

# Preface

I would like to thank the Springer publishing group for their faith and trust in me to organize the special topic on the emerging role of epigenetics in cancer development and progression in the book entitled *Epigenetics and Cancer*. This book illustrates the complexities of the regulation and deregulation of genes in the development and progression of human malignancies through epigenetics. It is well known that genetic aberrations, especially inherited through parents (somatic genetic alterations), contribute to the development of less than 10 % of all cancers, yet epigenetic alterations in genes are responsible for the development and progression of the vast majority of all cancers. Among many alterations in the expression of genes, epigenetic regulation of genes, especially through selective methylation and acetylation, appears to play an important role in the development and progression of human cancers. Understanding the role of epigenetics in the regulation of genes, especially through deregulated expression of microRNAs (miRNAs), will allow scientists to devise targeted therapeutic strategies for re-expression of the lost genes or down-regulating the genes that are over-expressed in order to eradicate cancer. It is hoped that targeting epigenetics will not only target cancer cells, but it will also target the tumor microenvironment (more like the entire tumor environment such as the entire host) for achieving better treatment outcomes for patients diagnosed with cancer toward the objective of complete eradication of cancer.

This book contains 15 chapters – which begins with the concept of systems and network biology for investigating the epigenetics of cancer, which has been well summarized by Muqbil et al. from Dr. Azmi's group – illustrating that an integrated approach of systems biology and network modeling would be important for investigating the role of miRNAs and their target genes in the biology of pancreatic cancer. This could indeed be applicable for all cancers, and such a strategy will allow the development of miRNA-targeting therapeutics as part of the personalized medicine for the treatment of human malignancies. This chapter is followed by the chapter on the role of miRNAs in cancer epigenetics by Dr. Fabbri's laboratory, and then a specific example on the epigenetic regulation of EZH2 and its targeted miRNAs has been documented in the chapter from Dr. Wong's laboratory. The next three chapters are focused on the epigenetic regulation of miRNAs. The first one is on the

epigenetics and miRNAs in renal cancer contributed by Majid et al., followed by the next chapter from Dr. Khare's laboratory, documenting epigenetic regulation of miRNAs in colon cancer. The third chapter is presented by Dr. Dong's laboratory, documenting the state of our knowledge on the epigenetic regulation of miRNAs in breast cancer development and progression.

It is becoming increasingly clear that cancer stem cells (CSCs) are important in the development and progression of cancer, and CSCs are important in therapeutic resistance, treatment failure and tumor recurrence. To highlight the importance of CSCs and epigenetics, Dr. Houchen's laboratory contributed a very timely chapter on the epigenetic variations of stem cell markers in cancer, including miRNAs. Subsequently, two chapters are focused on prostate cancer epigenetics: one is contributed by the laboratory of Dr. Bianco-Miotto on recent updates on epigenetic biomarkers for prostate cancer and the second one is by Dr. Rybicki describing the epigenetics and racial disparities in prostate cancer.

Emerging evidence suggests that epigenetic modifiers could be useful for cancer therapy as documented by the above chapters, and it is becoming increasingly clear that epigenetics plays an important role in the expression of genes including miRNAs, and thus finding novel strategies by which one could up-regulate or down-regulate genes and miRNAs through epigenetic-targeting agents would be welcome news for patients diagnosed with cancer. In order to provide state of our knowledge on epigenetic therapeutics, an example on the role of epigenetics and breast cancer is presented by Dr. Anant who summarized the state of our knowledge on the current drugs for targeting epigenetics that are in the drug pipeline. In the next chapter, Dr. Jazirehi's laboratory has summarized epigenetics in the context of immunotherapy and BRAF kinase inhibitor in the chapter entitled "Exploiting Epigenetic Modifiers to Circumvent Melanoma Dual Resistance to TCR-Engineered Immunotherapy- and BRAF<sup>V600E</sup>-Kinase Inhibitor". This is followed by another therapeutic chapter on radiation therapy and epigenetics, which is a novel area of research as documented by Dr. Zielske in his chapter entitled "The Role of Epigenetics in Radiation Therapy and the DNA Damage Response".

There exists some novel agents that could target epigenetics in the therapeutic settings, but many such agents as presented above have already shown limitation because of unwanted adverse systemic toxicity. Therefore, further efforts are underway for testing the role of natural agents as possible non-toxic epigenetic-targeted therapeutics. This concept is presented by an exciting chapter from Dr. Gupta's laboratory, which documented that natural agents (cancer chemopreventive agents) could serve as epigenetic modifiers in the chapter entitled "Plant Polyphenols as Epigenetic Modulators of Glutathione *s*-transferase p1 Activity". Next, Dr. Li has provided a comprehensive view by describing the state of our knowledge on the epigenetic regulation of genes by natural agents (nutraceuticals) in the chapter entitled "Epigenetic Regulations of mRNAs and miRNAs by Nutraceuticals", which clearly suggests that selected nutraceutical agents could be useful as novel epigenetic-targeted therapeutic agents for the deregulation of specific genes, because nutraceuticals by definition are non-toxic to humans. Therefore, these agents could be administered safely and easily either alone or in combination

with conventional therapeutics to achieve better treatment outcomes for patients diagnosed with cancer.

It is now becoming increasingly clear that for cancer therapy to be a success, one must consider several aspects such as targeted agents for genes that are mutated, amplified or over-expressed in cancer cells, but targeting epithelial cancer cells only may not be the optimal therapeutic strategy. For that reason, drugs must be developed, which will also target cells that have undergone epithelial-to-mesenchymal transition (EMT phenotypic cells) as well as CSCs. Moreover, just targeting cancer cells, although they are heterogeneous, may still not be optimal to eradicate tumors, and for this one must take a holistic approach for developing drugs that could also target the tumor microenvironment and tumor dormancy that are regulated through epigenetics. Keeping abreast with this thought process, the concluding chapter contributed by the laboratory of Dr. Sheng provides such a concept in the chapter entitled “Towards Curative Cancer Therapy with Maspin: A Unique Window of Opportunity to Target Dormancy”. This provides an example, but similar strategies could be developed for targeting the tumor dormancy and the tumor microenvironment by developing drugs that will specifically target epigenetics.

This book provides tip of the iceberg collection of articles on the state of our knowledge on epigenetics and cancer, which would likely be useful for bringing newer generations with broader perspectives in launching cutting-edge innovative molecular research that will certainly help in designing targeted clinical trials in order to realize the dream of tailored therapeutic approach for the prevention and/or treatment of human malignancies without causing any systemic toxicity. Moreover, the knowledge gained would allow novel utilization of agents, such as nutraceuticals, as adjunct to both conventional chemotherapy and radiation therapy in order to improve the overall quality of life and survival of patients diagnosed with cancer.

Lastly, I would like to thank all the authors for their cooperation, hard work and talented contributions to bring this book to the readers in a timely fashion, and I sincerely believe that the content of this book will be useful in educating young scientists so that they can carry the torch in innovative research for realizing the benefits of epigenetic targeting in the treatment of human malignancies. I would also like to thank the publisher and the entire publishing group for their dedication and professionalism. Finally, I would like to dedicate this book to my family for their understanding, unconditional support and sacrifice to enhance my profession as a scientist.

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