

ABSTRACT

THE EFFECT OF PROGESTIN ON MAMMARY GLAND BRANCHING

MORPHOGENESIS IN VITRO

By

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Mouse mammary organoids that express progesterone receptor A (PRA) produce tubules in response to hepatocyte growth factor (HGF) when cultured in collagen gels. These structures resemble ducts in the mouse mammary gland. When treated with the combination of HGF and the synthetic progestin, promogestone (R5020), tubulogenesis is stunted to form shorter tubules that resemble sidebranches in early pregnancy. It was hypothesized that R5020 reduces early HGF/cMet signaling to produce sidebranch-like tubules. Therefore, the HGF-induced pathway controlling early extension formation was determined and how R5020 altered HGF/cMet signaling was analyzed. Using molecular inhibitors and shRNA, it was found that HGF activates Rac1 to form extensions in the first step of tubulogenesis and that Rac1 activity is Src and FAK dependent. In addition, it was discovered that R5020 increases extracellular laminin to reduce the Src, FAK and Rac1 pathway leading to reduced extensions. This is likely mediated through PRA, as PRA is the predominant PR isoform expressed in organoids. This may in part explain blunted tubulogenesis observed with combined HGF and R5020 treatment and further supports a role for PRA in sidebranching during pregnancy.