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Using a mouse model of breast cancer driven by Trp53 loss, Zhang and colleagues investigated the functional interaction between CD29hiCD24hi tumor-initiating cells (TIC) and a mesenchymal-like CD29hiCD24lo tumor cell subpopulation. These CD29hiCD24lo cells promoted the self-renewal capacity of TICs via secretion of soluble factors including WNT2 and chemokine (C-X-C motif) ligand 12 (CXCL12). Depletion of WNT2 and CXCL12 in CD29hiCD24lo niche cells or of the corresponding receptors in TICs impaired the ability of CD29hiCD24lo cells to promote TIC self-renewal in vitro. Furthermore, in limiting dilution transplantation assays, CD29hiCD24lo niche cells enhanced the tumor-initiating potential of TICs, which was decreased by knockdown of WNT2 in the CD29hiCD24lo subpopulation. These data highlight the importance of paracrine crosstalk between different tumor cell subpopulations in promoting tumor initiation. For details, please see the article by Zhang and colleagues on page 520.