The oncogenic properties of Amot80 in mammary epithelia

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Abstract:

While breast cancer is the second most commonly diagnosed cancer worldwide, its causes and natural history are not well defined. The female mammary organ is unique in that it does not reach full maturity until the lactation cycle following pregnancy. This cycle entails extensive growth and reorganization of the primitive epithelial ductal network. Following lactation, these same epithelial cells undergo an equally extensive program of apoptosis and involution. The mammary gland's sensitivity to pro-growth and pro-apoptotic signals may partly explain its proclivity to develop cancers. For epithelial cells to become transformed they must lose intracellular organization known as polarity as differentiated epithelial tissues are refractory to aberrant growth. One essential component of epithelial to mesenchymal transition is the intrinsic capacity of cells to repurpose polarity constituents to promote growth. Recently, a novel mechanism of organ size

control has been shown to repurpose the apical junctional associated protein Yap into the nucleus where it functions as a transcriptional coactivator promoting growth and dedifferentiation. The focus of my work has been on a family of adaptor proteins termed Amots that have been shown to scaffold Yap and inhibit growth signaling. Specifically, I have shown that the 80KDa form of Amot, termed Amot80, acts as a dominant negative to the other Amot proteins to promote cell growth while reducing cell differentiation. Amot80 was found to promote the prolonged activation of MAPK signaling. Further, Amot80 expression was also found to enhance the transcriptional activity of Yap. This effect likely underlies the ability of Amot80 to drive disorganized overgrowth of MCF10A cells grown in Matrigel? ™. Overall, these data suggest a mechanism whereby the balance of Amot proteins controls the equilibrium between growth and differentiation within mammary epithelial tissues.

Description:

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