Stingray venom activates IL-33 producing cardiomyocytes, but not mast cell, to promote acute neutrophil-mediated injury

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Supplementary Figure 1. Main mechanisms involved in acute neutrophilic inflammation driven by stingray venom. Components of the ray venom such as collagenolytic proteases can degrade extracellular matrix components, inducing epithelial cell damage accompanied by the release of IL-33 alarmin. IL-33 binds to the receptor ST2 on the cell membrane and induces recruitment of MyD88, thereby activating the downstream NF-κB, JNK, p38, and ERK pathways. Our experiments in deficient mice confirmed that ST2 engagement is critical in regulating the mobilization of neutrophils to inflamed tissue, independent of its expression on mast cells or the induction of AHR transcription factor. We found a requirement of TLR/TRIF priming signals and IL-17A for neutrophilia. IL-1β/IL-1R signaling or NLRP3_caspase-1/11 activities appeared dispensable for recruitment of neutrophils, showing that another ligand of IL-1R1 receptor as IL-1α can control the cell infiltration at the site of injury. Our data indicate that in the acute inflammation induced by ray venom, neutrophil recruitment relies on resident cell-derived IL-33, which amplifies innate immunity and cooperates to create an inflammatory microenvironment that triggers accumulation of neutrophils.