PS8 Invited

# Tyrosine phosphatases and their binding proteins in cancer

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The SH2 domain-containing protein-tyrosine phosphatase Shp2 is required for activation of the Ras/Erk pathway in response to most growth factors and cytokines. Shp2 also has variable, receptor- and cell context-dependent effects on other downstream signaling cascades. All of these actions require recruitment of to one or more binding proteins, including scaffolding adapters such as Gab proteins. Consistent with its positive signaling role, germline autosomal dominant mutations of Shp2 cause the human genetic disease Noonan syndrome (NS). A subset of NS patients develop myeloproliferative disorders (MPD), particularly, Juvenile Myelomyelogenous Leukemia (JMML), but also Acute Lymphoblastic Leukemia (ALL). Somatic Shp2 mutations affecting many of the same residues have been found in 35% of sporadic JMML and at lower frequency in other MPD and lymphoid leukemias. Their location within Shp2 and the genetics of NS and JMML suggest these are gain-of-function mutants. Whether all NS phenotypes result directly from Shp2 mutation, the mechanism(s) by which NS mutations perturb development and the relationship between particular Shp2 mutations and NS phenotypes remain unclear. To address these issues, we previously characterized a large allelic series of recombinant Shp2 mutants and generated murine models for NS and JMML. Our results show that disease-associated Shp2 mutants have distinct biological properties, and indicate that leukemogenic transformation requires recruitment to Gab2 and results from hyper-activation of the Ras/Erk, PI3K/Akt/Tor, and Stat 5 pathways. In contrast to the fairly frequent occurrence of Shp2 mutations in leukemia, such mutations are rare in solid tumors. However, in previous work, we observed that Gab2 is over-expressed in 25–30% of human breast tumors, and is located within the 11q13 region amplified in 10–15% of such tumors. We investigated the role of Gab2 over-expression ex vivo and in mouse models. Gab2 expression drives increased expression of MCF10A mammary epithelial cells in 3D culture, and can collaborate with anti-apoptotic genes to cause luminal filling reminiscent of a ductal carcinoma in situ-like phenotype. Gab2 can also collaborate with Her2/Neu to confer a loss of acinar polarity and an invasive like phenotype. Experiments with Gab2 mutants and Shp2 siRNAs indicate that Gab2 acts via Shp2 and drives hyper-activation of Erk. Treatment with Erk inhibitors can block Gab2-evoked proliferation and collaboration with HER2. Furthermore, the level of Gab2 (as set either by Gab2 transgenic or knockout mice) modulate susceptibility to Her2/Neu-evoked murine mammary tumors. Finally, FISH analysis indicates that amplification is a major cause of Gab2 over-expression in vivo. Our results suggest that assessment of Gab2 levels may important prognostic/therapeutic information in human breast cancer patients. Moreover, increased activation of the Shp2/Ras/Erk pathway, caused either by Shp2 mutation or by over-expression of Shp2 binding proteins, is a common theme in neoplastic disease.