# When cells reach out and touch

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MicroRNAs are single-stranded snippets that, not long ago, were given short shrift as genetic junk. Now that studies have shown they regulate genes involved in normal functioning as well as diseases such as cancer, everyone wants to know: What regulates microRNAs?

Scientists at Johns Hopkins were surprised to find an elegantly simple answer: touch. In a new study, published online April 9 in the Proceedings of the National Academy of Sciences, the researchers discovered that cell-to-cell contact revs up the manufacture of these small but mighty molecules.

"This study documents one of the very few clear examples of a stimulus that directly influences the global efficiency of microRNA production," says Josh Mendell, M.D., Ph.D., an assistant professor in the McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University School of Medicine. "No one anticipated, including us, that the production of microRNAs is linked to how densely cells are packed together."

In what Mendell describes as an "accidental discovery," the team was studying contact inhibition: a phenomenon in which non-cancerous cells growing in a dish stop multiplying when they touch each other. Cancer cells, on the other hand, lose contact inhibition and continue to proliferate even when they're touching. The researchers suspected that microRNAs might play a role in contact inhibition because whenever they studied these enigmatic bits -- only about 20 or so genetic building blocks comprise a microRNA -- they always saw more in the tissues of animals, where cells are packed together, relative to the amount they

found in isolated cells growing in culture.

To investigate, the team grew cancer cells and non-cancer cells to increasing densities in culture and, using a tool developed in the Mendell laboratory, measured the abundance of hundreds of microRNAs simultaneously. This analysis revealed that the more densely the cells were packed together, the more microRNA was produced in each cell.

The scientists then examined microRNA production in five additional commonly studied human and mouse cell lines, including human breast cancer cells, human colorectal cancer cells and human pancreatic cancer cells. They also tested fruit fly cells to determine whether or not the phenomenon is restricted to mammals.

In all tested cell lines, including the fruit fly cells, scientists observed a dramatic increase in microRNA abundance with increasing cell density.

"All evidence points to the fact that physical contact -- when cells actually touch each other -- is the critical factor that revs up the production of microRNAs," Mendell says. "Through additional experiments, we were able to identify the specific molecular steps at which microRNA production is affected. We expect that this phenomenon will profoundly influence how cells behave in normal development and disease."

The team's finding has practical importance for researchers who are investigating a range of biological processes that are most conveniently studied in cells growing in culture, Mendell says: "Little did we know the manufacture of microRNAs was so potently influenced simply by growing cells to different densities. We now recognize that this is a critical parameter that must be closely monitored when performing experiments with microRNAs in tissue culture."

A better understanding of how microRNA production is regulated is important because a reduction in the abundance of these molecules has been linked to the development of certain cancers. To date, one barrier to understanding how microRNAs are regulated in normal development and in disease states has been the lack of a simple system by which scientists could turn on and off a molecular pathway that controls microRNA production. Now, it seems, they may be able to toggle that pathway using cell-to-cell contact.

"If we can identify the mechanisms through which microRNA production is regulated in normal settings, such as under conditions of extensive cell-cell contact, we can then ask whether the same mechanisms block microRNA manufacture in diseases such as cancer," Mendell says. "This might allow the development of small molecules or other methods to turn microRNA production back on for therapeutic benefit."

Source: Johns Hopkins Medical Institutions