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ROLE OF miRNAS AND YAP IN THE PROMOTION OF COLORECTAL CANCER STEM CELL SELF-RENEWAL BY THE TIGHT JUNCTION PROTEIN CLAUDIN-2

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Colorectal cancer (CRC) is the third most lethal cancer worldwide, often due to post-treatment recurrence driven by a subpopulation of Cancer Stem Cells (CSCs). The tight junction (TJ) protein claudin-2 is overexpressed in human CRC, where it enhances cell proliferation, colony formation and chemoresistance *in vitro*. While several of these biological processes are features of the CSC phenotype, a putative role for claudin-2 in the regulation of these had hitherto not been explored. Here, we identify that elevated claudin-2 expression in stage II/III colorectal tumors is associated with poor recurrence-free survival after 5-FU-based chemotherapy, an outcome in which CSCs play an instrumental role. Using overexpression and/or down-regulation models in patient-derived organoids, primary cells and cell lines, we show that claudin-2 promoted CRC self-renewal *in vitro* and in multiple mouse xenograft models. Claudin-2 enhanced self-renewal of ALDHHigh CSCs and increased their proportion in CRC cell populations, limiting their differentiation and promoting the phenotypic transition of non-CSCs towards the ALDHHigh phenotype. Using Next Generation Sequencing in ALDHHigh cells, we establish that claudin-2 regulated the expression of several microRNAs known to control stem cell signalling. We demonstrate that, among these, miR-222-3p was instrumental for the regulation of self-renewal by claudin-2. We also found that the enhancement of self-renewal by claudin-2 required the activation of YAP, most likely upstream from miR-222-3p. Taken together, our results indicate that overexpression of the TJ protein claudin-2 promotes self-renewal within CRC stem-like cells, suggesting a potential role for this protein as a therapeutic target in CRC.

BIOGRAPHY

Frederic Hollande has completed his PhD in 1994 at the University of Montpellier, France. He worked as a Post-doctoral Research Fellow at the Ludwig Institute for Cancer Research and the University of Melbourne, and was recruited as a Research Fellow by the French National Centre for Scientific Research (CNRS) in 1996. He became Group Leader in 2000 and Head of the Oncology Research Department at the Institute of Functional Genomics (IGF) of Montpellier in 2011. In 2007, he co-founded a Biotech Company (colon cancer therapeutics) and was the Joint-Scientific Director until 2011. He has been an Associate Professor in the Department of Pathology at the University of Melbourne since September 2012. His laboratory is located at the new purpose-built Victorian Comprehensive Cancer Centre in Melbourne. His research interest lies in the study of tumour heterogeneity and the regulation of cancer stem cells in colorectal and other cancers

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