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PReS-FINAL-2336: Induction of MDSCs in Muckle-Wells syndrome

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Introduction

Muckle-Wells syndrome (MWS) is caused by mutations in the *NLRP3*-gene encoding cryopyrin, leading to overproduction of IL-1 β and other NLRP3 inflammasome products. Myeloid-derived suppressor cells (MDSCs) represent a novel innate immune cell subset, are generated in tumor, infective, and proinflammatory microenvironments and are capable of suppressing T cell responses. Consequently, MDSCs are considered a key intermediary in balancing innate and adaptive immune responses, particularly under chronic disease conditions.

Objectives

We hypothesized that NLRP3 inflammasome-dependent factors induce the generation of MDSCs in MWS.

Methods

We studied granulocytic MDSC numbers in 25 MWS patients under anti-IL-1 therapy with canakinumab and 20 healthy controls. After Ficoll density gradient sedimentation, granulocytic MDSCs were characterized as CD33^{high}CD66b^{high}IL-4Ra^{inter}HLA-DR^{low} neutrophilic cells in the PBMC fraction, according to previously established human MDSC analysis methods. The functionality of MACS-isolated MDSCs was assessed using polyclonal T cell proliferation and cytokine/chemokine secretion tests. Physician's global assessment of disease activity, CRP, ESR, and T helper cell subsets were determined at the same time points and correlated with MDSC levels. Serum samples of 22 MWS patients and 5 healthy controls were examined by multiplex technique for possible MDSC inducing factors.

Results

MWS patients under anti-IL-1 therapy displayed significantly elevated MDSC numbers (mean $1.65 \pm 0.33\%$; range 0.16 - 5.17%) compared to healthy controls (mean $0.45 \pm 0.05\%$; range 0.12 - 1.04%; $p = 0.0025$), although clinical MWS-disease activity was generally low at time of examination. MDSCs were functionally competent, as they suppressed polyclonal T cell proliferation, Th1, Th2, and Th17 responses. MDSCs correlated directly with Treg/Th17 and Treg/Th1 ratios indicating an influence on T helper cell subsets. Multiplex assays revealed the established MDSC-inducing growth factors GM-CSF and VEGF elevated in MWS sera even under anti-IL-1 therapy with canakinumab.

Conclusion

MWS patients under anti-IL-1 therapy display significantly elevated numbers of granulocytic MDSCs. Increased MDSCs in MWS might represent a novel autologous anti-inflammatory mechanism in autoinflammatory conditions and may serve as a future therapeutic target.

Disclosure of interest

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