Living microprocessor tunes in to feedback

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MicroRNAs (miRNAs) – tiny strands of non-protein-coding RNAs – start off as long strands of precursor miRNAs. These long strands get chopped up by a special kind of machinery, the "Microprocessor" complex, to transform them into their shorter functional form. The resulting miRNAs bind to messenger RNA (mRNAs) molecules, inhibiting their protein production capacity and thus regulating the levels of hundreds of different proteins.

But the Microprocessor complex can also cut up other forms of RNA, such as mRNAs, which sometimes generate a transient structure that resembles the target site of miRNAs. Cleaving the wrong RNAs could prove disastrous for the organism.

In a paper recently published in *Nature Structural and Molecular Biology*, Dr. Eran Hornstein, Prof. Naama Barkai and former Ph.D. students Drs. Omer Barad and Mati Mann of the Molecular Genetics Department focus on understanding how the Microprocessor machinery balances the interplay between efficiency and specificity in the production of miRNAs. "On the one hand, it should not be overly efficient, as this may come at the cost of also cleaving unwanted nonspecific RNA substrates. On the other hand, it should not be too 'picky' because exaggerated specificity comes with the risk of not sufficiently processing genuine miRNAs," says Hornstein.

In an interdisciplinary project, the scientists used mathematical modeling to characterize the Microprocessor system and then tested their theories in cells. They predicted that the balance between efficiency and specificity would be maintained via a feedback loop in which the Microprocessor detects the amount of [precursor](#) [miRNA](#) available in the cell and alters its own production accordingly.

Checking this premise in mouse and human tissue, the researchers were able to show that the Microprocessor is indeed attuned to levels of precursor miRNA, upping its own production if the cell is inundated with precursor miRNA, or halting production in response to a decrease in the flow of precursors. This is achieved by the digestion of Dgcr8 mRNA, which structurally mimics miRNA. By keeping levels in line with precursor miRNAs, the Microprocessor thus reduces its chances of chopping off-target RNAs.

Since small RNAs are produced synthetically as possible new therapies for a number of diseases, this research may direct efforts to efficiently produce such therapies in the future. In addition, many other biological systems need to balance efficiency with specificity, and the team's findings suggest that many may do so in a similar way.

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