FOXP3+ T Regulatory Cells (Tregs) in the Autoimmune Lesions of Sjögren's Syndrome (SS): Correlation with the Number of the Infiltrating Dendritic Cells and Macrophages

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Tregs are considered to participate in the modulation of autoimmune responses. The factors that mediate the differentiation and/or accumulation of Tregs at the site of inflammation continue to be dissected and are thought to include a conducive cytokine milieu and favorable interactions with dendritic cells (DC). In SS, a chronic autoimmune exocrinopathy (mainly of the salivary and lacrimal glands) associated with glandular lymphocytic infiltrates, we have previously shown that FOXP3+ Tregs are present in the minor salivary gland (MSG) inflammatory lesions and that their incidence correlates with the severity of the inflammatory infiltration.

PURPOSE: To investigate potential associations between the numbers of infiltrating Tregs and DC or other types of antigen-presenting cells (macrophages; MΦ) at the SS autoimmune lesions.

METHODS: MSG biopsy specimens from 30 SS patients and 13 controls were studied by immunohistochemistry. SS samples were classified according to MSG lesion severity in three groups (10 patients each), consisting of samples with mild, intermediate or advanced MSG lesions (Tarpley biopsy score 1+, 2+ or 3/4+), respectively. Control group included 6 sicca-complaining subjects with negative biopsy scores that did not fulfill the SS American-European classification criteria and 7 with sialadenitis [3 sarcoidosis, 4 viral (3 HCV, 1 HIV)-related]. Tregs, T cells, B cells, follicular DC, interdigitating DC and MΦ were identified by antibodies to FOXP3, CD3, CD20, fascin, S100 and CD68, respectively. Cells were counted field by field in each section. Statistical analyses were performed by Mann-Whitney and Spearman tests.

RESULTS: FOXP3+ Tregs were detected in all SS and sialadenitis-control samples, but not in the controls. The mean of the % FOXP3+/CD3+ cells ± SE was found 7.54 ± 1.13 in SS and 7.70 ± 1.81 in sialadenitis samples, whereas in the SS groups with mild, intermediate and advanced MSG lesions was 2.24 ± 0.50, 13.21 ± 1.93 and 6.65 ± 1.10, respectively. In both SS and sialadenitis-controls, FOXP3+ cells were found to significantly correlate to the number of infiltrating mononuclear cells (r:0.90, $p<0.0001$ and r:0.96, $p<0.01$ in SS and controls, respectively), fascin+ DC (r:0.80, $p<0.001$ and r:0.93, $p<0.01$), S100+ DC (r:0.59, $p<0.01$ and r:0.71, $p=0.09$) and CD68+ MΦ

(r:0.71, $p<0.0001$ and r:0.86, $p<0.05$), whereas they were negatively correlated to the CD3+/CD20+ cell ratio (r:-0.61, $p=0.006$ and r:-0.89, $p=0.01$).
CONCLUSIONS: The comparable FOXP3+ Treg incidence in the SS autoimmune and of other etiology inflammatory MSG lesions suggests that mechanisms related to Treg recruitment/induction are probably not impaired in SS. Although further investigation is needed to elucidate the factors mediating Treg accumulation at MSG infiltrates, DC and MΦ might be implicated.