Drive to Inhibit 'Master Switch' for Tumor Embryonic Growth

By Sharon Kingman
Staff Writer

LONDON – Identification of a protein that orchestrates many of the changes that permit a normal cell to turn into a cancer cell will open up an entirely new field of cancer therapeutics, the researchers who made the discovery predicted.

The team, from ICREA in Barcelona, Spain, also established a screening system to identify compounds that will inhibit the protein.

Raùl Méndez, group leader at the Institute for Research in Biomedicine in Barcelona, told *BioWorld Today*: "We have found the mechanism that tumors use to reactivate the properties of the embryo. The mechanism involves a protein, which is called CPEB1. It reprograms the cell from behaving as an adult cell in an organ, to behaving like an embryonic cell in a tumor."

It was known that such changes occurred in cancer cells, but until now no one knew exactly how they came about, Méndez said.

The team reported its work in a paper in the Feb. 24, 2013, issue of *Nature*, titled "CPEB1 coordinates alternative 3'-UTR formation with translational regulation."

Together with Frederic Allain and colleagues at the Swiss Federal Institute of Technology (ETH) in Zurich, Méndez and his group also solved the structure of CPEB1 . "We are currently writing up this paper, but now that we have the structure, we can go ahead and design compounds to inhibit this protein," Méndez said.

Méndez's main interest until recently was the regulation of gene expression in embryonic development, particularly that exerted by the CPEB family of RNA-binding proteins. The role of those proteins is to promote cell proliferation – which is, of course, required for growth of the organism – and to maintain the correct degree of plasticity, in order to allow embryonic cells to differentiate into a range of specialized cells.

"But last year," Méndez explained, "we discovered – and reported in *Nature Medicine* – that some members of the same family of proteins are overexpressed in tumors, and thus re-establish a more embryonic pattern of gene expression."

That observation fitted with the team's knowledge that CPEB1 is a master regulator of more than 200 genes related to cell proliferation and tumor progression. When they investigated further, the researchers found that, in cancer cells, CPEB1 binds to and shortens messenger RNA. In the process, it removes vital "stop" signals that normally ensure an adult cell remains quiescent and differentiated. Without the "stop" signals, the way is clear for the cell to manufacture hundreds of RNAs that stimulate proliferation and de-differentiation.

"CPEB1 'takes off the brakes' for these RNAs, allowing them to be made into proteins," Méndez said. "In addition to removing the brakes in the nucleus, however, CPEB1 also accompanies RNA to the cytoplasm, where it speeds up the production of these proteins."

The team also found that the CPEB family of proteins have interchangeable functions in normal cells, but have different roles to each other in tumor cells.

Felice Alession Bava, first author of the paper in *Nature* and a post-doctoral fellow in Méndez's team, said: "This finding is positive from a therapeutic viewpoint, because it means that if you remove CPEB1 from healthy cells, its function can be taken over by any other CPEB protein." In contrast, in tumors, only CPEB1 is able to remove the "brake" that tips the cell into the embryonic pattern of growth. As a result, therapies aimed at inhibiting CPEB1 should be specific for tumor cells and will not, the researchers hope, have too many secondary effects on normal cells.

Méndez and his colleagues already have conducted laboratory tests showing that inhibiting CPEB1 can re-establish normal gene expression in tumor cells. "These strategies are not suitable for clinical use, but we found that when we inhibited CPEB, the tumor cells stop growing and do not become vascularized," Méndez said. "This indicates that the CPEB family of proteins are good therapeutic targets."

It also will be important to find out, he added, which tumors are suitable for that type of treatment. Preliminary studies by the group have identified up to 20 common tumors that show reactivation of the embryonic pattern of growth.

The search is now on to identify therapeutic compounds that will inhibit CPEBs but have little or no effect on

healthy cells.

It will be important to consider the role of CPEB1 when designing other therapeutic strategies, Méndez emphasized. He pointed out that microRNAs – small segments of RNA that can regulate the translation of RNA to protein – bind to the messenger RNAs in precisely the same region that is removed by CPEB1. The *Nature* study lists almost 300 genes that would be affected in that way.

"Many antitumor therapies attempt to interfere with microRNA binding, but we have now revealed that CPEB proteins remove these regions beforehand," Méndez said. "[Our data will allow] the pharmaceutical companies that are developing anti-microRNA compounds to predict whether their targets will be affected in this way."

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