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Giant obscurins act upstream of the PI3K/Akt pathway in breast epithelial cells

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Obscurins, encoded by the single *OBSCN* gene, are giant cytoskeletal proteins containing tandem adhesion and signaling domains. The *OBSCN* geneis highly mutated in multiple types of cancer, including breast cancer, resulting in a 2-fold reduction of its mRNA levels. Consistent with this, obscurin proteins are nearly lost from human breast cancer cell lines and advanced stage 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-mesenchymaltransition (EMT),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, and increased invasion in3D matrices. They are also capable ofextending 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,at least in part ofincreased PI3K activity, a key regulator of tumorigenesis and metastasis. Pharmacological and molecular inhibition of the PI3K/Akt pathway in obscurin-depletedbreast epithelial cells results in reversal of EMT, (re)formation of cell-cell junctions,diminished mammosphere formation, and decreased cell migration and invasion. Coimmunoprecipitation,pull-down, and surface plasmon resonance assays revealedthat obscurins are in a complex with the PI3K/p85 regulatory subunit, and that theirassociation is direct and mediated by the obscurin-PH domain and the PI3K/p85-SH3domain with a K_D of ~50 nM. We therefore postulate that giant obscurins act upstreamof the PI3K/Akt cascade in normal breast epithelial cells, regulating its activation throughbinding to the PI3K/p85 regulatory subunit.

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.