Cell Cycle 12:16, 2523–2523; August 15, 2013; © 2013 Landes Bioscience

Found in transcription

FOXO1 upregulates miRNAs on chromosome X

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The phosphatidylinositol-3-kinase (PI3K)/AKT signaling pathway is one of the most fundamental regulators of cellular functions.[1] There is hardly a cellular process that is unaffected by this enzymatic cascade. Hyperactivation of PI3K and AKT is one of the hallmarks of cancer, and new contributions of activated AKT to oncogenesis are still being discovered. Among the best-researched targets of AKT phosphorylation are transcription factors of FOXO family.[2] FOXO regulate genes that control cell metabolism, suppress cell growth, and detoxify dangerous chemical moieties, such as reactive oxygen species. AKT phosphorylation inactivates FOXO, making a cell more likely to proliferate, but also more vulnerable to oxidative stress. AKT-independent regulation of FOXO and complex feedback mechanisms between FOXO and AKT have been described as well,[2] and these mechanisms may determine success or failure of some for the emerging anticancer therapies.[3]

Important insights into molecular pathology of cancer and other disorders could be gained through a better understanding of which targets are responsible for the biological consequences of FOXO suppression or induction. Previously, these insights were sought from the patterns of expression of protein-coding genes. This yielded much of what is known about FOXO function today. However, it is increasingly clear, that a comprehensive view on a biological role of a transcription factor has to include non-protein coding targets as well. Among the latter, microRNAs have attracted the most attention as important regulators of various processes, including cancer[4] and senescence.[5] MicroRNAs (miRNAs) are 22-nt-long non-coding RNAs found in plants and animals that inhibit gene expression by targeting mRNAs to degradation or inhibiting translation of select mRNAs.[4] The human genome encodes thousands of miRNAs, which may regulate a large fraction of human transcriptome. In their recent report in *Aging*, the group of Dr Kandel has taken a look at the miRNAs that are induced by FOXO1.[6] They report that a group of the most FOXO1-sensitive miRNAs (miR-506, miR-507, miR-508, miR-513a-1, miR-513a-2, miR-513b, and miR-513c) come from the same fragment of human X chromosome. While it is not clear whether the miRNAs are produced independently or from the same primary transcript, the effect of FOXO1 appears to be direct, and the polymerase responsible for their production is RNA polymerase II. Importantly, the miRNAs are controlled by the PI3K pathway in cancer cells, and their expression is elevated by a PI3K inhibitor. Most remarkably, the predicted targets of these miRNA include a nearly complete list of "who's who" in two major signaling pathways: that of MAP kinases, and that of PI3K itself. Since most of those proteins are produced in an inactive form and require activation by additional stimuli, the identified miRNAs might fine-tune the responsiveness of cells to a variety of growth- and survival-promoting signals. The role of the miRNAs as PI3K-sensitive brakes on tumor progression is consistent with the observed correlations between these miRNAs and the clinical features of human cancers.[7] Intriguingly, the miRNAs are also predicted to target FOXO1 and FOXO3, suggesting the existence of a negative feedback in regulation of these proteins.

Of course, these predictions remain to be firmly validated. Furthermore, miRNAs may also act at the level of chromatin structure, rather than translational control,[5] so that the full biological role of the FOXO1-dependent miRNAs is far from clear. Another remaining question is what other mechanisms, if any, control expression of the same miRNAs. For example, do they fall under the category of genes that are differentially regulated by different forkhead proteins?[8] The question of alternative regulation is directly relevant to the ability of the miRNAs to serve as indicators of the status of the PI3K–AKT–FOXO axis. Since miRNAs are relatively easy to measure in a variety of biological samples, the chromosome X cluster represents an attractive candidate to be evaluated as a prognostic and diagnostic marker in human malignancies.

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Submitted: 06/08/13; Accepted: 06/10/13

http://dx.doi.org/10.4161/cc.25829

Comment on: Singhal R, et al. Aging (Albany NY) 2013; 5:347-56; PMID:23748164