EDITORIAL

Noncoding RNAs in human cancer: one step forward in diagnosis and treatment

Cancer is a genetic disease involving multistep changes in the genome [1]. However, studies so far have focused mostly on the role of protein-coding genes in cancer, although noncoding sequences constitute up to 98% of the human genome. Until recently, the vast majority of the human genome was considered by many to be ‘meaningless’. Such a view has been overturned by the discovery of noncoding regulatory elements and noncoding RNA (ncRNA) genes. High-throughput sequencing profile studies demonstrated that up to 70% of the human genome is transcribed into RNA [2, 3]. To date, the precise role of functional, noncoding genes such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs) in cancer still remains largely unknown. ncRNAs represent the cutting edge of cancer research. Investigation of the functions of ncRNAs in cancer will lead to a greater understanding of molecular mechanisms of this disease, and should lead to novel clinical applications in oncology.

miRNAs are endogenous, ~18–25 nucleotide noncoding small RNAs, which regulate gene expression in a sequence-specific manner via the degradation of target messenger RNAs (mRNAs) or the inhibition of protein translation [4, 5]. The human genome may contain >2500 miRNAs according to the latest version of miRBase. miRNAs are predicted to negatively target up to one-third of human mRNAs. Each miRNA can target hundreds of transcripts and proteins directly or indirectly, while more than one miRNA can converge on a single transcript target. Therefore, the potential regulatory circuitry afforded by miRNA is enormous.

Long noncoding RNAs (lncRNAs) are operationally defined as transcripts that are >200 nucleotides and do not appear to have protein-coding potential [6–11]. lncRNA genes are similar to protein-coding genes in several ways: lncRNA genes consist of exons and introns, though they often have fewer exons than protein-coding genes; lncRNA transcripts are processed by the same spliceosome machinery; and lncRNA transcription is subjected to the same histone modification-mediated regulation as protein-coding genes. Compared with their protein-coding counterparts, lncRNA genes are more diverse across different species, which suggests weaker selective constraints during evolution. In addition, lncRNAs are generally in low abundance but often expressed in a strikingly cell type- and tissue-specific manner, and are in many cases, primate specific [2, 3]. lncRNAs can interact with proteins and other molecules in many different ways: as scaffolds or guides to regulate protein–protein or protein–DNA/RNA interactions; as decoys to bind proteins or miRNAs; and as enhancers to influence gene transcription, when transcribed from enhancer regions or their neighboring loci.

Increasing evidence indicates that ncRNAs may in fact be key regulators of processes such as development, cell proliferation, apoptosis, hematopoiesis and stem cell division. Most importantly, ncRNAs have been found to be highly deregulated in tumors [12]. Such findings are of particular interest because tumor development often requires multiple genetic alterations in the genome, and many of such alterations have been known to be in regions with no known protein-coding genes, also called ‘gene desert’ regions. Thus, it is reasoned that deregulation of ncRNAs may contribute to tumorigenesis. In fact, certain ncRNAs have been shown to function as oncogenes or tumor suppressors. Importantly, ncRNAs may be potential biomarkers and therapeutic candidates for cancer diagnosis and treatment. A method to detect prostate cancer antigen 3 (PCA3), a prostate cancer-associated lncRNA, in urine has been developed and approved by the Food and Drug Administration as a noninvasive prostate cancer diagnostic test [13]. The transition from ncRNA-based diagnostics to ncRNA-based therapies is also under intensive investigation.

In this Special Issue on ncRNAs in human cancer, we assemble a broad spectrum of reviewers on ncRNA biology in human cancer, ranging from basic research to translational application in oncology. We have invited some of the most influential researchers in the field of ncRNAs to help us delineate the current state-of-the-art as well as to identify opportunities and challenges for the further development of this exciting field. It is our hope that this special issue will stimulate the reader to explore diverse ways to understand the mechanisms by which ncRNAs facilitate the molecular aspects of cancer research. We would like to acknowledge and thank all authors for their valuable contributions. We also thank Dr. Alison Bentley from the Briefings Editorial Office for her guidance and support.

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References