THU0031

ABATECEPT ALTERS THE FREQUENCY OF IMMUNOREGULATORY AND EFFECOR T CELL SUBPOPULATIONS IN RHEUMATOID ARTHRITIS

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Background: Under physiological conditions, T regulatory cells (Tregs) are responsible for the downregulation of the immune response. In autoimmune diseases, such as rheumatoid arthritis (RA), auto-inflammation is driven by an imbalance of activation and downregulation of immunological pathways. Thus, treatment plans for autoimmune diseases often involve the enhancement of immunoregulatory pathways by administering inhibitors of costimulation, i.e. CTLA-4-Ig (abatacept, ABA), ABA binds specifically to CD80 and CD86 on anti- gen presenting cells (APC). Consequently, T cell activation via the CD28 receptor is blocked. Previous studies have demonstrated surprising effects of abatacept on Tregs, specifically decreased frequency of these cells but enhancement in immunoregulatory pathways by administering inhibitors of costimulation, i.e. treatment plans for autoimmune diseases often involve the enhancement of responsible for the downregulation of the immune response. In autoimmune sets were identified by flow cytometric means. CD3+CD4+ T cells were further tively) were drawn over a sampling period of 2 years. Freshly isolated PBMCs of 60.5 ± 1.3 years, female ratio: 0.7 , disease duration: 17.9 ± 2.1 years; respec-

Methods: Peripheral blood samples from 56 RA patients (median ± SE; age: 60.5 ± 1.3 years, female ratio: 0.7 , disease duration: 17.9 ± 2.1 years; respec-

Results: Eighteen out of 56 RA patients (32%) received ABA, 25 patients (45%) received TCZ and 13 patients (23%) were under CD20+ cell depletion ther-

Conclusion: Our data demonstrate that blockage of T cell stimulation via ABA leads to characteristic alterations in different regulatory and effector T cells not seen in patients treated with TCZ or RTX. Further studies must clarify whether the analysis of the peptide and effector T cell subpopulations before treatment initiation can be used as biomarker for treatment response.

References:

THU0032

MODIFIED PEPTIDES AS A NOVEL IMMUNOTHERAPY FOR RHEUMATOID ARTHRITIS

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Background: Rheumatoid arthritis (RA) is a highly prevalent and severe systemic autoimmune disease associated with permanent disability and strong socio-economic burdens. Currently, there is no therapeutic treatment and RA patients rely on lifelong, costly treatments. Imzyco develops modified peptides eliciting antigen specific cytolytic CD4 T cells (cCD4+T) that induce apoptosis of antigen presenting cells (APC) in a contact dependent manner. cCD4+ T cells also inhibit activation of autoantigen-specific bystander T-cells, activated by the same APC thus eliminating the risk of general immunosuppression. Peptides consist of MHC class II T cell epitopes of a target autoantigen modified in their flanking region by the addition of an amino acid sequence containing a thio-disulfide oxidoreductase active motif.

Objectives: The goal of this study was to synthesize modified peptides from a target RA autoantigen and test their potency to generate in vitro specific and cytolytic CD4+ T cells from RA patients.

Methods: We designed modified peptides from a target RA autoantigen after in silico and in vitro assessment to identify MHC II core binding region, HLA class II binding capacities and physicochemical properties. CD4+ T cells were purified from PBMC of a newly diagnosed seropositive RA patient and co-cultured with autologous APC in the presence of the modified peptide. The CD4+ T cells were restimulated periodically. Peptide’s ability to generate specific CD4+ T cells was evaluated by flow cytometric analysis of the expression of surface activation marker CD154 (CD40L) The peptide specific CD4+ T cell lines were sorted based on their surface CD154 expression. The anti-apoptotic activity was assessed after overnight (O/N) co-culture of CD4+ T cells with fluorescent tracer labelled autologous lymphoblastoid cells lines (LCL). Flow cytometry quantification of LCL apoptosis was mea-

Results: CD4+ T cells were in vitro expanded after six consecutive stimulations with peptide. We investigated their specificity by flow cytometry and showed that 69% of CD4+ T cells that were stimulated O/N in the presence of the peptide expressed the activation marker CD154 versus 29% of CD4+ T cells that were stimulated in its absence. These cells were sorted based on CD154 expression following specific stimulation. Cell enrichment was then assessed by flow cyto-

Conclusion: The preliminary but very promising data show that our modified peptide generates peptide-specific CD4+ T cells with lytic properties that lyse target APC in an HLA class II specific manner. Our plan is to show that these CD4+ T cells can also induce apoptosis in bystander T cells and to further validate our results in additional RA donors.

References:

Disclosure of Interests: Eleni Arakioti Grant/research support from: This work was supported by Pfizer Inc. and by Wallon Region, Ludivine Herman Grant/research support from: This work was supported by Pfizer Inc. and by Wallon Region, NGoc Quynh Nhu Nguyen Grant/research support from: This work was supported by Pfizer Inc. and by Wallon Region, Roxana Roohi Ahangarani Grant/research support from: This work was supported by Pfizer Inc. and by Wallon Region, Roxya Roohi Ahangarani Grant/research support from: This work was supported by Pfizer Inc. and by Wallon Region, Bernard Lauverys: None declared, Patricia Durez: Speakers bureau: AbbVie, Bristol-Myers Squibb, Celltrion, Eli Lilly, Pfizer, Sanofi, Vincent Geenen: None declared, Aaron Winkler: Shareholder of: Share-

Disclosur of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.4894

THU0033