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MicroRNA regulatory networks and human disease

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MicroRNAs are a class of naturally occurring small non-coding RNAs that control gene expression by a posttranscriptional repression mechanism [1–3]. Since their discovery [4–6], thousands of microRNAs have been identified to date in a variety of organisms. For example, over 1,000 human microRNAs are reported in miRBase version 18 (<http://mirbase.org>). Like protein-coding genes, microRNAs are transcribed mainly by polymerase II as long primary transcripts (pri-microRNAs) in the nucleus. However, distinct from protein-coding genes, they are subsequently cleaved to produce stem loop structured precursor molecules (pre-microRNAs) by the nuclear RNase III enzyme Drosha along with other factors [7]. The pre-microRNAs are then exported to the cytoplasm by exportin-5 [8], where the RNase III enzyme Dicer further processes them into mature microRNAs (~22 nt) and subsequently incorporated into the RNA-induced silencing complex (RISC) to exert silencing function. Evidence suggests that microRNAs target mRNAs mainly through translational repression or mRNA cleavage or altering mRNA stability. Unlike short interfering RNAs (siRNAs) that require almost identical sequences to targets to exert their silencing function, microRNAs usually require partial sequence homology to 3'-untranslated region (3'-UTR) of target genes. Because of this unique feature of microRNA targeting, a single microRNA can have multiple targets and thus, microRNAs could directly regulate a large number of protein-coding genes [9,10], providing a new layer of gene regulation mechanism.

As master gene regulators, microRNAs are able to impact a variety of cellular pathways and functions. Early studies have shown that microRNAs are critical to developmental timing, cell death, cell proliferation, immunity and patterning of the nervous system. Dysregulation of microRNAs can lead to a variety of human diseases. Thus, it is critical to understand how microRNAs are regulated in normal cellular processes as well as during disease processes. Last year, I chaired a webinar session on microRNA regulatory networks and human disease (www.targetingmeeting.com; April 26, 2011), which covered a variety of topics related to microRNAs and their roles in human diseases. This field has advanced very rapidly. To provide an update on this subject and to expand its breadth, we compiled a review series from six groups working in different fields, covering from Alzheimer's disease, cardiac hypertrophy, immunological disorders to cancer.

The role of microRNAs in cellular immunity is well established [11–13]. A number of microRNAs have been shown to play a critical role in various aspects of cellular immunity; among them is miR-29. Dysregulation of the miR-29 family causes malignancy in mouse [14] and is associated with human cancer. Importantly, miR-29 is a key player for both innate and adaptive immune responses to intracellular bacterial infection [15]. Liston et al focus on adaptive immune system. Specifically, they discuss critical roles of the miR-29 family in setting the molecular threshold for infection-associated thymic involution, T cell polarization, B cell oncogenic transformation, thus shedding light on the importance of miR-29 regulation in the cellular adaptive immune responses.

Accumulating evidence has implicated microRNAs such as miR-34 [16] in neurodegenerative diseases, one of which is Alzheimer's disease (AD). Schonrock and Jürgen Götz discuss the importance of non-coding RNAs including microRNAs in AD. Their review emphasizes the complexity of the non-coding RNA world and how this is reflected in the regulation of the amyloid precursor protein (APP) and Tau, two proteins with central functions in AD. Thus, a better understanding of this intricate regulatory network involving non-coding RNAs is essential to development of diagnostic and therapeutic tools for AD.

Cardiac hypertrophy is a thickening of the heart muscle (myocardium) which results in a decrease in size of the chamber of the heart, often due to altered stress or injury. Although there are many factors involved, recent studies have suggested the importance of microRNAs in the pathological cardiac hypertrophy and heart failure in humans and mouse models of heart diseases. In particular, dysregulation of specific microRNAs could alter the cellular responses of cardiomyocytes and non-cardiomyocytes to specific signalling upon the pathological hemodynamic overload, leading to cardiac hypertrophy and heart failure. Wang and Yang overview the cell-autonomous functions of cardiomyocyte microRNAs regulated by different pathways and the roles of non-cardiomyocyte microRNAs in cardiac hypertrophy.

A large number of microRNAs impact cell growth and proliferation; this may explain why many of them are implicated in human malignancy. We have three papers discussing the role of microRNAs in cancer. Liu focuses on microRNAs important for breast cancer initiation and progression involving cancer stem cells. Breast cancer is a well characterized disease although there are still a lot more to be learned. Early work on microRNA profiling identified a number of microRNAs that are aberrantly expressed in clinical specimens. Further studies suggest that some microRNAs function as oncogenes, while others function tumor suppressors, including miR-21, miR-145, miR-34 and miR-10b. Current focuses have been shifted to functions of microRNAs in normal mammary stem cells, breast cancer initiating cells and metastatic cancer cells, and therapy-resistant cancer cells. She also discusses their potential clinical applications, which, to a great degree, will rely on the successful identification of microRNA signatures as cancer biomarkers and the development of microRNA based-targeted therapeutics.

Compared to breast cancer, sarcomas are relatively rare, accounting for about 1% of all malignant tumor types in humans. However, sarcomas are unique because they are a heterogeneous group of tumors with mesenchymal origins. Evidently, there is a critical need for a better understanding of sarcoma pathobiology. Subramanian and Kartha provide a current understanding of microRNA regulatory networks in various sarcoma types as well as a perspective of the complex multilayer of microRNA-mediated gene regulation in sarcomas.

It is well known that a variety of cell signalling pathways play a critical role in cancer, and among them is the phosphoinositide-3 kinase (PI3K)-mediated signalling pathway. The serine/threonine kinase (Akt)/protein kinase B (PKB) serves as its key downstream target. Of considerable interest, recent evidence suggests that microRNA-mediated gene regulation interconnects with the Akt pathway, forming Akt-microRNA regulatory networks. This is because microRNAs can directly or indirectly regulate Akt activity; on the other hand, microRNAs can also serve as Akt effectors. Xu and Mo update on recent advances of how microRNAs impact the Akt activity as well as how microRNAs are regulated through the Akt pathway. Thus, a good understanding of the Akt-microRNA regulatory network may improve current strategies for the PI3K/Akt pathway-based cancer therapy.

One important lesson we learned from microRNA research is that the same microRNA can participate in various cellular pathways, and thus it can be involved in different diseases. For example, miR-21, as an oncogene, promotes tumor cell growth and metastasis; at the same time miR-21 impacts muscle differentiation. Similarly, miR-34 functions as a tumor suppressor, and it is also implicated in AD. Hence, we need to pay attention to cell or tissue specific features of microRNA-mediated gene regulation because the cellular context may ultimately affect microRNA targeting specificity. It is my hope that this review series provide much needed information to those who work in this field as well as to those who are interested in this type of research.

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