ABSTRACT

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Grant Title: Role of Neuraminidase 1 in Psoriasis development

Psoriasis is an autoimmune condition characterized by a chronic immune-mediated inflammatory skin disease. The disease affects up to 4% of the population worldwide and is characterized by a chronic and non-curable pathology leading to severely reduced quality of life. T cells, considered to be the mastermind of the immune response in the disease, produce pro-inflammatory cytokines including, IL- 1β, IL-17, IL-22, and IFNγ that, in turn, trigger release of chemokines like MIP-1α and β from myeloid and tissue cells, maintaining immune cell flow and exacerbating local inflammation. Lysosomal neuraminidase NEU1 has been implicated in immune cell recruitment and local inflammation of the skin. The objectives of this study were: (1) to evaluate whether genetic depletion of NEU1 in constitutive and tamoxifen-inducible *Neu1* knockout mice attenuates psoriasiform features in an imiquimod (IMQ)-induced model, and (2) to assess the effects of topical pharmacological NEU1 inhibition using selective inhibitors C9-BA-DANA and CG259-11 on clinical and cellular hallmarks of inflammation. Male and female 16-week-old WT C57BL/6, constitutive *Neu1* KO, and tamoxifen-inducible *Neu1*Δ*Ex3* (iNeu1 KO) mice were treated daily for 7 days with 5% IMQ or Vaseline on dorsal skin. Inducible KOs received tamoxifen or vehicle one week prior. WT mice were additionally treated with potent selective NEU1 inhibitors, C9-BA-DANA (ears) or CG259-11 (dorsal skin), applied 4 h after IMQ. Inflammation was monitored by PASI scoring and ear thickness; skin samples were collected for histology, immunohistochemistry, and flow cytometry to assess tissue inflammation and immune cell infiltration. After 7 days of IMQ application, WT mice developed marked psoriasiform lesions, whereas *Neu1*-deficient mice (constitutive or inducible) showed reduced PASI scores, skin thickening, and decreased immune cell infiltration into the skin, indicating attenuated local inflammation. Topical application of NEU1 inhibitors similarly reduced clinical scores and visibly decreased skin thickness. Flow cytometry revealed lower numbers of inflammatory monocytes and γδ T cells in inhibitor-treated mice, reflecting diminished recruitment of pathogenic immune cells. These preliminary findings suggest that NEU1 contributes to the development of psoriasiform lesions by promoting local immune cell infiltration and tissue inflammation. Both genetic depletion and topical pharmacological inhibition of NEU1 attenuate clinical and cellular features of IMQ-induced psoriasiform inflammation, highlighting NEU1 as a potential therapeutic target for chronic inflammatory diseases of skin.