Development of RNAi-based anti-cancer therapeutics
30 June 2017

Zebrafish model was used to evaluate the in vivo effects of overexpressing candidate miRNAs in lung cancer cells to induce cell death (left) and inhibit angiogenesis (right). Credit: University of Malaya

Understanding the interactions between miRNAs with their specific cancer gene targets is an ongoing effort to identify new therapeutic strategies. Researchers from University of Malaya carried out investigations to study the relationship between natural compound and miRNA expression in cancer cells.

Lung, cervical, and breast cancer remain the major health problems worldwide. In Malaysia, lung cancer is the third most common cancer diagnosed predominant in males. The overall five-year survival rate for patients with non-small cell lung cancer (NSCLC) is less than 15% and has remained largely unchanged for the last three decades. On the other hand, breast cancer is one of the top cancers among women worldwide, while cervical cancer is the third most common cancer in women after breast and colorectal cancer, and seventh most common cancer in the entire general population. The poor survival rate of cancer is likely due to multiple factors including late presentation of disease, lack of biomarkers for early detection, and molecular heterogeneity.

Cancer is a genetic disease that is characterised by the transformation of normal cells to a neoplastic state. This progression is enabled through the acquisition of various hallmark capabilities that allow cells to become tumourigenic and ultimately malignant. These distinctive and complementary capabilities that enable tumour growth and metastatic dissemination include mutation of cancer related genes, sustaining proliferative signaling, tumour-promoting inflammation, activation of invasion and metastasis, induction of angiogenesis, evasion of growth suppressors, avoidance of immune destruction, enabling replicative immortality, resistance to cell death, deregulation of cellular energetics and genome instability.

MicroRNAs (miRNAs) are a class of evolutionarily conserved small non-coding RNAs that regulate target genes post-transcriptionally. It is postulated that a single miRNA is capable of regulating up to 100 different target genes on average and each of these miRNAs play critical roles in various biological processes, such as, tumourigenesis, cell proliferation, and programmed cell death, with cancer cells showing perturbed expression of various miRNAs. Therefore, it is hypothesised that dysregulation of miRNAs contributes to cancer progression and that miRNA expression might be able to predict cancer prognosis and/or response to specific therapies.
In our laboratory, we investigated various phenomenon related to cancer cells, among which is apoptosis. Apoptosis, a form of programmed cell death, is essential for the development and maintenance of multicellular organisms via removal of aged, autoimmune or damaged cells. The balance between cell survival and cell death is dependent upon proper apoptotic signaling, and dysregulation can occur through the disruption of the balance between pro-apoptotic and anti-apoptotic proteins, decreased caspase function, and compromised signaling of death receptors. Studies have shown that in NSCLC, the expression of anti-apoptotic B-cell lymphocyte xL (Bcl-xL), a major prototype of the B-cell lymphocyte 2 (Bcl-2) gene, is overexpressed and contributes to cell survival through neutralization of pro-apoptotic Bcl-2 associated X protein (Bax) and Bcl-2-associated death promoter (Bad). In our study two miRNAs (miR-361-5p and miR-608) were found to be dysregulated in response to Bcl-xL silencing in NSCLC cells, and the molecular mechanism by which they regulate apoptosis was determined through the identification of novel direct targets.

Another notable investigation we have carried out was to study the relationship between natural compound and miRNA expression in cancer cells. For many years, natural compounds have been used in cancer treatment either as stand-alone or adjuvant to improve therapeutic efficacy. Studies have reported that natural compounds have lesser toxicity and are able to target multiple signaling pathways compared to some conventional anti-cancer agents. Furthermore, it was also shown that natural compounds can modify miRNAs expression, and alterations in the expression of these miRNAs can subsequently affect their anti-cancer activities. The 1'S-1'-acetoxychavicol acetate (ACA), which is isolated from the wild ginger Alpinia conchigera, is an example of such
natural compound. Both miR-210 and miR-629 have been reported to be up-regulated in many different cancers including cervical cancer, indicating a possible oncogenic role for these two miRNAs in cancers. Our results demonstrated that down-regulation of miR-210 and miR-629 conferred sensitivity towards ACA by reducing cell proliferation and augmenting apoptosis in cervical cancer cells, and this is mediated by targeting tumour suppressors SMAD4 and RSU1, respectively.

While cancer is routinely treated by chemotherapy, radiotherapy, surgery, or a combination of these procedures, relapse is not uncommon. Furthermore, treatment failures due to toxicity and acquired resistance in chemotherapy remain a major clinical problem. Consequently, there is an on-going effort to identify new therapeutic strategies, which can lead to an improved overall survival, progression-free survival and response rate. It is hoped that the insights from these studies could provide us with a better understanding in the interactions between miRNAs with their specific gene targets and consequently, help us to delineate the molecular mechanism underlying anti-cancer drug response, tumour dissemination (metastasis and angiogenesis), and induction of apoptosis and anoikis. This study will provide a platform for anti-sense gene therapy or miRNA over-expression systems whereby miRNA expression can be exploited and manipulated to inhibit tumourigenesis.

**More information:**


Provided by University of Malaya