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Dickkopf-3 potentiates YAP/TAZ signalling to promote aggressive behaviours in cancer-associated fibroblasts

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NOTE - I suggest Tumour Microenvironment Section for this study (I could not choose from above).

Cancer-associated fibroblasts (CAFs) constitute a significant proportion of the stromal compartment in many solid tumours. As opposed to normal fibroblasts (NFs), CAFs present a pathological activated phenotype that enables them to generate environments for cancer cells to propagate and acquire aggressive phenotypes. In CAFs, signalling pathways such as Heat-Shock Factor 1 (HSF1) and YAP/TAZ are activated in response to cellular stress and mechanical cues, respectively. In turn, HSF1 affects signalling to cancer cells promoting tumour growth whereas YAP promotes cancer cell invasion and angiogenesis through remodelling of the extracellular matrix (ECM). Thus, each pathway is regulated by different mechanisms and controls a defined set of functions; whether these molecular events are interconnected to regulate the emergence of a fully activated CAF phenotype is not known. Here, we show that stromal expression of Dickkopf-3 (DKK3) is associated with aggressive breast, colorectal and ovarian cancers. We demonstrate that DKK3 is a HSF1 effector that modulates the pro-tumorigenic behaviour of CAFs *in vitro* and *in vivo*. DKK3 orchestrates a concomitant activation of β-catenin and YAP/TAZ. Whereas β-catenin is dispensable for CAF-mediated ECM remodelling, cancer cell growth and invasion, DKK3-driven YAP/TAZ activation is required to induce tumour-promoting phenotypes. Mechanistically, DKK3 acts via canonical Wnt signalling by interfering with the negative regulator Kremen and increasing the cell-surface levels of LRP6. This work reveals an unpredicted link between HSF1, Wnt signalling and YAP/TAZ relevant for the generation of tumour-promoting CAFs.

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