MicroRNAs, signaling pathways and diseases

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Author's introduction: Dr. Jiezhong Chen has studied intracellular signaling transduction pathways in several diseases including cancer, diabetes and cholestasis for many years. His studies have been examined how obesity, genetic mutations, microRNAs and viruses alter the activities of signaling pathways and how aberrant signaling pathways are involved in pathogenesis of diseases, in particular, cancer. Dr. Chen has published more than 100 scientific articles and many of them are in prestigious journals such as *Science Signaling*, *Lancet*, *Hepatology*, *Obesity Rev*, and *Nat Rev Gastroenterol Hepatol*.

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Intracellular signalling pathways controlled by environmental stimuli and gene expression play key roles in cellular functions. Tightly regulated signalling pathway activities are necessary for normal development and maintenance of cells. Dysregulation of signaling results in diseases including cancer and heart disease. For example, increased PI3K/Akt pathway activity causes increased cell proliferation, survival and immune escape abilities, leading to carcinogenesis (1,2). MicroRNAs (miRNAs) can regulate gene expression and thus affect activity status of signalling pathways. Not surprising, aberrantly expressed miRNAs are associated with many diseases.

MiRNAs are small non-coding RNAs which can bind to mRNAs, causing their degradation or ceasing their translation. The Mechanisms were accounted for by RNA interference (RNAi) recently although miRNAs were discovered in 1970s. RNAi was initially discovered in plants by Waterhouse and Wang as a defended mechanism of plants against viral infection (3). Infectious viruses derived dsRNAs were processed to produce siRNAs that bind to and degrade viral RNAs. In the same year, Fire *et al.* discovered the same phenomenon in *Caenorhabditis elegans* (4). The finding rewrote the central dogma of molecular biology. RNAs were identified as regulators of gene expression in addition to as vehicles to transform information on DNAs into proteins. For the discovery, Waterhouse and Wang were awarded Australian 2007 Prime Minister's prize for Science while Fire and Mello were awarded 2006 Nobel Prize in physiology or medicine. MiRNAs work in the

same mechanism as siRNA although their biogenesis differ. MiRNAs are important regulators of gene expression and dysregulation of miRNAs are associated with many diseases including cancer and heart disease; two major diseases responsible for disease-related deaths. In this column, several articles are grouped to discuss miRNAs in cancer and heart disease.

In cancer miRNAs can function as oncogenes (called as oncomiRs) to promote carcinogenesis or tumor suppressors to target oncogene mRNAs (5). MiRNAs are involved in the effects of many siganlling pathways such as EGFR, PI3K/Akt, MAPK, STAT3 and Notch pathways (6,7). These pathways are frequently activated in many cancers by genetic mutations, environmental factors and viral infection (8), causing increased cell proliferation, survival, migration as well as immune escape (1,9).

In this issue, Rossi *et al*. summarize the central roles of more than dozen of miRNAs in the pathogenesis of multiple myeloma and therapeutic implications. This review extensively discusses how these miRNAs are dysregulated in malignant plasma cells and related microenvironment, as well as how dysregulated miRNAs cause increased survival and proliferation through signaling pathways. These miRNAs are involved in several pathways. Most of them act on key signaling molecules in PI3K/Akt pathway which is often activated in myeloma (10). Clinical applications to design miRNA-based therapies against multiple myeloma cells are proposed.

HPVs are causes of most cervical cancers and many other malignancies. The vaccines have successfully decreased HPV-caused cancers (11). In the review "HPV-p53-miR-34a axis in HPV-associated cancers", the roles of miR-34a in HPV-caused cancers are summarized. HPV oncogenes cause multiple signaling pathway dysregulation (12-14). Among them, inactivation of p53 by E6 plays a key role. This review discusses how miR-34a is transcriptionally regulated by tumour suppressor p53 and mediates the effects of p53. Decreased levels of miRNA-34a cause the increased expression of multiple genes including cyclin D1, Bcl-2 and snail which regulate cell cycle, apoptosis and migration respectively.

Drug resistance, either primary or acquired, is the main cause leading to treatment failure of cancer therapy. Dysregulated signalling pathways play important roles in drug resistance (15,16). The review "Role of microRNAs in chemoresistance" summarizes the roles of miRNAs in drug resistance to chemotherapy in different tumours including lung, breast, colon, ovarian cancers, cholangiocarcinoma and leukemia. Decreased levels of miRNA tumour suppressors or increased oncomiRs result in activation of pro-survival pathways such as PI3K/Akt pathway to cause drug resistance. Thus, application of miRNA mimics to miRNA tumour suppressors or antagonists to oncomiRs could overcome drug resistance to increase treatment efficacy of chemotherapeutic drugs.

Curcumin is a well-known phytochemical that has various anti-cancer effects via inhibition of multiple prosurvival signalling pathways. In the review, the roles of miRNA-21 in the anti-cancer effects of curcumin and regulatory mechanisms for the effects of curcumin on miR-21 are summarized. MiR-21 can increase PI3K/Akt pathway by targeting its negative regulator PTEN. It also increases programmed cell death 4 (PDCD4) and NF-κB pathways to mediate carcinogenesis. Curcumin decreases miR-21 levels, through both increasing miRNA-21 exclusion and inhibition of its transcription, and thus decreases cancer incidence.

Heart disease is still a main cause of disease-related deaths. In this issue, Smith *et al*. summarize the roles of miRNAs in congenital heart disease (CHD) including atrial septal defects, ventricular septal defects, patent ductus arteriosus and tetralogy of Fallot. The development of heart is regulated by signaling pathways. Dysregulation of these miRNAs causes structural abnormalities in the heart and vasculature via multiple signalling pathways. The review also discusses the manipulation of these miRNAs for therapeutic implications.

Studies of miRNAs provide us further understanding of the pathogenesis of diseases and the causes of treatment failure. Dysregulation of miRNAs causes aberrant signalling pathways, which in turn cause abnormal cell growth and differentiation, leading to cancer, heart disease and many other diseases. Manipulation of miRNAs could have therapeutic implications. For example, applications of bone marrow stem cells through injection or tissue engineering are promising approaches for the treatment of heart disease (17,18). In tissue engineering, stem cells and survival pathway stimuli are applied to a scaffold which is planted on heart. The survival factors can promote stem cell differentiation to mature and functional cells (19). MiRNAs may be used as such a survival factor (20,21). In cancer, manipulation of miRNAs could alter dysregulated signalling pathways to increase treatment efficacy of chemotherapy.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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