

AB073. Attenuation of pathogenic pro-inflammatory signals in colorectal cancer via an NR4A1 agonist cytosporone B

Mohamed Ismaiel^{1,2}, Brenda Murphy^{1,2}, Sarah Aldhafiri², Hugh Giffney², Ciara Keogh², Mukhopadhyaya Anindya², Sarinj Fattah², Kevin Thornton², Eoin Cummins², Helen Mohan^{1,2}, David Brayden², Evelyn Murphy², Alan Baird², Daniel Crean², Des Winter^{1,2}

¹Department of General Surgery, St. Vincent's University Hospital, Dublin, Ireland; ²Department of School of Veterinary Medicine and Conway Institute, University College Dublin, Belfield, Dublin, Ireland

Background: Colorectal cancer (CRC) is a main cause of cancer-associated mortality globally in spite of advances in treatment. Furthermore, a strong link between chronic inflammation and CRC has been established. Nuclear orphan receptor family 4, subgroup A, member 1 (NR4A1) has emerged as a key regulator of inflammatory pathways, albeit its function in CRC remains unknown.

Methods: Human colorectal tissues (normal and tumour) (n=33), omentum (n=13) and mesenteric (n=14) tissue (adjacent to the tumour tissue) was obtained from patients undergoing colorectal resection and subsequently exposed to a NR4A1 agonist [cytosporone B (Csn-B)] for 8 hrs *ex vivo* in a tissue culture incubator. A cytokine/chemokine

array was performed examining 105 proteins associated with tumour inflammation, and subsequent to that enzyme-linked immunosorbent assay (ELISA) and qRT-PCR was used to confirm targets of interest. Moreover, ELISA data was then stratified based on patient characteristics including gender, location, and whether they had chemoradiotherapy.

Results: The additions of NR4A1 agonist Csn-B (100 µM) was efficacious in attenuating pro-inflammatory mediators in colorectal tumours. This was not global attenuation and was specific to certain targets, such as IL-8, MCP-1, IL-1β, CCL3/4 and TNFα. Mesenteric tissue exposed to Csn-B (100 µM) displayed significantly less (P<0.001) IL-1β compared to mesentery alone, while omentum tissues remained unchanged. ELISA data stratification revealed some intriguing results revealing that Csn-B affects tumour inflammatory states from patients who have not had chemoradiotherapy, and more so who are male.

Conclusions: NR4A1 agonist CsnB attenuates pathogenic pro-inflammatory mediators in CRC *ex vivo*.

Keywords: Colorectal cancer (CRC); nuclear orphan receptor family type 4A1 (NR4A1); cytosporone B (Csn-B); inflammation; inflammatory mediators; omentum; mesentery

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