The NKp30/B7H6 Axis Contributes To Pathogenesis In Primary Sjögren's Syndrome

Abstract: #2771

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Background/Purpose: NK cells are an important subset of cells involved in innate immunity. Their possible role has never been studies in pSS pathogeny. We aimed to assess the involvement of NCR3/NKp30, a NK-specific activating receptor regulating the cross-talk between NK and dendritic cells and type II IFN secretion, and its receptor named B7H6 in pSS pathogenesis.

Methods: First, a cohort of 584 pSS patients (ASSESS + KB cohort) and 451 controls of Caucasian ancestry, addressed by 48 AIMs, was used for exploratory genetic study. Nine single nucleotide polymorphisms (SNPs) within the 6p21.3 *NCR3* locus and 3 additional SNP proxies for *HLA-DR2,HLA-DR3* and *TNF-308* were genotyped. Two *NCR3* SNPs (rs11575837, rs2736191) and the SNP proxy for HLA-DR3 (rs2187668) were genotyped in the replication study that included 436 pSS Scandinavian patients and 441 healthy controls. Then, NKp30 mRNA levels were investigated in 102 pSS patients from the French ASSESS cohort according to their genotype. Second, we performed phenotypic characterization of NK cells in 38 pSS patients compared to 30 age-matched controls. The functional relevance of expression levels of NKp30 on NK cells was assessed by a cross-linking assay to analyze degranulation and IFN-γ secretion. Third, we assessed the presence of NK cells by immunohistochemistry (IHC) and transcriptional level of B7H6 within salivary glands. Last we investigated the NKp30-dependent cross-talk between NK cells and epithelial cells within salivary glands.

Results: Our case-control study of genetic polymorphisms of the NCR3/NKp30 gene demonstrated that the rare allele of the rs11575837 (G>A) residing in the promoter was protective for pSS and was associated with reduced gene transcription and function. We also demonstrated that circulating levels of NCR3/NKp30 were markedly increased among pSS patients compared with controls and correlated with higher NCR3/NKp30 IFN-γ secretion by NK cells. Excess accumulation of NK cells in minor salivary glands correlated with the severity of the exocrinopathy. B7-H6, the ligand of NKp30, was expressed by salivary epithelial cells and regulated by TNF-α triggering NKp30 mediated-effector functions.

Conclusion: These findings suggest that NK cells are involved in pSS pathogeny. Different levels of evidence (genetics, mRNA expression, function in blood, presence in the target organ as well as the ligand) demonstrate an NKp30-dependent inflammatory state in salivary glands. Blockade of the B7H6/NKp30 axis could be clinically relevant in pSS.