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Therapeutic roles of TGF-β-induced regulatory T cells in the established autoimmune and inflammatory diseases

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While it has been well recognized that both natural Foxp3+ regulatory T (nTreg) cells and TGF-β-induced Treg (iTreg) cells can prevent autoimmune diseases in animal models, recent studies reveled that injection of nTregs has less therapeutic effects on established autoimmune diseases. It is less clear if iTregs can treat the established autoimmune diseases. We now provide evidence that unlike nTregs, injection of iTreg cells can markedly ameliorate the established autoimmune asthma, arthritis and lupus. We observed that adoptive transfer of either nTreg or iTreg significantly suppressed airway and peri-vascular inflammation. However, inflammatory suppression by iTreg cells was more effective than that of nTreg cells, particularly in the lung tissues surrounding airways. Interestingly, adoptively transferred iTreg cells, but not nTreg cells, significantly inhibited the elevation of Th2 cytokines in peripheral lymphatic tissues, as demonstrated by the level of IL-5 produced in CD4+ cells of adjacent draining lymph nodes. Both antigen-specific and polyclonally induced iTregs also suppressed established collagen-induced arthritis (CIA) although antigen-specific iTregs had a superior therapeutic effect. CIA mice given iTregs have a significantly lower incidence of disease and lower clinic scores than mice given nTregs, Teff cells or no cells. We found while nTregs were converted into Th1/Th17 cells in vitro and in vivo in the inflammatory milieu, iTregs were resistant to T effector cell conversion in the similar condition. Injection of iTregs to naïve mice and immune deficient mice displayed similar levels of Foxp3 stability as comparing with nTregs. Of note, the stability of Foxp3 expression was only found in iTreg cells during established CIA. iTregs suppressed Th17 cell and osteoclast differentiation that paralleled with improved clinical scores, CII-specific IgG production and bone erosion. Injection of iTregs to the established lupus mice significantly decreased the levels of anti-dsDNA and proteinuria, and markedly prolonged the survival of lupus. Blocking of TGF-β/TGF-βR pathway using anti-TGF-β antibody or TGF-βRI (ALK5) inhibitor, or anti-IL-10R antibody almost completely abolished the therapeutic effects of iTregs on lupus, suggesting that TGF-β and/or IL-10 secreted by iTregs play a crucial role in the cell therapy. We further observed that DC isolated from lupus mice received iTregs but not control cells expressed lower levels of CD80 and CD86 and adoptive transfer of these DCs to another lupus mouse can suppress the disease development, however, this effect cannot be observed in TGFRII DC KO mice. We therefore suggest that iTregs are stable and able to target DC in the inflammatory milieu, these DC then have become tolerogenic DC through TGF-β signal on DC and further suppress disease progression through its direct or indirect effect (inducing new iTregs) in autoimmune and inflammatory disease settings.

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