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EDITORIAL

MicroRNAs: A New Era for Cancer Therapeutics

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INTRODUCTION

Cancer is a multistep process in which normal cells experience genetic changes that progress them through a series of pre-malignant states (initiation) into invasive cancer (progression) that can spread throughout the body (metastasis). Cancer is a genetic and epigenetic disease that requires activation of proto oncogenes and inactivation of tumors suppressor genes. Mutated DNA sequences are transcribed to mRNA, which are finally translated into functionally aberrant proteins. Cancer may arise as a primary lesion originating in any tissue of the body rarely by extension from neighbouring anatomical structures or by metastasis from a distant site of origin. The resulting transformed cellular phenotype has several distinct characteristics that enables cells to proliferate excessively in an autonomous manner; cancer cells are able to proliferate, independent of growth signals, unresponsive to inhibitory growth signals, evade programmed cell death (apoptosis) pathways, overcome intrinsic cell replication limits, induce and sustain angiogenesis and form new colonies discontinuous with the primary tumor.

New global cancer data suggests that the global cancer burden has risen to 18.1 million cases and 9.6 million cancer deaths. According to a previous report, the new statistics of India reveals 570045 male cancer cases and 587245 new female cancer cases in India, lip and oral cavity cancer ranking second, while breast cancer ranking first in Indian Scenario[1]. The incidence of Lung cancer followed by breast and colorectal cancer rank the top in global scenario. Lip and Oral cancers rank the 12th highest among the 36 types of cancers. About 95% of solid tumors occur in people over 40 years of age. The average age at the time of diagnosis is about 50 years, although cancer is now occurring more frequently in much younger patients. Several times it has been noticed that cancers can be slow growing and go un-noticed till the third stage such as in breast cancer, however, in the case of oral cancer, it can be aggressive and difficult to treat and are often diagnosed at an advanced stage after the cancer has spread (metastasized) to the lymph nodes of the neck[2].

Treatment options include surgery, radiation and chemotherapy. Other options include targeted therapy by altering specific aspects of cancer cells that fuel their growth, Cetuximab (Erbitux) is one targeted therapy approved for treating head and neck cancers, these and other targeted drugs, can be used in combination with chemotherapy or radiation therapy. Other targeted drugs which are in clinical trials, include drugs that target or enhance the patient's immune system (immunotherapy).

Early stage detection is easily curable through Surgery, Radiation therapy, Chemotherapy and Chemo-radiation; whereas, patients with advanced cancer at late stages often present high mortality rates with little chance for receiving effective treatment. The 5 years overall survival of patients is still only around 50% or less, except when detected early survival could be better. Hence, it is essential to discover new

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therapeutic targets that are imperative for treating cancer development and progression. These other options include: (1) MicroRNAs, (2) Target finding (genes/SNPs), (3) Signalling Pathways (interruptions), (4) Immunotherapies and (5) Gene therapies.

As early as 2007, several microRNAs have received attention due to their properties to have links with some types of cancer[3]. The molecular pathogenesis and the use of such biological therapies to specifically targeted molecules altered in carcinomas are emerging in recent times. The microRNAs are a class of small non coding molecules 20 nucleotides in length. The microRNAs have been reported to rewrite the rules of molecular biology, as they can regulate gene expression in animals and plants through binding to the untranslated region of mRNAs of their target genes and leading to mRNA cleavage or translation repression[3].

There are many classes of small endogenous RNA molecules, such as small transfer RNA (tRNA), ribosomal RNA (rRNA), small nucleolar RNA (snoRNA), small interfering RNA (siRNA) and microRNA (miRNA). MiRNA and siRNA are biochemically and functionally indistinguishable. Both are 19-20 nucleotides (nt) in length with 5'-phosphate and 3'-hydroxyl ends and assemble into RISC to silence specific gene expression. Therefore, these molecules are distinguished based on their respective origins. MicroRNA is derived from the double-stranded region of a 60-70nt RNA hairpin precursor while siRNA is generated from long double-stranded RNA (dsRNA).

The first microRNA was discovered in 1993 by members of the Ambros lab[4-6] and Bertal[7,8], they identified the first microRNA, the product of *lin-4*, a heterochronic gene of *C. elegans*. Since then, the role of microRNAs in development has been a major focus of his research also further elucidating this work[9,10]. However, additional insight into its mode of action required simultaneously published work by another scientist[11]. It is estimated that 30% of human genes are regulated by microRNAs. Numerous recent studies have shown that alteration of microRNAs play a critical role in cancer development by regulating the expression of proto oncogenes or tumour suppressor genes. It was also reported the importance of microRNAs, as post-transcriptional regulators of nearly every biological process in the cell and also play a key role in the pathogenesis of human disease[12].

As a result, there are many drug discovery programs that focus on developing miRNA-based therapeutics[13]. The expression of various genes is regulated by microRNAs and several microRNAs act in reciprocal negative feedback loops with protein factors to control cell fate decisions that are triggered by signal transduction activity. These observations implicate small RNAs as important mediators of gene regulation in response to cell-cell signaling. The mechanism by which microRNAs silence gene expression is post translational; possibly influencing the stability, compartmentalization and translation of mRNA.

MicroRNAs have emerged as key regulators of cancer cell biology[14]. More than a thousand articles are now available on MicroRNAs, showings its role in many diseases and especially in cancers. MicroRNA signatures can define tumor types, susceptibility, prognosis and response. Circulating microRNAs provide a potential source of biomarkers. Hence, Scientists have recognized that modulation of specific microRNA activities could be seen as a potential therapeutic avenue. MicroRNAs (miRNAs) are small non-coding endogenous RNAs that mediate gene expression at the post-transcriptional level by degrading or repressing target messenger RNAs (mRNA). They have been described as, about 22 nucleotides in length and regulate mRNA translation by base pairing to partially complementary sites, predominantly in the 3 untranslated region (3 UTR) of mRNA.

Lacunae is the knowledge of these molecules and its basic expression profiling is proving to be clinically relevant to cancer diagnosis, progressions and outcome. It is now widely accepted that miRNA bind to their target mRNA and negatively regulate its expression. It is amazing to realize that a single miRNA guide can regulate several mRNA targets and conversely multiple miRNAs can cooperatively regulate a single mRNA target.

Deregulation of microRNA in cancer was first reported in 2002, when a cluster of two microRNAs, miR-15 and miR-16 was identified at chromosome 13q14.3, a frequently deleted region in chronic lymphocytic leukemia (CLL). This deletion was shown to act at least in part through allowing higher expression of the miR-15/16 anti-apoptotic target B-cell lymphoma 2 (BCL2). Since then it has been documented that microRNAs have roles in all of the cancers and formed the hallmarks defined and are implicated in the clinical management of cancers at every stage[15]. MicroRNAs (miRNA) have started a revolution in molecular biology and emerged as key players in carcinogenesis. These conserved posttranscriptional regulators of gene expression are integral to almost all known biological processes, including cell growth, proliferation, differentiation and metabolism and development of organism. Over the past decade, many studies have been established the importance of miRNAs in cancer biology by controlling expression of their target messenger RNAs (mRNAs) to facilitate tumor growth, invasion, angiogenesis and immune evasion.

A clear picture of the various types of RNA biogenesis and their role in cellular events has been lucidly elucidated recently. In oral cancers it was shown that miR-21, miR-7, miR-34b, miR-155, miR-182, miR-15b, miR-185 and let-7 are regulated, while some miRNAs that were downregulated included miR-23b, miR-125a and miR-125b. It has been reported that miR-125b42 and miR-145 have a dramatic effect in controlling cell proliferation. Furthermore, it has been reported that modulation of miR-125b expression helps to overcoming radio-resistance in OSCC.

The greatest risk factors for OSCC include an impaired ability to repair DNA damaged by mutagens and genetic aberrations causing immune defects[16]. The tumor initiation properties of cancer stem cells, such as self-renewal, tumorigenicity and drug-resistance are regulated by miRNAs. In the previous study, someone had thrown the light on the aspects of microRNA as therapeutic agents[16].

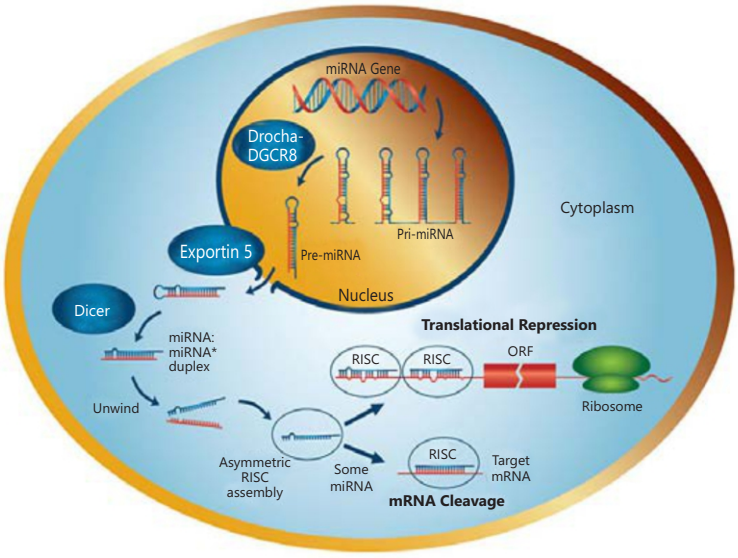

Fig. 1: Biogenesis of microRNAs

Figure 1 represents in general the biogenesis of microRNAs, the players in this event include two important enzymes Drosha in the nucleus promotes primary double stranded microRNA and Dicer in the cytoplasm prepares the single strand non coding mature microRNA. The third enzyme Export in the works between the two enzymes as it transports pri-microRNA from nucleus into the cytoplasm.

The most interesting work appears from the studies[17], in which exhaustive article confirms from several recent studies that altered expression of microRNAs in oral carcinoma had key biological roles in tumorigenesis functioning either as tumor suppressors or as tumor promoters. Further, it was shown that MicroRNA expression levels correlated with clinicopathological variables and had a diagnostic and prognostic value in oral carcinoma. Hence, microRNA is a hot topic in oral cancer research which provides a lead and scope of research in all cancers. Fig.2 adopted from the published article of Manasa and Kannan[17] summarizes published reports of miRNAs associated with oral cancer and oral premalignant lesions.

Association between miRNAs altered in oral cancer and such maps can be done for various other cancer hallmarks. The upregulated and downregulated miRNAs are depicted by up and down arrows, respectively.

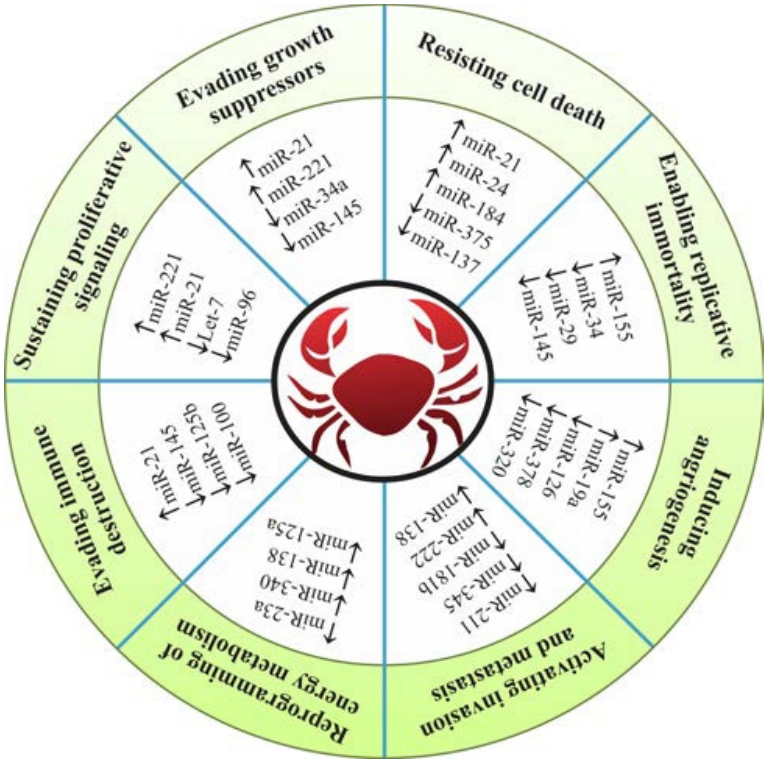

Fig. 2: Impact of microRNA dynamics on cancer hallmarks: An oral cancer scenario (SOURCE: Manasa and Kannan[17])

Future of microRNAs: The future sees MicroRNAs offer an attractive option as stable biomarkers for cancer detection, diagnosis and prognosis assessment in both the tumor tissue and circulation. It will then be important to focus more on prospective clinical trials in well-defined, large patient groups and it would also be important to correlate that particular microRNAs as signature microRNA, better characterized functionally. Recent trends indicate that a number of candidate microRNA signatures are emerging and clinical trials assessing some of these are underway. It is expected that microRNA alterations will be observed in tumour heterogeneity and these

alterations may be drivers of heterogeneity. Paradoxically as the functions of hundreds of microRNAs are known to be present in our cells and their expressions are being discovered in different forms of cancers, but their specific roles remain as total mysteries.

Characterization of microRNA as potential non-invasive biomarkers is important and can prove to be greatly effective for the diagnosis and management of cancers and oral diseases. MicroRNA target prediction and modulation of their expression can be used for therapeutic purposes. For the last few years, microRNA has been a hot topic in cancer research owing to its potential value as diagnostic and prognostic marker for cancer management.

These alterations could represent new targets for cancer diagnosis and treatment in the future. Over expression of RNA may reduce protein products of tumour suppressor genes on the other hand use of tumour suppressor microRNA expression may cause elevated levels of oncogenic proteins. One or both of these alterations could represent new targets for cancer diagnosis and treatment in the future. MicroRNA knowledge creates new understanding of cell transformation which could extend to other types of cancers and even to stem cells. The emergence of microRNA knowledge and its potential creates a new understanding of a new era for cancer therapeutics.

Sources of data: Information for this editorial was identified by searches of PubMed and references from my own and other relevant articles using the search terms "microRNA", "cancer" and "therapeutics", it may not be exhaustive.

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