Persisting deficiency of mucosal associated invariant T cells in dermatomyositis

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Mucosal associated invariant T (MAIT) cells are innate like lymphocytes found in peripheral blood and mucosa; they are decreased during systemic lupus erythematosus and other auto-immune diseases. However, MAIT cell levels and functions have not previously been investigated in dermatomyositis (DM). Herein, we studied MAIT cell levels and activation status before and after treatment during DM (n=21) and compared them to healthy controls (n=19), psoriasis (n=7) and atopic dermatitis (n=5). We showed that DM was associated with a dramatic reduced number of circulating MAIT cells median 0.12% [0.07-0.25%] versus 2.13% [0.15-3.94%], p < 0.0001. This disappearance was specific to DM. Residual MAIT cells displayed an activated/exhausted phenotype with higher expression of CD25, CD19, CTLA4 and increase of the TREGMA state. We found an inverse correlation between CD25 and CTLA4 expression on MAIT cells and the level of circulating MAIT cells. After a median follow up of 0.9 year, we observed a slight increase of MAIT cells (median: 0.25% [0.24-0.66%] versus 0.73% [0.47-1.16%], p = 0.002). Nevertheless, it did not return to normal healthy controls level. We next compared skin from DM with healthy controls for PLZF, the master transcript of MAIT cells thanks to microarray analysis. PLZF was not elevated in lesional skin. Finally, preliminary in vitro assays showed that strong stimulation by both TCR and IL-21 could not return to normal healthy controls levels. Also, the reactivation of skin MAIT cells led to decreased expression of CD161 and higher mortality. Taken together, our data indicate that in DM peripheral blood MAIT cells, which are thought to have regulatory role, are dramat-ically reduced in skin lesions with an activated abnormal phenotype potentially leading to activation induced cell death rather than their migration in affected tissue.

Role of effector and regulatory B cells in patients with systemic sclerosis

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Scleroderma is an autoimmune connective tissue disease characterized by fibrosis and inflammation. While the role of effector B cells is well established in the pathogenesis of scleroderma, the role of regulatory B cells is not fully understood. We investigated the interaction of Scleroderma B cells with fibroblasts in vitro and in vivo. We examined the effect of culture with autologous fibroblasts on B cells from patients with systemic sclerosis (SSc) and healthy controls (HC). In vitro, Scleroderma B cells showed a reduced capability to inhibit proliferation of fibroblasts compared to HC. In vivo, we followed biopsies from lesional skin and found a positive correlation between the number of B cells and the degree of fibrosis. Furthermore, the frequency of IL-6 producing effect B cells positively correlated with the extent of skin fibrosis in SSc patients. The result suggested that the dysregulation of B cells play an important role in SSc pathogenesis. However, two opposing B cell subsets exist: effector and regulatory B cells. IL-6 producing B cell present autoimmune properties and IL-10 producing regulatory B cells are known to inhibit fibrosis. In preclinical models involving human skin. We have studied in human skin explants whether vitamin D3 analogs allow emigrating skin DCs to promote human Th2 responses. In line with a previous report, topical application of calcipotriol cream or calcitriol addition in the culture medium increased the rate of CD14+ DCs recovered after 3 days of culture. Using immunofluorescence microscopy of cultured skin and monocyte-derived dendritic cells (MoDCs) cultured with calcitriol, we showed that CD14 upregulation is a direct consequence of vitamin D3 structure rather than hormone action. After 3 days of culture, CD14+ DCs were collected and cocultured with naive CD4+ T cells from a different donor. This resulted in a clear orientation towards Th2 differentiation, for which CD14+ DCs appeared sufficient. Finally, we found that both analogs of vitamin D3 induced TLR3 production by human skin. However, poor correlation between TLR3 amounts and the Th2-driving capacity of skin DCs suggested a TLR3-independent effect. Of note, vitamin D3-stimulated MoDCs also yielded strong Th2 differentiation in the absence of TSLP. Therefore, our findings reveal possible TSLP-independent effects of vitamin D3 on T cell responses, which are currently under investi-gation. Altogether, we confirmed vitamin D3 as a potent Th2 inducer in a human skin system, paving the way towards accurate modeling of the initiation steps of atopic dermatitis.