Towards an extension of the two-variable model of carcinogenesis through oncogenes and tumour suppressor genes

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ABSTRACT

Currently, carcinogenesis is considered to be the result of mal-expression of tumour suppressor genes and oncogenes, leading either way to uncontrollable and disorganized cell mitosis. Recently a novel class of genes has drawn the interest of the scientific community. These are microRNAs (miRNAs), a class of noncoding RNAs, 20-23 nucleotides in length, that can up or downregulate gene expression of downstream gene targets (including transcription factors, oncogenes, and tumour suppressor genes) at the post-transcriptional level. Some members of this new class of genes seem to have the potential to act simultaneously either as oncogenes or as tumour suppressor genes depending on the molecular microenvironment of the cell. We elaborate on this hypothesis by giving examples of miRNAs (e.g. *mir-9*, *miR-17-92*) which seem to function by the abovementioned mechanism. This could mean that the deterministic notion of carcinogenesis as a result of merely tumour suppressor genes and oncogenes deregulation could be revised to contain the fact that certain members of this novel class of genes have the potential to play both roles simultaneously.

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INTRODUCTION

Tumour cells differ from their normal counterparts in a variety of basic cellular functions including cell-to-cell interactions, growth control, protein production, and gene expression. For several years, a basic concept of molecular biology regarding oncogenesis has been that the abovementioned cellular deregulation that leads to cancer induction is due to the existence of genes that act either pro-oncogenically or as tumour suppressors. Various oncogene–tumour suppressor cascades have been described but all of them rely on the notion that a gene can be either a protoncogene or a tumour suppressor gene. However, recent basic research findings may suggest that the truth is not so deterministic.

MicroRNAs have attracted the scientific community's interest for their unique features. They are small noncoding RNAs that seem to regulate the expression of approximately one-third of all human genes post-transcriptionally [1-2].

This class of genes seems to have a multitasking role in carcinogenesis and thus the categorization between oncogenes and tumor suppressor genes may not apply to them, since this is an oversimplifying approach. *Mir-9* and *m-17-92* demonstrate the abovementioned notion characteristically since they may function either as oncogenes or as tumour suppressors depending on the corresponding molecular environment.

In this context the two-variable model of oncogenes and tumour suppressor genes could be revised to contain a new class of genes whose activity depends on a complex system of gene expression feedbacks, therefore having the potential to play different roles in cancer development and pathogenesis.

MICRORNAs AND CARCINOGENESIS

MicroRNAs are a recently discovered class of noncoding RNAs, 20-23 nucleotides in length, that negatively regulate gene expression of downstream gene targets (including transcription factors, oncogenes, and tumour suppressor genes) at the post-transcriptional level by pairing to the 3' UTR of their target mRNAs, thus leading to mRNA degradation or translational inhibition [3]. A series of crucial for the development of cancer genes have been found to be either up or downregulated by miRNAs, including vascular endothelial growth factors, hypoxia-related genes, matrix metalloproteases (MMPs), MMP inhibitors (or TIMPS), and plasminogen-related proteases [4].

Recent studies have reported the association of specific patterns of microRNA activity with the development of various malignant neoplasias such as chronic lymphocytic leukemia, mantle-cell lymphomas, multiple myeloma, prostate cancer, pancreatic carcinoma, esophageal cancer, thyroid cancer, lung and breast cancer, as well as neuroblastomas and glioblastomas (Table 1).

Table1: The miRNAs involved in various malignancies. The types of miRNAs that seem to have the potential to act both as oncogenes and tumour suppressors for specific cancer types are highlighted in bold letters.

Type of neoplasia	**miRNA involved**
Chronic lymphocytic leukaemia/ mantle-cell lymphomas/ mantle-cell lymphomas [5]	*miR15 and miR16*
Prostate cancer [6-8]	*miR-125b* ***miR-17-5p***
Pancreatic cancer [9]	*miR-217, miR-196a*
Breast cancer [10]	*mir125b, mir-145, mir-21, mir-155*
Lung cancer [11-12]	*hsa-mir-155 and low hsa-let-7a-2,* ***mir-9***
Esophageal squamous cell carcinoma [13]	*mir21, mir205, mir143, mir145*

Type of neoplasia	miRNA involved
papillary thyroid carcinoma [14]	*miR-21, miR-146a*
Neuroblastoma [15]	*MicroRNA-542-5p*

DATA SUPPORTING THE HYPOTHESIS

A number of different miRNAs have been found to possibly play a 'dual' role in the development of certain cancer types, depending on various gene interactions.

The miRNA *mir-9* has been found to regulate E-cadherin expression [16]. While increased *mir-9* expression is reported to be associated with the carcinogenesis of lung cancer [12], other studies report the exact opposite [11], thus indicating the flexibility of these genes' class to function in different or opposite ways. Furthermore basic research in cancer cell lines has demonstrated both the pro-oncogenic [17] and tumor suppressor [16] potential of this gene via its complex interrelation with E-cadherin and VEGF and the regulation of tumor invasion and angiogenesis. More specifically while *mir-9* seems to inhibit tumor invasion to surrounding tissues by downregulating the production of E-cadherin it can also act in the opposite way via the upregulation of beta-catenin signalling resulting in increased expression of VEGF and consequently promotion of angiogenesis [16-17].

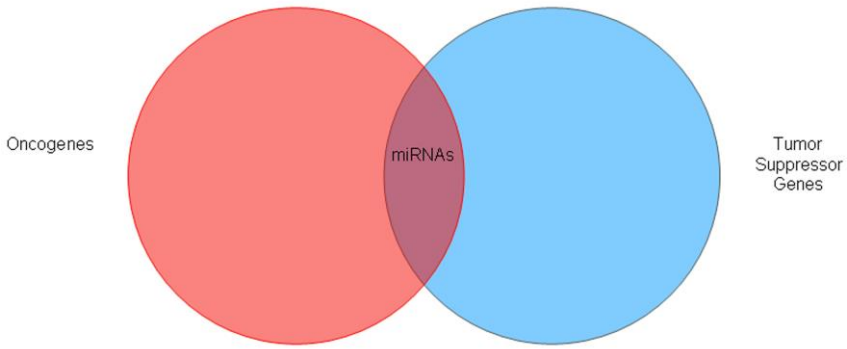
miR-17-92 belongs to a family of highly conserved miRNA clusters and seems to function under certain circumstances either pro-oncogenically or as a tumor suppressor depending on the expression of other genes such as the well known *c-myc* oncogene [18-19]. It has been shown that not only *miR-17-92* is implicated in a negative loop involving E2F and Myc but it has been reported that its oncogenic and tumor suppressor properties are crucial for the interaction between E2F and Myc [20].

In addition, *miR-17-5p* has been described in the literature as a tumor suppressor in prostate cancer [7] but other studies show that it is actually upregulated in a variety of cancers including prostate cancer [8].

CONCLUSION

In the present article, we presented the hypothesis that miRNAs not only function as an intermediate link for carcinogenesis but we also reported findings suggesting that they may have a unique characteristic: a single gene of this family has the potential to play both the role of a tumour suppressor or an oncogene depending on the expression of other genes. The idea of carcinogenesis can be revisited under the hypothesis that cancer is not only the result of oncogene or tumour suppressor gene deregulation but of miRNA deregulation, which consequently disrupts the physiologic role of oncogenes and tumour suppressor genes (Figure 1). The examples *miR-17-92, mir-9, miR-17-5p* showed this clearly. The elusiveness of the function of certain members of the miRNA family warrants further investiagation at the basic research level, since they may prove to be the third missing counterpart of carcinogenesis. This could be achieved by elaborating complex molecular techniques, such as real time PCR detection, in order to understand better the RNA-induced silencing, mediating the functions of miRNA.

Figure 1. Ven Diagram showing the role of miRNAs in carcinogenesis. It draws characteristics from both pools of genes: oncogenes and tumour suppressor genes.


Oncogenes
miRNAs
Tumor
Suppressor
Genes

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