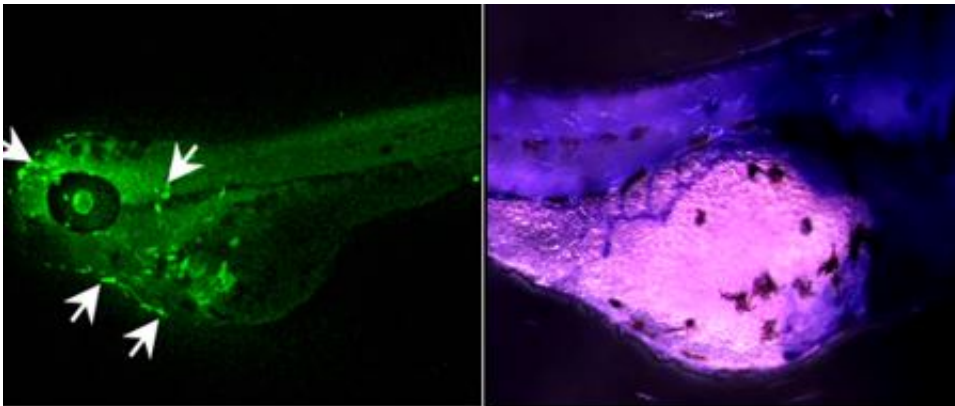


Development of RNAi-based anti-cancer therapeutics

June 30 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

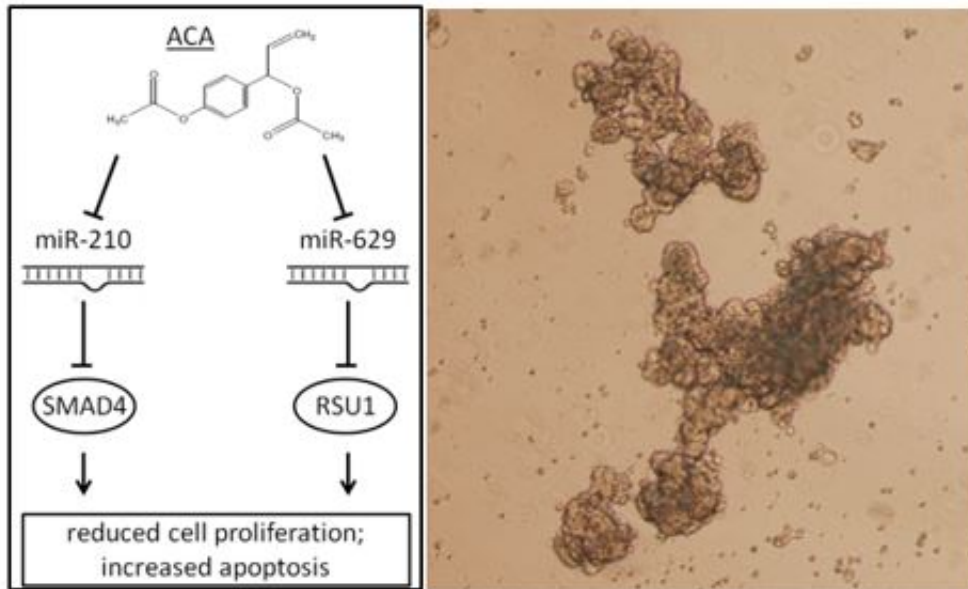
Understanding the interactions between miRNAs with their specific cancer gene targets is an on-going effort to identify new therapeutic strategies. Researchers from University of Malaya carried out investigations to study the relationship between natural compound and miRNA expression in cancer cells.

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.



Left: ACA suppressed growth and increased cell death in cervical cancer cells by modulating miR-210 and miR-629 expression; Right: Breast cancer cells grown in anchorage independent condition to investigate miRNA regulation of anoikis. Credit: University of Malaya

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.

We have also looked at other cancer cell phenotypes, such as anchorage independent growth and anoikis resistance. Anoikis is a regulatory mechanism that induces cell death upon detachment from extracellular matrix. This process ensures that cells do not detach from their original location and attach elsewhere in the body, causing undesired growth. However, cancer cells often undergo mutation to become resistant to anoikis, leading to metastasis and the acquisition of a more aggressive cancer phenotype. When cancer cells acquire resistance to anoikis, they are able to survive in the blood stream as circulating tumour cells (CTC), allowing them to evade detection and treatments, and seed a secondary tumour elsewhere in the body. We looked at how anoikis is regulated by miRNA in [breast cancer cells](#) and found a potential candidate, predicted to be a tumour suppressor, for further studies. When this miRNA was overexpressed, it was able to return anoikis sensitivity in both luminal A and triple negative type breast cancer cell lines. Presently, we are conducting additional studies to delineate how this miRNA functions and its effect in an in vivo model.

In addition to investigating [cell death](#) in cancer, we also examined cellular events that take place in the latter stage of tumourigenesis. Symptoms of lung cancer do not appear until the disease is in advanced stage, where primary tumour cells have spread to local or distant sites in the body. This development of secondary tumours, known as metastasis, is responsible for nearly 90% of cancer deaths, due to its systemic nature and resistance to chemo- and radiotherapies. Nevertheless, tumour expansion in foreign environments is only possible with neovascularisation or angiogenesis. New vessels are needed to "feed" growing tumours with nutrients and oxygen. In recent years, large numbers of studies have demonstrated the importance of miRNAs in

modulating cancer metastasis and angiogenesis. Our investigation into the roles of miRNAs in lung cancer metastasis and angiogenesis revealed that miR-378 promotes cell invasion while miR-1827 suppresses cell migration, by targeting RBX1, a ubiquitin protein and CRKL, an adaptor protein respectively. In addition, both miR-378 and miR-1827 work in opposite manner to mediate angiogenesis.

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.

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