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MicroRNA network study implicates rewired interactions in cancer

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Genes interact in complex networks that govern cellular processes, much like people connect a social network through relationships. Researchers are now discovering how biological networks change and are rewired in cancer. In a study published today in *Genome Research*, scientists have analyzed the genetic networks of microRNAs in tumors, shedding light on how interactions go awry in disease.

MicroRNAs (miRNAs) are short RNA molecules encoded by plant, animal, and viral genomes that have garnered significant interest for their ability to regulate gene expression. Many critical biological processes are regulated by miRNAs, and recent evidence has shown that alterations in miRNA expression is involved in human tumor development and metastasis.

Investigations into the role of miRNAs in cancer up until now have largely focused on the function and expression of individual miRNAs, but miRNA function is more complex and interwoven. "MicroRNAs were always considered as singles, generally unrelated to each other in the miRNA world," said Ohio State University researcher Carlo Croce. "We did not know much about how miRNAs cooperate."

Because a single miRNA is likely to regulate many genes, and each target gene may be regulated by more than one miRNA, Croce and an international team of colleagues suggested that in order to capture the complex patterns of miRNA expression in cancer, the system must be thought of as a "social network" that coordinates the delicate balance of

gene regulation.

Croce explained that in healthy tissues, miRNAs are connected in networks and different cell types have different network connections. In cancer, it is likely that normal network interactions have become disrupted or rewired, contributing to disease.

The group analyzed patterns of miRNA expression levels in a large set of normal and cancerous tissue samples, mapping groups of miRNAs exhibiting highly related patterns of expression. Once relationships were recognized, they could then build a genetic network revealing the most highly connected miRNAs, called "hubs."

When comparing the miRNA networks built from normal tissues to the networks built from tumor samples, Croce's team found cases where the miRNA networks have been reprogrammed in cancer. In some cases, they found that the highly connected miRNA hubs changed between cancer and normal tissues.

They also identified even more extreme cases of tumor network changes. "Groups of miRNAs go awry and exit from the 'social network' altogether," Croce said. "In solid cancers there can be a few, or more, groups of such misbehaved miRNAs, while in leukemias we found only one or two." Some of these "unsocial" miRNAs have well-known roles in cancer, but others had not been implicated until now.

This work is particularly significant in that novel cancer genes have been discovered utilizing a strategy based on relationships, rather than up or down regulation of expression. "The miRNAs we discovered can now be used as targets for drug development," Croce added, "or to pinpoint candidate proteins, which, in turn, they regulate."

More information: The manuscript will be published online and in

print on May 3, 2010. Its citation is as follows: Volinia S, Galasso M, Costinean S, Tagliavini L, Gamberoni G, Drusco A, Marchesini J, Mascellani N, Sana ME, Abu Jarour R, et al. Reprogramming of miRNA networks in cancer and leukemia. Genome Res
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