MicroRNAs and cancer: perspective on the discovery and function

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Extended Abstract

Introduction: Since microRNAs (miRNAs) discovery, the knowledge on miRNAs and cancer has been increasing exponentially (Figure 1). The first miRNA was discovered in 1993 by Victor Ambros and colleagues. By the year 2000, the Ambros and Ruvkun laboratories had discovered the two founding members of a family of small non-coding RNAs, now called miRNAs.

The detection of mature miRNA transcripts (21~22 nt transcripts) originated from larger precursor transcript. Two processes are necessary for generation of mature miRNAs: (i) pre-miRNAs from pri-miRNAs in the nucleus by Drosha and (ii) processing of pre-miRNAs into mature miRNAs in the cytoplasm by Dicer. The biological role and in vivo functions of most mammalian miRNAs are very different. In invertebrates, miRNAs regulate developmental timing, neuronal differentiation, cell proliferation, growth control, and programmed cell death. In mammals, miRNAs have been found to play a role in embryogenesis and stem cell maintenance, hematopoietic cell differentiation, and brain development. Till now, microRNAs expression has been found to be deregulated in a wide range of human diseases including cancer.

MiRNAs in cancer: The first report for miRNAs role in cancer, only two years after the discovery of the first human miRNA, by George Calin and colleagues was published. Up to day a lot of papers show miRNAs play a role in tumor invasion and metastasis. Many aspects of miRNAs roles such as MicroRNA networks in cancer, MicroRNAs as predictors of prognosis, MicroRNAs for classification of disease, MicroRNA polymorphisms predisposing cancer, MicroRNAs as non-invasive biomarkers and MicroRNAs as predictors of drug efficacy, was studied. One of the most important challenges to overcome cancer is early identification by biomarkers. A lot of studies highlight the potential of miRNAs as biomarkers for cancer. Furthermore the mutational status of miRNA binding sites in their protein coding targets can also be regarded as a diagnostic tool. Also, exist to strategy for MiRNAs as therapeutic agents. MiRNA inhibition was the first approach used to explore the potential of miRNAs in cancer therapy. The second strategy of miRNA therapeutics is to use miRNAs as a therapeutic agent as a replacement strategy.

Conclusions: Over recent years, miRNAs have emerged as major players in the complex networks of gene regulation and have been implicated in various aspects of human disease. These small RNAs have already significantly improved our understanding of carcinogenesis. microRNAs represent critical regulators of tumor cell differentiation, proliferation, cell cycle progression, invasion and metastasis. Based on microRNA arrays various
miRNAs have been described as oncogenes or tumor suppressors and many of them are used for diagnosis and as prognostic or predictive tools. But till now, two challenges are remained that requires further study: (i) the safety profile of miRNAs and (ii) clinic delivery.

Fig. 1. PubMed query for miRNAs and cancer (September 2015).

Designing and evaluating a new smart immunotoxins for targeting cancerous nerve cells

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Extended Abstract

Introduction: The term “brain tumours” refers to a mixed group of neoplasms originating from intracranial tissues and the meninges with degrees of malignancy ranging from benign to aggressive. Each type of this malignancy has its own biology, and could be lethal due to their site in the brain, their ability to infiltrate locally, and their propensity to transform to malignancy. Consequently, the lack of comprehensive science of brain tumours creates problems in describing the epidemiology and therapeutic approaches. So, despite advances in conventional treatment modalities for malignant brain tumours the prognosis for patients with high-grade astrocytic tumor remains dismal. However, conventional treatments are accompanied with many problems in some instances such as bleeding, hair loss, diarrhea, development of multidrug resistance, and immunosuppression. Irrespective the lack of science about brain tumours and problems that are accompanied with conventional treatments, BBB is a major obstacle in this cancer. Therefore, there is an urgent need for the development of novel therapies. Ideally anticancer agents for this tumor, while could be act exclusively against tumor cells, should be have the ability to crossing the BBB without any side effects on the human body. Advances in genomic and proteomic research indicate that treatment of brain tumor patients can be increasingly personalized according to the characteristics of the targeted tumor and its environment. Nonetheless, during the last two decades, a novel class of investigative drug candidates, Tumor-targeting protein, for the treatment of central nervous system neoplasia has emerged. Tumor-targeting protein which generally called immunotoxins, are composed of a toxic enzyme coupled to a specific cell binding domain that targets cancer-associated antigens. In this context, a growing number of them are in different phases of the clinical and preclinical pipeline. Bearing in mind, we investigated to designing and evaluation a new generation of immunotoxins with capacity to targeting tumor specific antigens of glioma as well as crossing the BBB.

Materials and methods: In this study at the first step a profile of specific antigen of tumor brains, bacteria and their therapeutic products, related receptors and corresponding affecting mechanisms were gathered. With the aim of achieving the required nucleotide and protein sequences NCBI, Uniprot and ExPASy were used. Protein sequence analyses were done with using web application software including InterProScan 5, CD Search and Motif Scan. 3D structure of selected products, as well as specific antigens and their matching ligands were retrieved or prepared via PDB, SWISS-MODEL and or Modeller programs. Furthermore, corresponding ligands of selected antigens were determined by using of the String. Moreover, the protein sequences of the selected products were analyzed via Protein Blast under various matrixes. Moreover, immunogenicity assays were performed via SVMTriPT program. Finally, the efficiency of the 3D structure of designed immunotoxins were measured with Rampage and visualized via Pymol.

Result and conclusion: The results of therapeutic products profiling led to discovery a comprehensive profile of protein toxins with very diverse in the resource bacteria, effective dosage, structure and functions. However, this investigation led to finding that some of them have previously been used in immunotoxin structure. Therefore, critical toxins were profiled and then characterized. The result of this analysis represented Diphtheria toxin-induced deaths domains with ribosyltransferase functionality (Figure 1).

On the other hand, similar analysis led to disclosure effective death domains in various toxins including glucanase domain, exotoxin A middle domain, and so forth with various length and activity. Furthermore, the results of homology protein searching led to the detection a series of similar sequences of effective domains such as Diphtheria toxin in other species of the bacteria such as Corynebacterium ulcerae that propounded as novel candidate for immunotoxins designing. However, some of domain searching didn’t have any

Fig. 1. Various domains that are embedded in the protein sequence of the Diphtheria toxin. As a instance of protein sequences characterization.

Fig. 2. Binding affinity of the SDC1 to corresponding specific antigens of tumor brains.