Interleukin-33 acts as a pro-inflammatory cytokine and modulates its receptor gene expression in highly metastatic human pancreatic carcinoma cells.

Abstract:

Human pancreatic cancer is one of the most fatal of all solid tissue malignancies. Pancreatic inflammation plays a key role in the development of pancreatic malignancy mediated by pro-inflammatory signalling cascades. Despite advances in surgery and radiation oncology, no significant improvements in overall survival have yet been achieved. Recent investigations suggest a crucial role of interleukin-33 (IL-33), a novel IL-1 family cytokine, in the pathogenesis of chronic pancreatitis and possibly pancreatic cancer. However, the precise role of IL-33 in pancreatic carcinogenesis is poorly understood. As IL-33 mediates its effects via the heterodimeric ST2L/IL-1 receptor accessory protein (IL-1RAcP) receptor complex, we investigated the influence of IL-33 alone, IL-33 combined with IL-1 and other inflammatory cytokines on IL-33 receptor/ligand mRNA expression and production of tumorigenic factors in the highly metastatic human pancreatic adenocarcinoma cell line Colo357. Our results demonstrated that IL-1 and IL-3 up-regulated IL-33 mRNA while IL-12 showed the opposite effect. We also detected a counter-regulatory effect of IL-33 and IL-1 on the mRNA expression of soluble IL-33 receptor ST2 and membrane-bound receptor ST2L. Furthermore, IL-33 and IL-1 acted synergistically in up-regulating secretion of pro-inflammatory IL-6. IL-33 alone stimulated spontaneous
release of pro-angiogenic IL-8, but it did not affect IL-1-induced IL-8 secretion. IL-33/IL-1 effects on cytokine production appear to be mediated via NF-κB activation. These data argue for the pro-inflammatory role of IL-33 in Colo357 cells implying that IL-33 might act as a crucial mediator in inflammation-associated pancreatic carcinogenesis.