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The role of focal adhesion kinase in mammary stem cell and tumorigenesis

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An emerging concept in breast tumorigenesis is that mammary stem cells (MaSCs) with dysregulated selfrenewal ability are likely to be the critical cells that propagate tumors. Thus, the characterization of key signaling proteins that regulate MaSC self-renewal and maintenance will be crucial for the development of novel treatment strategies targeting the mammary cancer stem cell (MaCSC) pool. Focal adhesion kinase (FAK), an intracellular tyrosine kinase integrating signals from integrin and growth-factor receptors, plays key roles in cell adhesion, survival, proliferation, migration and angiogenesis. Elevated FAK expression and activation have been found in different stages of breast cancer, yet the role of intrinsic FAK to promote mammary tumorigenesis *in vivo* remains to be defined. Recent identification of both alpha6 and beta1 integrins as surface markers of mouse MaSCs suggests that FAK-mediated integrin signaling may play an important role in these cells. Consistent with this, we found increased FAK activation in the mouse and human mammary epithelial cells (MaECs) enriched in MaSCs and MaCSC using independent markers. To investigate the role and mechanisms of FAK and its associated signaling pathways in MaSCs, we have created FAK conditional knockout mice (MFCKO) in the mammary gland by using Cre-loxP approach. Analysis of primary MaECs from MFCKO and control mice indicated that inactivated of FAK significantly decreased the MaSCs in the MFCKO mice. Using a mouse breast cancer model, we further showed that the decrease of the MaSCs in the MFCKO mice correlated with a suppression in the development of breast cancer in these mice. These results suggested an important role for FAK signaling pathways in the regulation of MaSCs self renewal and breast cancer development.

***Keywords*:** FAK, mammary stem cells, signal transduction, breast cancer

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