Cancer and Metastasis Reviews (2018) 37:3–4
https://doi.org/10.1007/s10555-017-9722-9

Preface

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Published online: 29 December 2017

Originally referred to as "junk DNA" as its importance and function were unknown, more than 98% of DNA from the human genome that does not code for protein-coding genes is actually discovered to be much more biologically active and significant than anyone could ever imagine. The majority of the human genome is transcribed into RNAs and encodes tens of thousands of non-coding RNAs, including microRNAs and long non-coding RNAs (lncRNAs). To date, more than 2500 miRNAs and almost 28,000 lncRNAs have been characterized, and many more await experimental confirmation, surpassing already the number of protein-coding genes, which are currently estimated to be ~20,000. It is no surprise that these non-coding RNAs are important in almost all physiological processes, and that their deregulation contributes to many pathological processes, including cancer.

This special issue of *Cancer and Metastasis Reviews*, *on Non-Coding RNA and Cancer*, contains a collection of seven review articles and one meta-analysis, written by authors who are among the leaders in their area of research, on different aspects of ncRNA involvement in cancer. They describe the role of ncRNAs in metastasis, their use as biomarkers and as targets of ncRNA-based therapeutics, and their link with drug resistance and epigenetics. This is a wide variety of topics, which are of great interest to a broad audience of readers.

Three reviews summarize some of the biological functions of ncRNAs, more precisely the importance of ncRNAs in metastasis and their correlation with epigenetics. Kim et al. describe how metastasis-regulating microRNAs, or metastamiRs, exert their function by targeting protein-coding oncogenes, tumor suppressors, and metastasis genes; by modulating cancer stem cell properties; by influencing epithelial-mesenchymal transition and mesenchymal-epithelial transition; and by modulating niche cells in the tumor microenvironment. Huang and colleagues focus on lncRNAs in metastasis and describe how specific key lncRNAs, including *HOTAIR*, *H19*, *CCAT2*, *LET*, *NKILA*, *DREH*, *MALAT1*, *FENDRR*, *Linc-ROR*, *Glnc1*, *LncRNA-ATB*, *SCHLAP1*, *BCAR*, *EBIC*, *SDMGC*, *and UCA1*, are linked to the cancer metastasis process. The review of Ferreira and Esteller ties together ncRNAs, epigenetics, and cancer by looking at ncRNAs as players in gene expression regulation and as epigenomic regulators, as well as how ncRNAs are affected by genetic variations and epigenetic regulation in cancer.

The meta-analysis by Pop-Bica, Pintea et al. and the review by Bayraktar and Van Roosbroeck focus on specific miRNAs, the miR-181 family and miR-155, respectively. The meta-analysis comprises 26 studies including 2653 patients and investigates whether miR-181 family members could predict the outcome of patients that suffer from different types of cancer. In their review on miR-155, Bayraktar and Van Roosbroeck summarize the role of miR-155 in normal physiology and cancer and describe in-depth the consequences of miR-155 overexpression in cancer therapy resistance, as well as potential therapeutic targeting of miR-155.

The three remaining reviews also partially focus on ncRNA-based strategies to treat cancer. On one hand, Romano and Kwong discuss the emerging applications of miRNAs as diagnostic tools and therapeutic targets in cancer immunotherapy and more specifically in immune checkpoint blockade, adoptive cell therapy, cancer vaccines, and cytokine therapy. On the other hand, Gutschner et al. discuss the use of lncRNAs as biomarkers in cancer and metastasis, different therapeutic strategies to target lncRNAs, and the promises and perils for using lncRNAs in the clinic. Finally, the review from Chen and colleagues gives a comprehensive overview of the therapeutic applications of RNA interference (RNAi) in cancer, viral infections, cardiovascular disease, and diabetes, as well as of RNAi-based delivery systems that can be used for

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systemic and targeted delivery, and the challenges associated with delivery of ncRNAs.

From modulators of essential biological functions and contributors to pathological processes, to biomarkers and therapeutic targets, ncRNAs hold great potential for clinical applicability in a wide variety of human diseases, including cancer. We hope that the extraordinary articles from this special issue of *Cancer and Metastasis Reviews* will convince you of that.

We would like to thank all the authors for their priceless contributions, and Ms. Caryn Volpe for her amazing assistance throughout the whole production process. Also, special thanks to the Co-editors in Chief of *Cancer and Metastasis Reviews*, Drs. Avraham Raz and Kenneth V. Honn, for including this exciting topic among the special issues of the journal.