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Background: The development of the B cell repertoire is regulated by the process of affinity maturation occurring within the inner part of the B cell follicles [germinal centers (GCs)] within secondary lymphoid organs (SLOs). In autoimmunity, this process might occur within aberrant aggregates of lymphocytes in target organs, such as the ectopic lymphoid structures (ELS) found in the salivary glands of patients with Sjogren’s Syndrome (SS) (1). The phenotypic and functional features supporting ELS which may sustain the development of autoimmune diseases have not been identified. Moreover, functional proof that ELS contribute to the development of autoimmunity independently from SLOs has not been provided.

Objectives: To characterise the transcriptome profile of human ELS isolated from SS salivary glands in comparison with SLOs.

Methods: Frozen minor salivary gland biopsies were obtained from SS patients and selected for presence of GCs+ ELS. Human tonsils were obtained by volunteers undergoing tonsillectomy for clinical need and used as SLO control. In order to detect GCs, all samples were stained for CD21, bc6, CD20 and CD3. Sequential sections were stained by cresyl Violet and GCs (CD21+ infiltrates) from both salivary glands and tonsil were selectively microdissected (Laser Capture Microdissection). Salivary gland small infiltrates and large CD21- infiltrates were microdissected too. RNA was isolated and transcribed. RNA sequencing studies were performed using ClonTech SMARTseq v4 kit. Changes and differences in the expression of specific genes of interest were confirmed with targeted qPCR studies.

Results: Transcriptomics analyses revealed that GCs from ELS and SLO exhibit markedly different gene expression profiles. Of note, sequencing unveiled that GCs from ELS are characterized by an aberrant cell-proliferation profile with downregulation of BCL6 and AID, the enzymes responsible for cell-affine maturation. Transcriptional analysis of other genes potentially implicated in impaired regulation of the B cell cycle and survival revealed that GCs forming in ELS exhibit a pathogenic inflammatory cytokine signature. Despite similarities in the organizational architecture of GCs in ELS and SLO, critical transcriptional differences emerge, which are likely functionally implicated in impaired regulation of the B cell cycle and survival of autoreactive B cell clones, ultimately leading to the development of autoimmune disease.

REFERENCE