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Need microRNA processing? Get Smad

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Researchers at Tufts University School of Medicine and Tufts Medical Center have found that Smad proteins regulate microRNA (miRNA) processing. Understanding the role of Smad proteins enables researchers to investigate abnormal miRNA processing which is a contributing factor in development of cardiovascular disorders and cancer. The study was published online today in *Nature*.

"We found that Smad proteins, the signal carriers of a group of proteins that help regulate cells, promote the processing of a subset of microRNA, including miR-21. Smad proteins control the processing of miRNA from a primary copy of RNA (pri-miRNA) to precursor miRNA (pre-miRNA)," explains corresponding and senior author Akiko Hata, PhD, assistant professor at Tufts University School of Medicine and a member of the biochemistry program faculty at the Sackler School of Graduate Biomedical Sciences.

"Smad proteins move to the nucleus of the cell and interact with a specific complex, called the Drosha microprocessor complex, to promote the processing of pri-miR-21 to pre-miR-21, eventually leading to an increase in mature miR-21 levels."

"Mature miR-21 targets a tumor suppressor gene important for programmed cell death in both cancer cells and in smooth muscle cells, the cells that help our veins and arteries contract and relax," contextualizes Brandi Davis, first author, and PhD candidate in the department of biochemistry at Tufts University School of Medicine. "Abnormal miRNA processing is a contributing factor in cardiovascular

disorders and cancer, yet little is known about its regulation."

Hata, Davis and colleagues designed a series of experiments to determine how members of a super-family of growth factors, called the transforming growth factor β (TGFβ) family, which is a group of proteins that help regulate cellular functions, can cause miRNA levels to increase. By exposing cells to members of the TGFβ family, the researchers were able to observe that, over time, levels of pre-miR-21 and mature miR-21 increased, while levels of pri-miR-21 did not change.

"Since pri-miR-21 levels did not change, we concluded that the TGFβ family of growth factors doesn't begin to play a role in miRNA processing until the pri-miRNA to pre-miRNA step," explains Hata, who is also an investigator in the Molecular Cardiology Research Institute (MCRI) at Tufts Medical Center.

"Smad proteins were thought to act exclusively by regulating the transcription of DNA into messenger RNA (mRNA) in response to TGFβ signaling. This finding reveals a new role of Smad proteins as regulators of miRNA processing," comments Giorgio Lagna, PhD, co-author, investigator in the MCRI at Tufts Medical Center and also an assistant professor at Tufts University School of Medicine. "If we want to generate a drug that regulates signaling by TGFβ, we now have the option to target different pathways downstream of TGFβ and achieve much more specific outcomes."

MiRNAs are small gene products that regulate gene expression by interaction with mRNA. The role of mRNA in a cell is to carry the instructions for making proteins from the DNA in the nucleus to another part of the cell where the instructions are carried out and the proteins are made.

"Thus, cells with abnormal miRNA levels may have abnormal protein levels, putting the organism at risk for many diseases including cancer and cardiovascular disorders. More research needs to be done to elucidate further the roles of miR-21 and other miRNA molecules," explains Hata "because better understanding of how miRNAs effect disease may lead to a clearer understanding of disease initiation and progression."

Source: Tufts University, Health Sciences