Suppressing cancer from within using microRNA

By identifying molecules that can stimulate the production of tumour-suppressing microRNAs in the body, the EU-funded RxmiRcanceR project aims to open the door to a new generation of cancer therapies.

Cancer is inextricably linked to genetics, and in most cases, to genetic mutations that occur during life. “These genetic mutations alter the behaviour of cells,” says RxmiRcanceR project coordinator Ethan Galun from the Hadassah Hebrew University Hospital of Jerusalem in Israel. “This usually involves multiple genetic changes in the tissue, which leads to cancer.”

The RxmiRcanceR project, funded by the European Research Council, sought to treat cancer at the genetic level. This is hugely challenging: in the example of pancreatic cancer, it is common to find 60 different mutations in a single case.

“This helps to explain why developing effective therapies is so difficult,” adds Galun. “Even if we can treat a few cancer cells, others will be resistant, and overcome any treatment we give.” To address this, Galun focused on specific genetic elements called microRNAs.
“MicroRNAs are small sequences of RNA molecules that are made from our DNA,” he explains. “What makes microRNAs interesting is that they regulate other genes – and some microRNAs, such as microRNA 122, are known to have tumour-suppressive properties.”

Each microRNA can target many genes at the same time – in the case of microRNA 122, over 200 genes are targeted. This particular microRNA is expressed almost solely in liver cells, with every liver cell containing about 70 000 copies of this microRNA 122.

“What is interesting is that if numbers of microRNAs are increased, then they don’t stay in the cells,” adds Galun. “They are secreted by cells in vesicles called exosomes, which are about the size of a virus.” Galun recognised that regulating the expression of this tumour-suppressing microRNA could be a viable way to treat cancer.

**Gene therapy from within**

To investigate this further, Galun and his team performed high-throughput screening to identify other tumour-suppressive microRNAs. Next, they searched for small molecules capable of elevating the level of these relevant microRNAs in tumour cells and tissues.

A key benefit of microRNA-based therapeutics is that the delivery system is embedded within the body. This could be hugely significant, as researchers interested in gene therapy have long struggled to develop inexpensive and non-invasive delivery methods.

Identifying tumour-suppressing microRNAs, and screening for compounds that increase microRNA expression, could be a highly efficient and effective method of discovering and developing new cancer therapies.

“Pancreatic cancer patients usually die from metastasis, mainly in the liver,” notes Galun. “So imagine if microRNA could be expressed in liver cells, exported out of these cells because of its increased expression, then enter cells in surrounding tissue and start to inhibit tumours.”

The RxmiRcanceR project also discovered that microRNA 122 was found to target a handful of enzymes responsible for the production of triglycerides – a type of fat – in the liver. This could lead to possible new treatments for liver conditions such as non-alcoholic steatohepatitis, now the most common cause of cirrhosis.
The project’s findings are in the process of being published, and Galun expects that patents for effective compounds identified through this work will follow.

**Keywords**

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