

Plasmacytoid dendritic cells producing both IFN-alpha and IL-33 mediate chronic fibro-inflammatory responses in IgG4-related disease.

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Objectives:

IgG4-related disease (IgG4-RD) is characterized by massive infiltration of IgG4-expressing plasmacytes and fibrosis. In our previous studies, we reported that accumulation of plasmacytoid dendritic cells (pDCs) into the pancreas is seen in patients with IgG4-RD and that IFN-alpha produced by pDCs enhances IgG4 production by B cells (J Immunol 2015;195:3033-44). In this study, we addressed the role played by pDCs in the development of pancreatic fibrosis in IgG4-RD.

Methods:

Autoimmune pancreatitis (AIP) was induced in MRL/MpJ mice by repeated injection of poly (I:C). Pancreas surgical specimens were obtained from patients with chronic alcoholic pancreatitis and IgG4-related AIP.

Result:

Repeated injection of poly (I:C) into MRL/MpJ mice induced AIP with massive infiltration of pDCs. Repeated injection of poly (I:C) led to the development of pancreatic fibrosis as assessed by the measurement of hydroxyproline and by the tissue staining studies for Sirius Red, alpha-SMA, and fibronectin. Pancreas tissue obtained from poly (I:C)-treated mice exhibited higher expression of pro-fibrogenic cytokines such as IL-33, IL-13, and TGF-beta1 in addition to IFN-alpha as compared with non-treated mice.

The depletion of pDCs by 120G8 Ab or the neutralization of IFN-alpha by IFNAR Ab prevented the development of pancreas fibrosis as assessed by semi-quantitative measurement of positive areas for Sirius Red, alpha-SMA, and fibronectin staining. Furthermore, the blockade of IL-33-mediated signaling pathways by ST2 Ab prevented the development of pancreas fibrosis. Pancreatic mononuclear cells (PMCs) isolated from poly (I:C)-treated mice produced a large amount of IL-33 upon stimulation with CpG and/or poly (I:C), which effect was abolished by the blockade of IFN-alpha-mediated signaling pathways or by the depletion of pDCs. Immuno-fluorescence studies revealed that pDCs expressing PDCA1 were positive for IL-33 staining. Thus, these data suggest that pDCs producing both IFN-alpha and IL-33 mediate chronic fibro-inflammatory responses in murine AIP. Finally, the numbers of pDCs expressing IFN-alpha and IL-33 were significantly higher in the pancreas of patients with IgG4-RD as compared with those with chronic alcoholic pancreatitis.

Conclusions:

pDCs producing both IFN-alpha and IL-33 play a pivotal role in the chronic fibro-inflammatory responses of murine AIP and human IgG4-related AIP.
