Blocking of CTLA-4 reverts T cell exhaustion in patients with rheumatoid arthritis

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Background: Patients with rheumatic diseases such as rheumatoid arthritis (RA) or spondyloarthritis (SpA) suffer from increased incidence and enhanced severity of infectious diseases. This enhanced vulnerability to infections is confirmed either by the primary disease and/or the immunomodulatory treatment of the primary disease. Since CD4+ T cells orchestrate immunity against infections, we hypothesized that CD4+ T cells were dysfunctional in patients with rheumatic diseases.

Methods: We studied the activation status and the reactivity of CD4+ T cells upon anti-CD3/anti-CD28 stimulation from patients with RA, SpA, and of healthy controls by FACScan-based methods. Patient groups were analyzed for treatment with either tumor necrosis factor (TNF-α) blocking agents or abatacept (RA, n=28, SpA, n=30, control, n=30).

Results: The analysis of patient derived CD4+ T cells revealed an enhanced basal activation status as indicated by augmented spontaneous proliferation and increased expression of inducible T cell costimulator (ICOS) and the exhaustion marker programmed cell death 1 (PD-1) and cytotoxic T lymphocyte associated protein 4 (CTLA-4). Upon anti-CD3/anti-CD28 stimulation, patient derived CD4+ T cells showed significantly reduced IL-2 responses, expanded proliferation, and enhanced activation induced cell death (AICD). These data indicated a dysfunctional T cell compartment. RA T cells were exhausted. Intriguingly, RA patients treated with the second signal CTLA-4 inhibitor abatacept carried CD4+ T cells that were less exhausted than CD4+ T cells from otherwise treated patients. This observation is further supported by the previously published clinical observation that abatacept treated RA patients suffer less frequently from infections compared with RA patients treated differently. Similarly, anti-TNF-α treatment increased IL-2 expression of T cells from several RA and SpA patients in in vivo stimulation experiments.

Conclusion: T cells from RA and SpA patients show different levels of exhaustion, which can at least partially be reverted by treatment with checkpoint inhibitors. These observations highlight the need to specifically consider individualized treatments of patients with rheumatic disorders aiming at readjusting the balance between immunosuppression and auto-inflammation.

Figure 1: CD4+ T cells of RA and SpA patients are phenotypically exhausted. A Activation marker expression of CD7+CD4+ T cells in PBMC from healthy donors (control) and RA, or SpA patients (n=30 per group) B PD-1/ICOS expression of CD4+CD8+ T cells in synovial fluid of SpA patients (n=3).

Figure 2: CD4+ T cells of RA and SpA patients are functionally exhausted. A Intracellular IL-2 expression and C cell viability of CD4+CD8+ T cells in PBMC from healthy donors (control) and RA and/or SpA patients (n=30 per group) C CD4+CD8+ T cell proliferation was assessed 5 days post stimulation (n=30 per group).

Figure 3: Radial plot analysis of different analyzed entities. Mean values of different analyzed entities from Figures 1 and 2: healthy (grey), RA (red), and SpA patients (blue) normalized towards healthy controls (n=30 per group).

Figure 4: Disease-specific patterns of exhaustion-determining parameters. Pearson’s Correlations Coefficient analysis in combination with unsupervised clustering for the investigated variables (only correlations with p<0.05 are shown): positive correlation (blue), negative correlation (red) (n=30 per group).

Figure 5: Blocking of CTLA-4 can revert T cell exhaustion. A ICOS/CD25/CTLA-4 expression of CD4+CD8+ T cells in PBMC from healthy donors (control) or RA patients treated with/without abatacept. B Intracellular IL-2 expression and C cell viability of CD4+CD8+ T cells in PBMC from healthy donors (control) or RA patients treated with/without abatacept were analyzed 24 h post stimulation with anti-CD3/anti-CD28 beads. CD3/CD8+ T cell proliferation was assessed 5 days post stimulation (n=8 RA + abatacept; 30 RA - abatacept, control).

Figure 6: Working model. A Upon infections with pathogens, CD4+ T cells are activated by T cell receptor (TCR) triggering plus second signals of activating receptors such as CD80/86 interacting with CD28. This activation leads to T cell proliferation and cytokine expression. The upregulation of the inhibitory receptor CTLA-4, which is binding CD80/86 with higher affinity than CD86, confers T cell inhibition and cell death to down-modulate the T cell response. B In chronic inflammatory diseases constant antigen triggering causes T cell exhaustion. Upon ex vivo stimulation exhausted T cells show less proliferation, less cytokine expression, but increased cell death upon TCR-stimulation. Blocking CD80/86 by abatacept treatment reverts T cell exhaustion in patients with rheumatoid arthritis while preventing auto-immunity by reconstituting the equilibrium of T cell activation and inhibition.

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