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SCF^{FBXW7} LINKS INTESTINAL STEM CELLS TO EMT IN CARCINOGENESIS

Abdolrahman Shams Nateri
University of Nottingham, United Kingdom

Colorectal cancer (CRC) patients develop recurrence after chemotherapy owing to the survival of stem cell-like cells referred to as cancer stem-like cells (CSCs). The origin of CSCs is linked to the epithelial-mesenchymal transition (EMT) process. Currently, it remains poorly understood how EMT programs enable CSCs residing in the tumour microenvironment to escape the effects of chemotherapy. Our recent study identifies that the microenvironment surrounding intestinal stem cells, via FBXW7/ZEB2 defects may contribute to tumour formation and progression. Using a modified yeast-2-hybrid system and 2D gel-based proteomics methods, we show that the E3-ubiquitin ligase FBXW7 directly binds and degrades the EMT-inducing transcription factor ZEB2 in a phosphorylation-dependent manner. Loss of FBXW7 induces an EMT that can be effectively reversed by knockdown of ZEB2. The FBXW7-ZEB2 axis regulates such important cancer cell features, as stemness/de-differentiation, chemoresistance, and cell migration *in vitro*, *ex vivo* and in animal models of metastasis. High expression of ZEB2 in cancer tissues defines reduced ZEB2 expression in cancer-associated stroma in patients and in murine intestinal organoids, demonstrating a tumour-stromal crosstalk that modulates a niche and EMT activation. Our study thus uncovers a new molecular mechanism, by which the tumour microenvironment promotes stemness and intrinsic resistance to chemotherapy in CRC.

a.nateri@nottingham.ac.uk