Frontiers in Clinical Drug Research

(Anti-Cancer Agents)

Editor:
Atta-ur-Rahman, *FRS*

Bentham Books

Frontiers in Clinical Drug Research - Anti-Cancer Agents

(Volume 6)

Edited By

Atta-ur-Rahman, *FRS*
Kings College
University of Cambridge
Cambridge
UK

Frontiers in Clinical Drug Research – Anti-Cancer Agents

Volume # 6

Editor: Prof. Atta-ur-Rahman

ISSN (Online): 2215-0803

ISSN (Print): 2451-8905

ISBN (Online): 978-981-14-7843-7

ISBN (Print): 978-981-14-7841-3

ISBN (Paperback): 978-981-14-7842-0

©2021, Bentham eBooks imprint.

Published by Bentham Science Publishers Pte. Ltd. Singapore. All Rights Reserved.

BENTHAM SCIENCE PUBLISHERS LTD.

End User License Agreement (for non-institutional, personal use)

This is an agreement between you and Bentham Science Publishers Ltd. Please read this License Agreement carefully before using the ebook/echapter/ejournal (**"Work"**). Your use of the Work constitutes your agreement to the terms and conditions set forth in this License Agreement. If you do not agree to these terms and conditions then you should not use the Work.

Bentham Science Publishers agrees to grant you a non-exclusive, non-transferable limited license to use the Work subject to and in accordance with the following terms and conditions. This License Agreement is for non-library, personal use only. For a library / institutional / multi user license in respect of the Work, please contact: permission@benthamscience.net.

Usage Rules:

1. All rights reserved: The Work is the subject of copyright and Bentham Science Publishers either owns the Work (and the copyright in it) or is licensed to distribute the Work. You shall not copy, reproduce, modify, remove, delete, augment, add to, publish, transmit, sell, resell, create derivative works from, or in any way exploit the Work or make the Work available for others to do any of the same, in any form or by any means, in whole or in part, in each case without the prior written permission of Bentham Science Publishers, unless stated otherwise in this License Agreement.
2. You may download a copy of the Work on one occasion to one personal computer (including tablet, laptop, desktop, or other such devices). You may make one back-up copy of the Work to avoid losing it.
3. The unauthorised use or distribution of copyrighted or other proprietary content is illegal and could subject you to liability for substantial money damages. You will be liable for any damage resulting from your misuse of the Work or any violation of this License Agreement, including any infringement by you of copyrights or proprietary rights.

Disclaimer:

Bentham Science Publishers does not guarantee that the information in the Work is error-free, or warrant that it will meet your requirements or that access to the Work will be uninterrupted or error-free. The Work is provided "as is" without warranty of any kind, either express or implied or statutory, including, without limitation, implied warranties of merchantability and fitness for a particular purpose. The entire risk as to the results and performance of the Work is assumed by you. No responsibility is assumed by Bentham Science Publishers, its staff, editors and/or authors for any injury and/or damage to persons or property as a matter of products liability, negligence or otherwise, or from any use or operation of any methods, products instruction, advertisements or ideas contained in the Work.

Limitation of Liability:

In no event will Bentham Science Publishers, its staff, editors and/or authors, be liable for any damages, including, without limitation, special, incidental and/or consequential damages and/or damages for lost data and/or profits arising out of (whether directly or indirectly) the use or inability to use the Work. The entire liability of Bentham Science Publishers shall be limited to the amount actually paid by you for the Work.

General:

1. Any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims) will be governed by and construed in accordance with the laws of Singapore. Each party agrees that the courts of the state of Singapore shall have exclusive jurisdiction to settle any dispute or claim arising out of or in connection with this License Agreement or the Work (including non-contractual disputes or claims).
2. Your rights under this License Agreement will automatically terminate without notice and without the

need for a court order if at any point you breach any terms of this License Agreement. In no event will any delay or failure by Bentham Science Publishers in enforcing your compliance with this License Agreement constitute a waiver of any of its rights.

3. You acknowledge that you have read this License Agreement, and agree to be bound by its terms and conditions. To the extent that any other terms and conditions presented on any website of Bentham Science Publishers conflict with, or are inconsistent with, the terms and conditions set out in this License Agreement, you acknowledge that the terms and conditions set out in this License Agreement shall prevail.

Bentham Science Publishers Pte. Ltd.
80 Robinson Road #02-00
Singapore 068898
Singapore
Email: subscriptions@benthamscience.net

CONTENTS

PREFACE

Frontiers in Clinical Drug Research - Anti-Cancer Agents presents recent developments in various therapeutic approaches against different types of cancer. The book is a valuable resource for pharmaceutical scientists, postgraduate students, and researchers seeking updated and critical information for developing clinical trials and devising research plans in anti-cancer research.

The five chapters in this volume are written by eminent authorities in the field. Chapter 1 deals with the role of the PI3K/AKT/mTOR pathway in the survival of malignant cells as a potential target to combat relapse in AML patients. It also covers therapeutic agents involving a new class of inhibitors for plausible approaches to treat patients with relapsed or refractory AML diseases. Chapter 2 discusses the role of some natural products as potential novel anti-tumor agents treat CRPC patients. Chapter 3 presents an overview of key proteins and their coordinating and/or cooperating partner proteins in protein pathways which can be useful to design innovative chemotherapeutics. Chapter 4 deals with the effectiveness of Hepatic Arterial Infusion Chemotherapy (HAIC) for advanced hepatocellular carcinoma. Chapter 5 summarizes the current strategies and discusses lead molecules which have found their way to preclinical and clinical studies for targeting cancer stem cells.

I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new and novel therapies against cancers.

I am grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications) and Mrs. Salma Sarfaraz (Senior Manager Publications) at Bentham Science Publishers.

Atta-ur-Rahman, *FRS*
Kings College
University of Cambridge
Cambridge
UK

List of Contributors

Ademar A. da Silva Filho	Faculty of Pharmacy, Department of Pharmaceutical Sciences, Federal University of Juiz de Fora, Juiz de Fora, Brazil
Aykut Özgür	Tokat Gaziosmanpaşa University, Artova Vocational School, Department of Veterinary Medicine, Laboratory and Veterinary Health Program, Tokat, Turkey
Bilal Rah	Immunology and Molecular Medicine, Sher-i-Kashmir Institute of Medical Sciences, Jammu and Kashmir, India
Danilo S. Costa	Faculty of Pharmacy, Department of Pharmaceutical Sciences, Federal University of Juiz de Fora, Juiz de Fora, Brazil
Dil Afroze	Adavnced Centre for Human Genetics, Sheri-Kashmir Institute of Medical Sciences, Jammu and Kashmir, India
Douglas C. Brandão	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil
Ezgi Nurdan Yenilmez Tunoğlu	Istanbul University, Aziz Sancar Institutes of Health, Division of Molecular Medicine, Istanbul, Turkey
Firdous A. Khanday	Department of Biotechnology, University of Kashmir, Srinagar,, Jammu and Kashmir-190006, India
Gabriela S. Guimarães	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil
Hilal Ahmad Mir	Department of Biotechnology, University of Kashmir, Srinagar,, Jammu and Kashmir-190006, India
Hitoshi Yoshiji	Department of Gastroenterology and Hepatology, Nara Medical University, Address: 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
Igor M. Campos	Faculty of Pharmacy, Department of Pharmaceutical Sciences, Federal University of Juiz de Fora, Juiz de Fora, Brazil
İrfan Koca	Yozgat Bozok University, Faculty of Arts and Sciences, Department of Chemistry, Yozgat, Turkey
Javid Rasool	Department of Haematology, Sher-i-Kashmir Institute of Medical Sciences [SKIMS], Jammu and Kashmir, India
Kei Moriya	Department of Gastroenterology and Hepatology, Nara Medical University, Address: 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
Khurshid I. Andrabi	Department of Biotechnology, University of Kashmir, Jammu and Kashmir, India
Lara Vecchi	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil
Lütfi Tutar	Ahi Evran University, Faculty of Science, Department of Molecular Biology and Genetics, Kırşehir, Turkey
Mariana A.P. Zóia	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil
Matheus A. Ribeiro	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil
Mehmet Gümüş	Yozgat Bozok University, Akdağmadeni Health College, Yozgat, Turkey
Paula M.A.P. Lima	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil

Rabia Hamid	Department of Nanotechnology, University of Kashmir, Srinagar, Jammu and Kashmir-190006, India
Roshia Ali	Department of Biochemistry, University of Kashmir, Srinagar,, Jammu and Kashmir-190006, India Department of Biotechnology, University of Kashmir, Srinagar,, Jammu and Kashmir-190006, India
Sahar Saleem Bhat	Division of Biotechnology, SKUAST-K, FVSc& AH, Shuhama, Srinagar, Jammu and Kashmir, India
Sara T.S. Mota	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil
Servet Tunoğlu	Istanbul University, Aziz Sancar Institutes of Health, Division of Molecular Medicine, Istanbul, Turkey
Shazia Ali	Adavnced Centre for Human Genetics, Sheri-Kashmir Institute of Medical Sciences, Jammu and Kashmir, India
Tadashi Namisaki	Department of Gastroenterology and Hepatology, Nara Medical University, Address: 840 Shijo-cho, Kashihara, Nara 634-8522, Japan
Thaise G. Araújo	Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil
Yusuf Tutar	University of Health Sciences, Hamidiye Institute of Health Sciences, Division of Molecular Oncology, Istanbul, Turkey Hamidiye Faculty of Pharmacy, Department of Basic Pharmaceutical Sciences, Division of Biochemistry, Istanbul, Turkey

CHAPTER 1

Immunomodulating Agents in the Treatment of Acute Myeloid Leukemia: A Combinatorial Immunotherapeutic Approach

Shazia Ali[1], Dil Afroze[1,*], Javid Rasool[2], Bilal Rah[4] and **Khurshid I. Andrabi[3]**

[1] *Adavnced Centre for Human Genetics, Sheri-Kashmir Institute of Medical Sciences, Jammu and Kashmir, India*

[2] *Department of Haematology, Sher-i-Kashmir Institute of Medical Sciences [SKIMS], Jammu and Kashmir, India*

[3] *Department of Biotechnology, University of Kashmir, Jammu and Kashmir, India*

[4] *Immunology and Molecular Medicine, Sheri-Kashmir Institute of Medical Sciences, Jammu and Kashmir, India*

Abstract: Regardless of the diverse modes of treatment, the prognosis and clinical response of AML (Acute myeloid leukemia) remain low as the conventional modes of treatment, including cytarabine and anthracycline have their limitations. Moreover, chemotherapy-induced cytotoxicity triggers the remission, thus most of AML patients succumb to relapse. The monotherapy is also not helping much due to the rapid growth of AML, while an insufficient period of time is a major barrier in immunotherapy. Therefore, the current focus has been on combination therapy, with different agents, possibly because chemotherapy for AML is associated with infection, inflammation and could be rather toxic when combined with immunotherapy. Thus, there is the utmost need for developing a new approach and treatment for AML. Recent therapies focus on various novel signaling pathways and proteins that promote the survival of cancer cells in AML patients. This single or combinatorial approach may be more effective with less harmful effects. In this context, here we are discussing the role of PI3K/AKT/mTOR pathway in the survival of malignant cells as a potential target to combat relapse in AML patients. Accordingly, the therapeutic agents with a new class of inhibitors for plausible approaches to treat the patients with relapsed or refractory AML diseases could be advocated.

Keywords: Acute myeloid leukemia, Inhibitors, Kinase, Rapamycin, Signaling, TORC1.

[*] **Corresponding author Dil Afroze:** Adavnced Centre for Human Genetics, Sheri-Kashmir Institute of Medical Sciences, Jammu and Kashmir, India; E-mail: afrozedil@gmail.com

Atta-ur-Rahman (Ed.)
All rights reserved-© 2021 Bentham Science Publishers

INTRODUCTION

Acute myeloid leukemia [AML] is a dysregulated proliferation of myeloid precursor cells leading to genomic instability. AML generally affects the people of older age and rarely occurs before the age of 45 and is thus a disease of later adulthood. 174,250 people were diagnosed with AML, in 2018, in the US alone. The overall incidence rate per 100,000 populations was reported in 2017 for leukemia based on age. 9.5 percent of the deaths was reported to be due to cancer in 2018, based on the predicted total of 609,640 cancer deaths [1, 2] The reckless progression of AML is fatal within a week or two if left untreated [3]. It is a multi-clonal disease involving the expansion of aberrant cells resulting in the impairment of the hematopoietic process, eventually leading to clinical relapse and death. The clonal heterogeneity in a large number of these patients intrigues different outcomes to chemotherapy in various individuals with AML.

Leukemogenesis is a multifactorial phenomenon involving genetic disposition, physical, chemical, or radiation exposure and chemotherapy. Many genetic aberrations have been associated with hyperproliferation and undifferentiated clonal populations in patients with AML. The distinct pattern of clonal cytogenetic abnormalities gives rise to acute myelogenous leukemia. Thus, the characterization of such clonal population and chromosomal aberrations will provide insights to understand the origin and development of leukemia. The mutations in epigenetic and transcriptional regulators represent one of the hallmarks of AML. There are numerous mutated genes present in AML, *e.g.*, FLT-3, fms-like tyrosine kinase-3, and IDH, isocitrate dehydrogenase associated with the sub-clonal population, which are difficult to analyze by an advanced technique like flow cytometry. It cannot be differentiated as to which sub-clone has refractory/ relapse properties. The mutations could be evaluated only after remission induction therapy in these patients for 5-7 days, which kills leukemic and normal blood marrow cells giving us an assessment of the improvement for the erased mutation after induction. Such trials can lead to identifying sub-clones having relapse markers by different techniques like cytogenetics, sequencing [4].

Chemotherapeutic Drugs Used in the Treatment of AML

Most of the patients can respond to the initial cytotoxic induction therapy; the common cause of death is the relapse of disease. The various chemotherapeutic regimes used for the treatment of AML are cytarabine, anthracycline, daunorubicin. Some of them are mentioned in Table **1**. The other option for treatment is aggressive therapy to provide a path to an allogeneic hematopoietic stem cell transplant [alloHSCT], which is the promising option for patients with refractory or relapsed AML [RR-AML]. Patients should have at least a complete

response before undergoing alloHSCT and fewer side effects with a suitable donor and in good health condition. The standard chemotherapy regimens do not help eliminate leukemia in patients showing relapse. It is due to the activation of various signaling cascades in leukemia stem cells and early leukemic precursors actively help in stimulating their survival. These signaling pathways are further targeted by several targeted agents. Some of the targeted agents are mentioned in Table **2**, along with new combinational approaches of immunotherapeutic agents studied in clinical trials mentioned in Table **3**. Such agents provide a potential therapeutic output and different signaling pathways like PI3K, mTOR can be targeted for the treatment of leukemia. New strategies and methods for treating AML individuals are being executed like a gene test variant of a patient, which helps in designing a drug and predicting the exact drug working for a specific patient [5].

The clinical relapse occurs due to three main sources; disease was chemosensitive with partial treatment and reoccurred with multiple mutations, a subclone originated from an initial clone at low frequency, but after treatment clone gets benefitted due to the decreased chemotherapy sensitiveness and a denovo generation of AML because of side effects from treatment. AML is treated with chemotherapy at the initial stage with an additional hematopoietic stem cell transplant depending on the patient's response [6].

AML Relapse

The relapse in AML occurs at any stage of the treatment or after completion of treatment. The standard recommendations by world health organization include monitoring blood counts for platelets every 1 to 3 months for the first two years and every 3 to 6 months thereafter for another three years [7]. The general practice of clinicians for treatment includes enrollment in a clinical trial, the reintroduction of a similar induction regimen if a relapse happens at a later stage [>12 months], or with a salvage regimen followed by allogeneic hematopoietic stem cell transplant. The relapse factor depends on age, pre-treatment cytogenetics, and chemotherapeutic drugs required for the first complete response. The prognosis factor is one of the important factors to be kept in mind at the time of relapse of disease. Relapse is one of the leading causes of death in such patients. The prognostic factor will help in facilitating appropriate chemotherapeutic agents for the successful treatment of disease [8, 9].

PI3K/mTOR Pathway

PI3K/mTOR, a mechanistic target of Rapamycin pathway is one of the main regulatory signaling cascades in mammals maintaining activities of a cellular system by regulating the transcription of genes encoding pro-oncogenic proteins

CHAPTER 2

Potential Natural Products For Prostate Cancer Management: Prospects For Castration-Resistant Patients

Thaise G. Araújo[1,*], Lara Vecchi[1], Danilo S. Costa[2], Sara T. S. Mota[1], Paula M. A. P. Lima[1], Igor M. Campos[2], Mariana A. P. Zóia[1], Douglas C. Brandão[1], Gabriela S. Guimarães[1], Matheus A. Ribeiro[1] and **Ademar A. da Silva Filho[2]**

[1] *Institute of Biotechnology, Federal University of Uberlandia, Uberlandia, Brazil*

[2] *Faculty of Pharmacy, Department of Pharmaceutical Sciences, Federal University of Juiz de Fora, Juiz de Fora, Brazil*

Abstract: Prostate Cancer (PCa) is a major global health burden with alarming epidemiological indices. Research advances in this area have revealed complex molecular aspects associated with the disease, thus necessitating the novel development of diagnostic methods and therapeutic strategies. The main molecular target is the androgen receptor (AR), which is involved in both normal development and malignant transformation. However, many patients become resistant to conventional treatments, and the disease progresses to a castration-resistant stage (CRPC) in which tumor aggressiveness is driven by a constitutive activation of AR signaling. Tremendous effort has been made for elucidating CRPC and chemoresistance. In fact, multiple signaling pathways are related to the insurgence and maintenance of CRPC, highlighting the need for continuously updating such a complex scenario. Different drugs have been tested and used for CRPC treatment, facing unfavorable heterogeneity and leading to substantial morbidity and mortality. Thus, the clinical impact of advanced PCa with poorer outcomes still underscores the need for new compounds. The discovery and current use of natural products has given way to promising possibilities, offering alternative tools that aim to control the disease and to better manage patients. These natural products are versatile and effective molecules with different mechanisms of action and structures. In the present chapter, we explore the challenges of PCa and describe recent scientific contributions in this field, with special attention devoted to CRPC. We also discuss and suggest natural products as potential novel anti-tumor agents to overcome clinical limits and to treat and cure CRPC patients.

[*] **Corresponding author Thaise Gonçalves Araújo**: Laboratory of Genetics and Biotechnology, Institute of Biotechnology, Federal University of Uberlandia, Rua Major Jerônimo, 566, Sala 604, 384700-128, Patos de Minas, MG, Brazil. Tel: +55 34 3814-2027; E-mail: tgaraujo@ufu.br

Atta-ur-Rahman (Ed.)
All rights reserved-© 2021 Bentham Science Publishers

Keywords: Castration-Resistant, Chemotherapy, Phytochemicals, Prostate Cancer, Treatment.

INTRODUCTION

Prostate cancer (PCa) is a hormonally-driven tumor that ranks fourth in incidence among human cancers and caused 358, 989 deaths worldwide in 2018 [1, 2]. When PCa is localized to the prostate and surrounding tissues, the overall survival (OS) rates are significantly high since these patients are efficiently treated with surgery and radiotherapy [3]. However, over 20% of patients evolve to a lethal treatment-refractory stage of the disease with OS ranging from 26% to 30% at 5 years [4].

Advanced PCa is treated with chemotherapy and, mainly, associated with androgen deprivation therapy (ADT) [5]. In chemotherapy, cytotoxic drugs are introduced to control or cure the disease, targeting circulating tumor cells. However, it also affects normal cells, which results in undesirable side effects [6]. In some PCa patients, it is not possible to reach a complete abrogation of the androgen receptor (AR)-mediated functions through ADT. Such a scenario is due to the ability of PCa cells to elicit aberrant AR signaling that sustains tumor progression towards castration-resistant PCa (CRPC) [7].

Current chemical therapies often fail to control PCa, especially CRPC [3]. Notably, the fact that Natural Products (NPs) present fewer side effects and greater efficacy, together with their ability to act on several cellular mechanisms, makes them particularly promising in the treatment of tumors. The ability of NPs to inhibit PCa has already been described and, owing to their low toxicity, they confer clear advantages over synthetic compounds used to control CRPC [6]. Herein, we discuss general aspects of PCa, focusing on CRPC. Considering that CRPC is characterized biochemically by increasing levels of AR-targeted genes, blocking the receptor-dependent transcriptional programmers is of particular interest. Hereafter, we describe the mechanisms of action of different NPs and their potential application for the management of advanced PCa, especially for modulating AR signaling.

OVERVIEW OF PROSTATE CANCER

Epidemiology and Etiopathology

The development of the human body is a complex and highly regulated process that needs a molecular equilibrium in order to carry out its essential functions [8]. Such an equilibrium is lost in the tumorigenesis process during which normal cells progressively evolve towards a neoplastic state. There are six hallmark traits

that enable cells to become malignant, including sustained proliferative signaling, growth suppression evasion, cell death resistance, replicative immortality, sustained angiogenesis, and tissue invasion and metastasis. Such characteristics are also associated with genomic instability, reprogramming of energy metabolism, inflammation processes and evasion from immune destruction, which are responsible for the promotion and progression of cancer [9 - 11].

The progressive colonization of several sites of the body is the main cause of cancer-induced morbidity and relies on the capacity of cancer cells to invade tissues. During invasion, the extracellular matrix (ECM) is degraded and cancer cells survive in the lymphatic and vascular systems [12 - 15]. Epithelial-mesenchymal transition (EMT) is at the center of the metastatic process since it confers to cancer cells a more aggressive potential and allows the generation and accumulation of cancer stem cells (CSCs) in a highly dynamic and heterogeneous tumor microenvironment [14, 16].

Despite the notable advances in treatment methods and in detection of malignant neoplasms, cancer remains a major public health problem. Its epidemiological indexes are alarming, including its high incidence and mortality [17, 18]. The incidence of cancer in Brazil and in the world is growing at an accelerated pace, following the aging of the population (due to the increase in life expectancy) and the change in global lifestyles [19]. In 2017, according to the World Health Organization (WHO), there were 8.8 million cancer deaths worldwide with the vast majority in developing countries. About 12 million deaths are predicted by the year 2030 [17].

PCa, in absolute global values, is the fourth most common type and has the second highest incidence among men [17]. In 2018, 1.3 million new cases of PCa were registered worldwide with 358,989 deaths. The highest incidence of the disease was in Europe (449,761 - 35.2%), followed by Asia (297,215 - 23.3%), North America (234,278 - 18.4%), Latin America and the Caribbean (190,385 - 14.9%), Africa (80,971 - 6.3%) and Oceania (23,496 – 1.8%). Regarding the number of deaths, the continents were ranked as follows: Asia (118,427 - 33%), Europe (107,315 - 29.9%), Latin America and the Caribbean (53,798 - 15%), Africa (42,298 - 11.8%), North America (32,686 - 9.1%) and Oceania (4,465 - 1.2%) [2]. According to the American Cancer Society, 174,650 new cases of PCa were diagnosed in American men in 2019, with 31,620 deaths from the disease [17].

PCa is considered a malignant tumor of the elderly, since about three quarters of cases worldwide occur after age 65 [20]. In Brazil, according to the estimates of the National Cancer Institute (INCA), about 65,840 new cases will be identified in

CHAPTER 3

Inhibition of Key Protein-Protein Interactions by Small Molecules for Cancer Drug Design

Aykut Özgür[1], Lütfi Tutar[2], Mehmet Gümüş[3], İrfan Koca[4,*], Servet Tunoğlu[5], Ezgi Nurdan Yenilmez Tunoğlu[5] and **Yusuf Tutar[6,7,*]**

[1] *Tokat Gaziosmanpaşa University, Artova Vocational School, Department of Veterinary Medicine, Laboratory and Veterinary Health Program, Tokat, Turkey*

[2] *Ahi Evran University, Faculty of Science, Department of Molecular Biology and Genetics, Kırşehir, Turkey*

[3] *Yozgat Bozok University, Akdağmadeni Health College, Yozgat, Turkey*

[4] *Yozgat Bozok University, Faculty of Arts and Sciences, Department of Chemistry, Yozgat, Turkey*

[5] *Istanbul University, Aziz Sancar Institutes of Health, Division of Molecular Medicine, Istanbul, Turkey*

[6] *University of Health Sciences, Hamidiye Institute of Health Sciences, Division of Molecular Oncology, Istanbul, Turkey*

[7] *Hamidiye Faculty of Pharmacy, Department of Basic Pharmaceutical Sciences, Division of Biochemistry, Istanbul, Turkey*

Abstract: Human genome sequencing has revealed the complex nature of the human proteome. Researchers have been focused on mapping the proteome to find the right target for drug design. Inhibition of target proteins may be complemented by redundant forms of the proteins in the pathogenesis of diseases. Therefore, it is important to determine key proteins and their coordinating and/or cooperating partner proteins in protein pathways to design innovative chemotherapeutics. Computational and experimental studies indicated that approximately 200.000 protein-protein interactions (PPIs) have been predicted, with only about 8% identified in humans. PPIs play key roles in many important cellular processes, and especially their up-regulation is closely associated with each step of the tumurogenesis in cancer cells. Therefore, the identification of protein interactions helps researchers to design drugs for target specific cancer treatment. To understand the relations between tumorigenesis and p53-MDM2, c-MYC-MAX, Bcl-2/Bcl-xL, Hsp90-Hsp70, β-catenin-TCF4, and Menin-MLL interactions are an important approach to design specific chemotherapeutics for

[*] **Corresponding authors Yusuf Tutar:** University of Health Sciences, Hamidiye Institute of Health Sciences, Department of Molecular Medicine, İstanbul, Turkey; Tel: +90 216 418 96 16, Fax: +90 216 418 96 20; E-mail: yusuf.tutar@sbu.edu.tr & **İrfan KOCA:** Yozgat Bozok University, Faculty of Arts and Sciences, Department of Chemistry, Yozgat, Turkey; Tel: +90 543 513 67 65, Fax: +90 543 513 67 65; E-mail: koca.irfan@gmail.com

Atta-ur-Rahman (Ed.)
All rights reserved-© 2021 Bentham Science Publishers

the treatment of individuals with cancer. This work focuses on key protein interactions on protein signaling pathways and designed inhibitors at these specific junctions in the literature.

Keywords: Apoptosis, Cancer, Drug design, Oncology, Protein-protein interactions.

INTRODUCTION

PPIs control essential cellular processes that are involved in several biochemical events such as receptor-ligand interactions, down-stream cell signaling cascade, and DNA transcription initiation [1, 2]. Interestingly, protein isoforms or their family members can display adverse effects from pro-apoptotic to anti-apoptotic response. This diverse function may be performed by coordinating with different partner proteins. Further, isoform or other members of the protein family may complement inhibited target protein function [3, 4]. These escape strategies provide an opportunity for cancer cells to bypass a metabolic barrier. Shortcuts and bypass mechanisms of metabolic diseases have yet to be elucidated, but key interactions must be targeted. However, current strategies focus on specific PPIs where the function is explicitly defined, and inhibition of the sites block desired metabolic event. Since several functions involve PPI complexes, inhibition of this process has gleaned interest in drug design of several human diseases. Genomics and proteomics studies revealed key PPIs targets for metabolic processes: c-My--Max, p53-MDM2, Bcl-2/Bcl-xL, β-Catenin/TCF4, Hsp90-Hsp70, and MENIN-MLL. The interaction networks reorganize in different diseases, and further, mutations that inhibit protein function may impact PPI networks [5 - 10]. Pharmaceutical studies to decipher PPI networks have been extensively searched by the pharmaceutical industry and research groups.

During the past century, many PPIs inhibitors have been clinically successful in the treatment of autoimmune diseases (abatacept, belatacept, and belimumab) and cancer (ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, and avelumab) [11]. Designing small molecules to inhibit PPIs is a difficult task since many limitations are present to design target specific PPIs inhibitors. PPIs are stabilized by large interfaces, and further, these interfaces have a variety of binding sites. Allosteric changes help PPI, and perturbation of allosteric changes by a small molecule leads to loss of interaction with a partner protein. However, many inhibitors have not been reported yet [12, 13]. Mutational analysis of protein interfaces indicated that some critical residues (hot spots) at the PPI interface play vital roles in the binding of small inhibitors. These residues show a tendency to localization at the center of the interface, to be hydrophobic, and to

show conformational adaptivity. Most of the clinical-stage inhibitors are designed that target PPI where the hot spot residues are clustered in a small binding site. Therefore, experimental assays have been developed to analyze critical residues in PPIs-based drug design studies [14, 15]. Critical residues at the PPIs interface can be detected by the alanine scanning approach in which target residue is converted to functionally "inert" amino acid alanine. Alanine scanning technique monitors the effect of interfacial residue mutations, and alterations of key residues may have major destabilizing effects. These hot spots may also be detected by *in silico* analysis, and the sites are critical in drug design [16, 17].

In this study, we focus on the biological activities of the significant PPIs and therapeutic activities of small inhibitors of the PPIs in target specific cancer drug discovery.

P53-MDM2 INTERACTION

Transcription factor p53 controls a major cellular pathway and prevents cancer development as a tumor suppressor. p53 is activated upon oncogenic stress and plays vital roles in the regulation of apoptosis, DNA repair, and cell cycle-related genes. Activation of p53 leads to cell cycle arrest, and this function plays an essential role in cancer protection. The arrest provides enough time for the repair mechanism to complete its function, and then cells are pushed to mitosis and replication. p53 also participates in the DNA repair mechanism, and if DNA cannot be repaired then, p53 drives the cell to apoptosis. Thus, this prevents potentially carcinogenic damaged DNA expansion. Since p53 is a tumor suppressor, it is inactivated in most cancer types. Modulating p53 activation by interfering with its regulation by mouse double minute (MDM2) is a potentially neat strategy for drug design research [18 - 20].

At the normal state of cells, MDM2 protein negatively regulates p53 protein. If p53 level increases, MDM2 binds to p53 and inhibits its transactivation domain activity. Further, MDM2 is an E3 ligase and targets p53-ubiquitin dependent degradation (Fig. **1**). MDM2 regulates p53 stability and activity, and several human cancer cells overproduce MDM2. The MDM2-p53 feedback loop is deregulated in cancer cells overexpressing MDM2 that leads to inefficient growth arrest and/or apoptosis. Therefore, blocking p53-MDM2 interaction releases p53 and restores its cell cycle arrest and pro-apoptotic activity [21 - 23]. Small molecule designs to perturb this interaction have drawn the attention of the pharmaceutical industry.

CHAPTER 4

Efficacy of Hepatic Arterial Infusion Chemotherapy (HAIC) for Advanced Hepatocellular Carcinoma

Kei Moriya[*], **Tadashi Namisaki** and **Hitoshi Yoshiji**

Department of Gastroenterology and Hepatology, Nara Medical University, Address: 840 Shijo-cho, Kashihara, Nara 634-8522, Japan

Abstract: As per the latest data of the International Agency for Research on Cancer, more than 8 million individuals die annually owing to the exacerbation of a given neoplasm, and the total number of annual deaths due to hepatocellular carcinoma (HCC) is 0.78 million, the second-highest of all cancer-related deaths. HCC has a very poor prognosis, reflected by the fact that the incidence-to-mortality ratio of HCC has been estimated to be more than 90%. Liver cancer is generally diagnosed only in the advanced clinical stage because HCC tends to be clinically silent during the early stages. With regard to HCC management, transarterial chemoembolization (TACE) and hepatic arterial infusion chemotherapy (HAIC), as well as molecularly targeted agents such as sorafenib and lenvatinib, have shown promising benefits for advanced HCC. However, even though the Barcelona Clinic Liver Cancer staging system has been widely accepted, controversies still exist regarding the best choice for the management of HCC in individual cases. In this chapter, we infer that HAIC treatment is not inferior to molecularly targeted therapies for the treatment of advanced HCC—particularly in case of intravascular invasion in both compensated and decompensated cirrhotic patients. Furthermore, the rate of adverse events leading to discontinuation of antitumor treatment appears relatively low. Given the hepatic function reserve preservation afforded by HAIC chemotherapy, we suggest that HAIC should be considered as an alternative strategy even for advanced-HCC patients with decompensated cirrhosis, who do not respond to TACE.

Keywords: 5-fluorouracil, Advanced stage, Chemotherapy, Child–Pugh classification, Cisplatin, Hepatic arterial infusion, Hepatic functional reserve, Hepatocellular carcinoma, Lenvatinib, Molecularly targeted therapies, Overall survival, Portal invasion, Progression-free survival, Reservoir, Sorafenib.

[*] **Corresponding author Kei Moriya:** Department of Gastroenterology and Hepatology, Nara Medical University, Address: 840 Shijo-cho, Kashihara, Nara 634-8522, Japan; Tel: +81-744-22-3051; Fax: +81-744-24-7122; E-mail: moriyak@naramed-u.ac.jp

Atta-ur-Rahman (Ed.)
All rights reserved-© 2021 Bentham Science Publishers

INTRODUCTION

Liver cancer is the sixth most commonly diagnosed cancer and the fourth leading cause of cancer-related death in the world [1]. In 2015, there were approximately 854,000 new liver cancer cases and compared with an estimated 810,000 liver cancer-related deaths annually, the ratio between incidence and the annual number of deaths is the second highest of all cancer-related deaths [2]. Hence, liver cancer is a highly fatal disease, with an incidence-to-mortality ratio approaching 1 [3]. Recent advances in diagnostic imaging techniques and various treatment methods have steadily improved the prognosis of patients with hepatocellular carcinoma (HCC) [4 - 7]; however, at the same time, these various options make the treatment of HCC difficult for clinicians to understand. This might be due to the complexity of various factors preempting a simple classification of the disease.

In this chapter, I would like to explain the advantages as well as the cautions in the case of selecting HAIC as a treatment of HCC. Additionally, HAIC combination therapy with molecularly targeted drugs or surgical resection and new derivation of modified HAIC are also described.

The Best Choice for Managing Advanced Hepatocellular Carcinoma

The major histology underlying primary liver cancer is HCC, the incidence of which remains highest in Asian countries (specifically in the East and southeast Asia) and in Italy [8]. Japan and Italy, for example, both have an aging population, and relatively many patients with HCC have comorbidities such as diabetes mellitus, hypertension, cardiac disease, cerebrovascular disease, chronic renal failure, or chronic obstructive pulmonary disease. Therefore, when choosing the most appropriate treatment for an individual case from among the various treatment options available, it is necessary to first evaluate the comorbidities and performance status of the patient, followed by an assessment of hepatic functional reserve (HFR). In general, many diabetic patients with cirrhosis have reduced hepatic insulin sensitivity and often require insulin due to marked postprandial hyperglycemia. Patients with long-lasting and/or poorly controlled diabetes mellitus are more likely to develop cardiovascular problems such as heart disease and cerebrovascular disease, as well as chronic renal failure. The degree of tumor progression is assessed only after these evaluations. With the exception of patients previously treated for HCC followed by subsequent routine imaging, it is not uncommon for patients with HCC to have advanced HCC by the time they visit a medical institution due to the general lack of symptoms in the initial stage [3].

HCC with vascular invasion is relatively common [9], and since HCC with portal vein invasion (Vp) is associated with a relatively high rate of distant metastases [10], it is necessary to identify any distant metastases in these cases. In addition,

whether the HCC is affecting both lobes or is confined to only one of these may be a criterion for considering surgical treatment. The degree of Vp may also be a criterion for considering arterial embolization.

The Barcelona Clinic Liver Cancer (BCLC) classification, which has been widely applied to evaluating the extent of tumor progression in HCC, has been included in the HCC treatment guidelines developed by the European Association for the Study of the Liver and the American Association for the Study of the Liver Disease [11, 12]. According to this classification, patients with Vp-HCC are classified as advanced-stage HCC (stage C) and are recommended to receive molecularly targeted therapies such as sorafenib and lenvatinib. On the other hand, no randomized study comparing hepatic arterial infusion chemotherapy (HAIC) with the standard of care or no medical treatment has been published, and so no evidence of its benefit or issues with side effects specific to the reservoir system (*e.g.*, vasculitis, peptic ulcers due to arterial occlusion, reservoir infections, and reservoir obstruction) has been reported to date. Subsequently, there has been no recommendation of HAIC to a patient with Vp-HCC as a standard of care in these guidelines. In addition, HAIC is not considered the standard of care in the consensus guidelines of the Asia-Pacific Association for the Study of the Liver (APASL) [13]. On the other hand, according to the treatment algorithm included in the clinical practice guidelines for HCC 2017 proposed by the Japanese Society of Hepatology, transarterial chemoembolization (TACE), hepatic resection, HAIC, and molecularly targeted therapies are recommended for advanced-HCC cases in patients with Child-Pugh class A of the HFR and vascular involvement, but without distant metastasis [14].

It is generally difficult to detect pathological vascular invasion (Vp1) using diagnostic imaging such as computed tomography (CT) and magnetic resonance imaging (MRI), and it is likely that in some cases where very large numbers of HCCs are identified in the liver, at least some of them will exhibit Vp1. In fact, treatment guidelines based on the BCLC classification state that the treatment strategy for “four or more and up to Vp1-HCC” is transcatheter arterial chemoembolization (TACE), molecularly targeted therapies, or best supportive care (BSC), and this strategy diverges significantly from the strategy applied in Japan, which is based on consensus-based HCC treatment algorithms. In fact, the indications for TACE are wide, and if the tumor is sufficiently hypervascular, treatment can be performed, as long as the vessels nourishing the tumor can be sorted out manually, and TACE can be used to treat portal vein tumor thrombi as small as Vp1 without any problems. That is why no clear criteria for the indications for TACE have been provided regarding upper treatment limits for tumor size or the number of tumors, and current guidelines in Western and Asian countries, including Japan, place TACE as the standard of care for intrahepatic

CHAPTER 5

Targeting Cancer Stem Cells: Implications in Health and Disease

Roshia Ali[1,2,*], Hilal Ahmad Mir[2], Rabia Hamid[3], Sahar Saleem Bhat[4] and **Firdous A. Khanday[2]**

[1] *Department of Biochemistry, University of Kashmir, Srinagar, Jammu and Kashmir-190006, India*

[2] *Department of Biotechnology, University of Kashmir, Srinagar, Jammu and Kashmir-190006, India*

[3] *Department of Nanotechnology, University of Kashmir, Srinagar, Jammu and Kashmir-190006, India*

[4] *Division of Biotechnology, SKUAST-K, FVSc& AH, Shuhama, Srinagar, Jammu and Kashmir, India*

Abstract: Cancer is a serious global health concern as it accounts for about 9.6 million deaths worldwide. Despite striking breakthroughs made in understanding, prevention, and treatment of cancer, the mortality rate is still high and no permanent cure has been found. The major concern is the lack of effective therapies against advanced metastasis. Thus, there is a dire need to implement new treatment approaches to combat this dreadful disease. Cancer stem cells (CSCs), being critical players of tumors can be the potential target for therapy. Currently, cancer stem cell therapy is gaining much attention from researchers because of its ability to target the CSCs, which are responsible for tumor initiation, progression, metastasis, therapeutic resistance, and recurrence. While most conventional treatment strategies target fast-growing tumor cells, CSCs may remain in the latent stage for extended periods thereby escaping the traditional therapies and leading to treatment resistance. Hence, specific targeting of the tumor-initiating cells has become the heart of cancer research, aiming at the complete elimination of malignancies. Major strategies against CSCs include targeting surface CSC biomarkers, blockage of self-renewal signaling pathways (Wnt, Nanog, Hippo/YAP, Notch, PTEN, Hedgehog, and/or STAT3), genetic targeting of CSCs, cell therapy, RNA interference utilizing miRNAs. Based on this concept, the present chapter summarizes the current strategies and the lead molecules which have found their route to preclinical and clinical studies. Since the evolution of clinical trials targeting CSCs holds a sanguine promise of affecting cancer medicine. This chapter will further throw light on rapid advancement made in this field, shortcomings faced in targeting CSCs, and several critical issues that are yet to be resolved.

[*] **Corresponding author Roshia Ali:** Department of Biochemistry, University of Kashmir, Srinagar, Jammu and Kashmir-190006 & Department of Biotechnology, University of Kashmir, Srinagar, Jammu and Kashmir-190006, India; Tel: 9018514288; E-mail: sheikhroshia@gmail.com

Atta-ur-Rahman (Ed.)
All rights reserved-© 2021 Bentham Science Publishers

Keywords: Apoptosis, Angiogenesis, Cancer recurrence, Cancer stem cells, CSC biomarkers, CSC niche, CSC origin, Differentiation, Immunotherapy, Metastasis, Mutation, Oncogenic signaling, Plasticity, Self renewal, Stemness, Targeted therapy, Transformation, Treatment resistance, Tumorigenesis, VSELs.

INTRODUCTION

Cancer remains one of the major public health concerns, with approximately 18.1 million cases and 9.6 million cancer-related deaths worldwide [1]. Despite substantial advancements in the diagnosis and therapeutics, metastatic dissemination, cancer recurrence, and drug resistance continues to be a major clinical concern. Cancer stem cells (CSCs) are immortal tumor-initiating cells characterized by exclusive abilities of self-renewal and multi-lineage differentiation that drive tumor growth and heterogeneity [2]. The stemness phenotype of these CSCs is a consequence of genetic mutations or abnormal epigenetic changes. The exact origin of CSC has been abstruse and cell of origin for tumor initiation varies across different cancer types. The cell of origin of CSC may arise from somatic cells, partially differentiated progenitors, or differentiated cells that acquire self-renewal and differentiation properties through various mechanisms [3, 4]. CSCs may also arise from normal noncancerous stem cells that acquire malignant phenotype over time through transformation and reprogramming [5]. CSCs are known to reside in a specialized microenvironment referred to as the niche, which is composed of diverse cell types that promote CSC survival and ameliorate their stemness phenotype. CSCs are considered to be a major cause of cancer therapy failure due to their resistance to current conventional therapeutics, resulting in tumor relapse and eventually metastasis [6]. Moreover, in recent times CSC based targeted therapies have proven to be beneficial in suppressing tumor development in various pre-clinical and clinical studies [7]. A thorough understanding of the CSC biology is crucial for developing novel cancer diagnostic and therapeutic strategies. CSC based therapeutics are aimed at interfering with the functions of surface markers, drug efflux transporters, stemness pathways, epigenetic regulators and oncogenic signaling pathways. Besides, immunotherapeutics and differentiation therapies have also been established to target CSCs. In this chapter, we have summarized the biological characteristics of CSCs, the role of the niche in CSCs, current therapeutic approaches to target CSCs, and the lead molecules that have found their route to preclinical and clinical studies.

STEM CELLS

Stem cells are a small subset of undetermined cells in the human body

characterized by remarkable self-renewal capability with perpetual multilineage potential [8]. These non-specialized cells strikingly differ in their capacity to differentiate into different cell lineages and based on their multilineage potential they can be hierarchically classified into totipotent, pluripotent, multipotent and unipotent. Totipotent stem cells are most versatile, having the highest differentiation potential. The embryonic totipotent cells differentiate into pluripotent embryonic stem cells which further differentiate into multipotent adult stem cells. However, with each differentiation the potency and phenotypic plasticity of embryonic stem cells gets restricted. Embryonic stem cells (ESCs) are pluripotent cell lines derived from the undifferentiated inner cell mass of blastocyst-stage early mammalian embryo. ESCs are unique in their ability to renew themselves indefinitely in a pluripotent state and retain the extraordinary potential to differentiate virtually into all the cell types of an adult organism, thereby, producing a diverse range of specialized cell types with varying phenotypes. These peculiar features make them a promising source of cells for regenerative and transplantation medicine, cell replacement therapy, basic biological research, compound screening for drug development, and in understanding developmental biology and gene function in adult organism [9 - 11]. Although ESCs offer enormous potential and hope for new innovative therapies in the treatment of a variety of diseases and debilities, however, the clinical application of these cells raises numerous ethical and safety concerns that limit their exploitation in cell-based therapeutics and research. In addition to ESCs, the tissues of our body are known to harbor diverse stem cell populations that have gradually evolved from ESCs and migrated to different organs or tissues during the course of development with the definite purpose to recoup tissue repair and homeostasis. These specialized stem cells are referred to as Adult stem cells or tissue-specific stem cells. In contrast to ESCs, adult stem cells are multipotent cells having the capacity to generate only several differentiated lineages for the specific tissues wherein they reside. Stem cells are known to interact with the dynamic physiological system that primarily governs the outcome of developmental morphogenetic events and organismal stress, as these cells have a crucial role in tissue generation, maintenance and repair. The stem cell niche is the specialized anatomic location where stem cells both reside and receive stimuli that provide an idiosyncratic microenvironment for the stem cell functioning as well as determine their fate. The behavior of stem cells in the niche is stringently regulated by a milieu of biochemical factors that ensure proper stem cell functioning [12 - 15]. Thus, stem cell niche is a basic unit of tissue physiology, having great anatomical as well as functional importance, integrating signals that orchestrate response of stem cells to the needs of organisms. The cell-cell and cell-matrix interaction of stem cells stimulate diverse signaling pathways that activate and/or repress transcription programs that maintain stem cells either in a

SUBJECT INDEX

A

All rights reserved-© 2021 Bentham Science Publishers

B

C

D

E

F

G

H

I

K

L

M

N

O

P

R

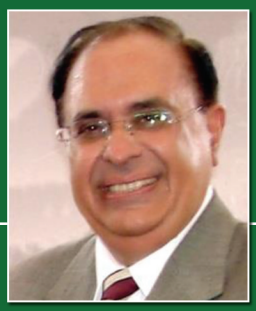
S

T

U

V

W



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

Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.