play an important role in cell growth, differentiation and development. The human 'epigenome' encompasses three major elements that interact with each other to co-operatively to either activate or silence gene expression, which involves direct chemical modification of DNA by methylation, alteration of DNA accessibility by histone modifications, and the selective silencing of mRNA levels by noncoding RNA.

The tight regulation of the epigenome is essential in normal cellular processes. Consequently, disruption of the epigenetic machinery can cause the inappropriate activation or silencing of genes, leading to the development of numerous diseases. The notion that epigenetic disruptions may be associated with cancer development was first proposed in the 1980's [1, 2]. Extensive research over the past two decades has clearly demonstrated that epigenetic dysregulation contributes to tumorigenesis by silencing of tumor suppressor genes [3 - 5]. With the advent of next-generation sequencing in conjunction with chromatin immunoprecipitation (ChIP-Seq) [6] and microarray technologies (*e.g.* Illumina 27K and 450K) [7], we are just beginning to appreciate the impact of epigenetic dysregulation in the development of cancers on a genome-wide scale [8].

Comprehensive molecular characterization of the cancer genome, transcriptome, epigenome and proteome by the Cancer Genome Atlas (TCGA) has further

highlighted the role of aberrant epigenetics across different types of cancer, such as promoter DNA hypermethylation in a subset of colorectal cancers [9] and extreme hypermethylation in Epstein-Barr virus (EBV)-associated gastric cancer [10]. Moreover, whole genome sequencing has unraveled a number of epigenetic regulators, such as chromatin modification enzymes, that are recurrently mutated in various cancers, indicating that they may be driver mutations in carcinogenesis [11].

Recent studies have revealed an intricate relationship between epigenetics and cancer metabolism [12 - 14]. Cancer cells exhibit metabolic alterations to support an increased biosynthesis [15] and adaptations to allow their proliferation under an adverse microenvironment [16]. For example, cancer cells consume more glucose than normal cells through aerobic glycolysis, an inefficient pathway that generates much less ATP than oxidative phosphorylation, a phenomenon also known as the 'Warburg's effect' [17]. Such a metabolic re-programming is crucial for cancer cell survival, and is activated by oncogenic signaling cascades such as PI3K-AKT-mTOR [18] and transcription factors such as the hypoxia-inducible factor (HIF) and MYC [19], and the inactivation of tumor suppressor signaling, *e.g.* LKB-AMPK [20].

Metabolic sensing by the epigenetic machinery represents a built-in mechanism to regulate cellular activities in response to environmental clues, and it is frequently deregulated in cancers [12, 16]. There exists a four-way cross-talk between epigenetics and metabolism in cancer: epigenetic dysfunction that 1) directly affects expression of metabolic enzymes; and 2) indirectly alters signaling transduction cascades involved in the control of cell metabolism; and metabolic alternations that 3) influence the availability of substrates and cofactors necessary for the proper functioning of epigenetic modification enzymes; and 4) result in the production of oncometabolites that act as agonists or antagonists for epigenetic modification enzymes. In this chapter, we will provide a brief background on the epigenetic and metabolic dysregulation in human cancers, followed by a detailed account of the cross-talk between epigenetics and cancer metabolism, its underlying cause, clinical significance and potential therapeutic implications.

CHAPTER 7

Apoptosis Targeting Therapeutics in Clinical Trials

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Abstract: Apoptosis (called as programmed cell death) is vital for maintaining homeostatic balance between cell survival/cell deaths in metazoan cells. Apoptosis is regulated through extrinsic (or receptor mediated) and intrinsic (or mitochondria mediated) pathways. The pro-apoptotic proteins (*e.g.* Bax, Bak, Bad, Bcl-Xs, Bid, Bik, Bim and Hrk) and the anti-apoptotic proteins (*e.g.* Bcl-2, Bcl-XL, Bcl-W, Bfl-1 and Mcl-1) are crucial to control the apoptotic pathways. Dysfunctions of apoptosis pathways are implicated in cancer as defects in these pathways not only promote tumorigenesis but also confer resistance to cancer cells to most conventional chemotherapies as well as radiotherapy. The apoptosis occurs by imbalanced pro-apoptotic and anti-apoptotic protein levels, impaired or reduced death receptor signalling and caspase function. Hence, targeting apoptosis pathways is considered as an attractive strategy for therapeutic intervention in cancer. The past decade recorded tremendous advances in this area especially small molecular intervention of apoptosis pathways for cancer treatment which resulted in several compounds under clinical development. This chapter reviews the current progressions in the development of bioactive molecules targeting apoptotic pathways with special emphasis on small molecular anticancer drugs under clinical trials. Some excellent examples are; nutlins, MI-888, MI-219 and SM-164 which target MDM2, ABT-263, AT-406 and GX15-070MS which target Bcl-2 family of proteins, birinapant, GDC-0917, HGS-1029 and LCL-161 which target IAPs (inhibitors of apoptotic proteins). The content of this chapter will be enlightening the readers in academic and research to update their knowledge on the anticancer drugs especially target proteins responsible for apoptosis.

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Keywords: Apoptosis, BCL family proteins, Cancer, Caspase, Clinical trials, IAP, MDM2, Nutlins, p53, Pro-apoptotic protein.

CANCER

Cancer is a life threatening, multifaceted disease that involves disruption of the normal balance of cellular life and death through dysregulation of cellular homeostasis and the prevailing mechanisms responsible for cell growth and replication. Mechanisms responsible for cancer development include dysregulated response to growth signals, angiogenesis, uncontrolled replication, tissue invasion and metastasis, and evasion of apoptosis. Statistically, cancers accounted for 8.2 million deaths and 14 million new cases in 2012 and the number of cancer related deaths is expected to rise to 22 million within the next two decades [1 - 3].

Anticancer drug discovery is a challenging task owing to high attrition rate mainly attributed to lack of efficacy, non-selectivity, toxicity and incompatible pharmacokinetic profiles of anticancer agents which are under clinical development. Hence, discovery of "safe and effective" anticancer drugs remains a priority area for researchers working on cancer worldwide. The effectiveness of drugs used for the cancer therapy is dependent on the type of targets which it modulates. Biochemical pathways necessary for growth and survival of cancer cells are attractive targets for anticancer drug discovery. The former comprises mainly of signal transduction pathways regulating growth and proliferation of cancer cells while the latter comprises of pathways which enhances survival of cancer cells by imparting ability to repair and evade cell death (apoptosis). Targeting apoptosis pathways for anticancer drug discovery is relatively a new avenue compared to the much established therapeutic strategies targeting pathways regulating growth and proliferation of cancer cells. Nevertheless, the increased understanding of molecular mechanisms that regulate apoptosis together with convincing proof-of-principle evidence obtained in several animal models confirming the validity of apoptosis targeted drug discovery for cancer led to the development of several apoptosis-based therapeutics for cancer therapy. This chapter reviews the advancements in the discovery and development of small-molecules attacking apoptotic pathways with special emphasis on the bioactive molecules under clinical trials.

APOPTOSIS

Apoptosis (programmed cell death) is essential for maintaining homeostatic balance between cell survival/cell deaths in metazoan cells. The role of apoptosis in the physiological and the pathological conditions remains to be an intensely investigated area in biological research [4]. Apoptosis is triggered by imbalance in the pro-apoptotic and anti-apoptotic protein levels resulting from impaired or reduced death receptor signalling and caspase functions. Apoptosis is accompanied by a series of biochemical changes including caspases activation, DNA and protein breakdown, membrane changes and recognition by phagocytic cells [5, 6]. Dysfunction of apoptosis pathways are implicated in cancer as defects in these pathways not only promote tumorigenesis but also confer resistance to cancer cells to most conventional chemotherapies as well as radiotherapy. Hence, targeting the apoptosis pathways is considered as an attractive strategy for therapeutic intervention in cancer [7].

MECHANISMS OF APOPTOSIS

Understanding the mechanism of apoptosis formation is vital to comprehending the pathogenic circumstances developed from disordered apoptosis (Fig. **1**) [5]. Apoptosis is triggered either through mitochondria (intrinsic) or death receptor mediated pathways (extrinsic). A myriad of stress signals caused by therapeutics (chemo and radiotherapies) activate the intrinsic pathways of the apoptosis. Subsequently, the signal is relayed to the mitochondria upon the stress, leading to the mitochondrial outer membranes permeabilization (MOMP). This allows the apoptotic proteins including cytochrome c and second mitochondrial-derived activator of caspases (SMAC) to be released into the cytosol from mitochondria. The cytochrome c causes the formation of a multiprotein complex (apoptosome)-cytochrome c, apoptotic protease activating factor 1 (APAF1) and procaspase-9, initially. This causes activation of the caspase-9 activity and downstream caspase cascade from procaspase-9. Further, the release of SMAC stimulates caspase activation by neutralizing IAPs, which regulates apoptosis through inhibition of caspases [5, 6].

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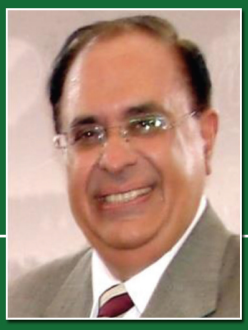

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