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Met signaling regulates growth, repopulating potential and basal cell-fate commitment of mammary luminal progenitors

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Despite expressing stem cell markers, basal-like breast tumors are proposed to derive from luminal progenitors, which are downstream of stem cells in the mammary epithelial hierarchy. However, the mechanisms that regulate this backward transition remain unclear. Using mouse models, we found that the Met receptor for HGF, which is frequently hyperactivated in basal-like tumors, is preferentially expressed in luminal progenitors. Constitutive activation of Met in purified progenitors stimulated clonogenic activity in vitro and conferred repopulating potential in vivo, leading to enhanced ductal side branching and hyperplasia. This aberrant morphogenesis was accompanied by an increase in the number of cells with basal characteristics and a concomitant reduction of cells expressing markers of terminal luminal differentiation. Hence, deregulated Met signaling targets luminal progenitors for expansion, impairs their differentiation towards the mature luminal phenotype and enables their commitment towards the basal lineage. These results underscore a critical role for Met in encouraging deregulated proliferation and basal plasticity of normal luminal progenitors, which might be permissive for sustaining the functional and phenotypic properties of basal-like tumors.

Keywords: Met tyrosine kinase receptor, mammary morphogenesis, stem cells, differentiation, basal-like breast cancer, mouse models