Activation of the Constitutive Androstane Receptor Enhances Wound Healing – a New Link Between Xenobiotic Sensing and Intestinal Mucosal Homeostasis?

Grace Hudson¹, Alexandra Zamponi¹, Laurie Alston¹, Angela Zhao¹, Laurie Alston¹, Thomas Chang² & Simon A. Hirota¹

¹ – Snyder Institute for Chronic Diseases, University of Calgary, Calgary, Alberta, Canada
² – University of British Columbia, Vancouver, British Columbia, Canada

Background: Compounds released from the intestinal microbiota may play a role in maintaining mucosal homeostasis, but little is known about the receptors that sense and respond to these compounds. Recently a cytosolic xenobiotic sensor, called the pregnane X receptor (PXR), was identified as a receptor for microbial metabolites, and shown to play a key role in regulating intestinal epithelial barrier and wound healing following mucosal injury. In the current study, we sought to determine whether the constitutive androstane receptor (CAR), which shares similar structural, functional and pharmacological features with the PXR, plays a role in regulating wound healing.

Methods: Caco-2 intestinal epithelial cells were used to model wound healing. Wounds formed using Ibidi culture inserts were treated with CITCO, a selective CAR agonist, and imaged for 24 hours. To interrogate the intracellular events involved in the CITCO-induced responses, wound healing assays were performed in the presence of agents to inhibit p38 and ERK1/2 signaling. CAR-induced cell proliferation and migration were also assessed. Lastly, p38 and ERK1/2 activity were assessed in Caco-2 monolayers treated with CITCO.

Results: Activation of the CAR enhanced wound closure in Caco-2 monolayers. This effect was associated with increased cell proliferation and migration. At concentrations that enhanced wound closure, CITCO increased p38 and ERK1/2 activity. Lastly, inhibition of p38 or ERK1/2 signaling significantly reduced CITCO-induced enhancement of wound closure.

Conclusion: Our data suggest that the CAR regulates the cellular events that contribute to wound healing. While the microbe-derived compounds that activate the CAR have yet to be identified, its close relative, the PXR, has been shown to respond to such ligands. Taken together, we posit that xenobiotic receptors play a key role in regulating the response to injury and may provide new therapeutic targets to enhance mucosal repair.