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Silencing the pro-tumour crosstalk between cancer-associated fibroblasts and the tumour microenvironment in cancer.

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Cancers develop within complex tumour microenvironments (TMEs), composed by genetically stable stromal cells and the extracellular matrix (ECM), that enable tumour progression, dissemination, and therapeutic resistance. Cancer-associated fibroblasts (CAFs) constitute a significant proportion of the stromal compartment in many solid tumours and are key players in ECM remodelling and signalling to cancer, endothelial and immune cells, actively affecting cancer cell invasion and growth. Thus, CAFs are emerging as an alternative therapeutic target with great potential that, contrary to immunotherapies or antiangiogenic therapies, has not been exploited in the clinic.

Previous studies informed of a constitutive activation of Wnt signalling in CAFs when compared to normal fibroblasts (NFs) in different types of tumours. Canonical Wnt operates through different effectors, including members of the Hippo pathway (YAP/TAZ) as well as ?-catenin. YAP has already been described as a pivotal element in controlling mechanotransduction signalling that promotes aggressive phenotypes in CAFs. However, the role of ?-catenin in the control of the pro-tumour functions of CAFs still needs to be fully characterized.

To address this question, we have employed gain-of-function and loss-of-function models of ?-catenin activity in NFs/CAFs. A thorough *in vitro* methodology was developed, including ECM remodelling, invasion, and proliferation of tumoral cells, analysis of CAFs interaction with other stromal cells such as immune cells, as well as preclinical models in which pathobiological functions of CAFs in tumoral progression and dissemination can be evaluated.

Our data shows that the aberrant activation of ?-catenin in CAFs plays a critical role in modulating CAF-cancer cell crosstalk by controlling the production of factors that affect cancer cell growth and motility, suggesting a potential modulation of cancer aggressiveness/EMT. Similarly, we also have observed that aberrant ?-catenin signalling in CAFs modulate macrophages towards pro-tumoral phenotypes. Indeed, M2-like macrophages are associated with the generation of immune-suppressive TMEs in cancer, and our data correlates a significant reduction in the cytotoxic CD8+ T-cells with an increased signalling of ?-catenin in CAFs.

Overall, our data suggest that ?-catenin activity may be a key regulator of paracrine signalling between CAFs and their environment, actively contributing to the chemical remodelling of the TME. We propose that the inhibition of this signalling cascade (or any associated mechanism) in CAFs may block their capacity to generate aggressive TME and significantly affect the tumour growth and increase the response to therapy.