Aikaterini Kontrogianni-Konstantopoulos, Madridge J Cancer Stud Res. 2016
http://dx.doi.org/10.18689/2640-5180.a1.002

Giant obscurins: Novel tumor and metastasis suppressors in breast cancer

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Obscurins, encoded by the single *OBSCN* gene, are giant cytoskeletal proteins containing tandem adhesion and signaling domains, including an active RhoGEF motif that directly binds and activates RhoA. The *OBSCN* gene is highly mutated in breast cancer resulting in a 2-fold reduction of its mRNA levels. Consistent with this, obscurin proteins are nearly lost from breast cancer cell lines and human biopsies, independently of their hormonal status or molecular differentiation. Loss of giant obscurins from breast epithelial cells confers them with a survival and growth advantage following exposure to common chemotherapies. Obscurin-depleted breast epithelial cells fail to form adhesion junctions, undergo epithelial-to-mesenchymal transition and generate primary and secondary mammospheres bearing markers of cancer-initiating cells. Moreover, obscurin-deficient breast epithelial cells display markedly increased motility as a sheet in 2-dimensional (2D) substrata and individually in confined spaces, increased invasion in 3D matrices, and extend microtentacles mediating the attachment of circulating tumor cells to the endothelium, an advantage that persists even after paclitaxel treatment. More importantly, loss of giant obscurins from breast epithelial cells promotes primary tumor formation and lung colonization *in vivo*. These major phenotypic alterations appear to be the result of reduced RhoA activity and increased PI3K/Akt activity. Collectively, our findings reveal that loss of giant obscurins from breast epithelium results in disruption of cell–cell contacts and acquisition of a mesenchymal phenotype that leads to enhanced tumorigenesis, migration and invasiveness *in vitro* and *in vivo* by affecting RhoA- and PI3K/Akt-mediated processes. In addition, our data suggest that loss of obscurins may represent a selective advantage for breast cancer cells during metastasis, and that treatment with paclitaxel may exacerbate this advantage by preferentially allowing obscurin-deficient stem-like cells to attach to the endothelium at distant sites, a first step towards colonizing metastatic tumors. To the contrary, treatment of obscurin-depleted breast cancer cells with PI3K inhibitors, currently in phase III clinical trials, appears to be highly beneficial by reducing their survival, growth, motility and invasive capabilities.

Biography:

Aikaterini Kontrogianni-Konstantopoulos received her Ph.D. from the Department of Cell Biology at Baylor College of Medicine in Houston, TX. After graduating from Baylor, she joined the laboratory of Dr. E.J. Benz, Jr., in the Division of Hematology, at Johns Hopkins University, School of Medicine as a post-doctoral fellow. In 2007, she joined the Department of Biochemistry and Molecular Biology in the University of Maryland School of Medicine as Assistant Professor, and in 2012 was promoted to Associated Professor. Her research focuses on the elucidation of the roles of cytoskeletal and membrane-associated proteins as structural and signaling mediators. Using the muscle and epithelial cell as model systems, my laboratory has pioneered the molecular and functional characterization of the obscurin subfamily and its binding partner Myosin Binding Protein-C slow in health and disease. Her research has been funded by several organizations, including NIH, Muscular Dystrophy Association and American Heart Association.