RNA DYNAMICS

Destabilizing mRNAs promotes metastasis

> destabilization of mRNAs by a protein that binds structural elements of mRNAs can regulate cancer progression

A new study has shown that destabilization of mRNAs by a protein that binds structural elements of mRNAs can regulate cancer progression.

Although mRNA transcript stability changes have previously been implicated in cancer progression, the underlying mechanisms remained unclear. Goodarzi *et al.* investigated post-transcriptional modulators of RNA activity and stability by determining the decay rates of mRNAs in the non-metastatic parental breast cancer cell line MDA-MB-231 (MDA) and an *in vivo*-selected highly metastatic subclone (MDA-LM2). They discovered a family of structural RNA stability elements (sRSEs) embedded in transcripts that had reduced stability in MDA-LM2 cells, relative to MDA cells. This suggests that these sRSEs may mediate transcript stability differences. The authors further hypothesized that there is a *trans* factor that binds to these sRSEs and can mediate stability.

To test this hypothesis, they devised intracellular decoys (consisting of tandem repeats of the most common sRSE) to prevent the *trans* factor from binding and destabilizing endogenous sRSE-containing transcripts in cell culture. As expected, they saw upregulated expression levels of sRSE-containing transcripts in the presence of the decoys, confirming the existence of a *trans* factor. To determine its identity, the authors used a computational approach to search in published breast cancer gene expression profiles for RNA-binding proteins (RBPs) that had expression profiles that correlated with those of sRSE-containing transcripts. This identified three RBPs, including TARBP2. Further experiments verified that knockdown of TARBP2 increases the levels of sRSE-containing transcripts.

The authors also found increased levels of TARBP2-bound transcripts in metastatic cell lines and, in accordance with this, highly metastatic human breast tumours had higher levels of TARBP2 expression relative to lower grade tumours. Moreover, experiments using tail vein-injection and orthotopic mouse models of metastasis showed that cells with knocked down TARBP2 generated significantly fewer metastatic nodules compared with cells with wild-type TARBP2. In addition, in orthotopic mouse models of breast cancer, primary tumours derived from cells with knocked down TARBP2 did not have reduced growth relative to primary tumours with wild-type TARBP2. Together, these results suggest that the role of TARBP2 in cancer is specific to metastasis.

To determine specific targets of TARBP2 that are relevant to metastasis, the authors screened MDA-LM2 cells for transcripts that were increased following TARBP2 knockdown. Surprisingly, they identified two genes that had previously been associated with Alzheimer's and Huntington's disease, namely amyloid precursor protein (*APP*) and zinc finger protein 395 (*ZNF395*). Silencing either of these genes in TARBP2-negative MDA-LM2 cells enhanced metastasis following tail vein injection. Furthermore, patients whose tumours had a reduced expression of *APP* or *ZNF395* had lower survival rates than patients with higher levels of these genes.

Collectively, this study identifies TARBP2 and its downstream targets *APP* and *ZNF395* as novel factors that are important for breast cancer metastasis, and it highlights RNA stability as a crucial mechanism in this process.

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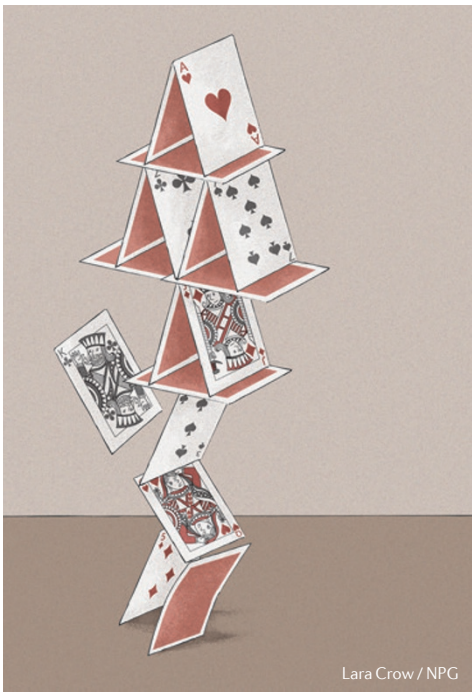
ORIGINAL RESEARCH PAPER Goodarzi, H. *et al.* Metastasis-suppressor transcript destabilization through TARBP2 binding of mRNA hairpins. *Nature* http://dx.doi.org/10.1038/nature13466 (2014)



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