Extracellular vesicles transmit epithelial growth factor activity in the intestinal stem cell niche

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Extracellular vesicles (EV) are membrane‐surrounded vesicles that represent a novel way of intercellular communication by carrying biologically important molecules in a concentrated and protected form. The intestinal epithelium is continuously renewed by a small proliferating intestinal stem cell (ISC) population, residing at the bottom of the intestinal crypts in a specific microenvironment, the stem cell niche. By using 3D mouse and human intestinal organoids, we show that intestinal fibroblast‐derived EVs are involved in forming the ISC niche by transmitting Wnt and epidermal growth factor (EGF) activity. With a mouse model that expresses EGFP in the Lgr5+ ISCs, we prove that loss in ISC number in the absence of EGF is prevented by fibroblast‐derived EVs. Furthermore, we demonstrate that intestinal fibroblast‐derived EVs carry EGF family members, such as amphiregulin. Mechanistically, blocking EV‐bound amphiregulin inhibited the EV‐induced survival of organoids. In contrast, EVs have no role in transporting R‐Spondin, a critical niche factor amplifying Wnt signaling. Collectively, we prove the important role of fibroblast‐derived EVs as a novel transmission mechanism of factors in the normal ISC niche.