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Hyaluronan and Hyaluronan-Associated Genes in Human CD8 T Cells

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Abstract : The glycosaminoglycan hyaluronan (HA) is a major component of the extracellular matrix, typically produced by fibroblasts of the connective tissue but also by immune cells. Here, we investigated the capacity of human peripheral blood CD8 T cells from healthy donors to produce HA and to express HA receptors as well as HA degrading enzymes. Further, we evaluated the effect of pharmacological HA inhibition on CD8 T cell function. Using immunocytochemistry together with quantitative PCR analysis, we found that HA synthesis is rapidly induced upon antibody-induced T cell receptor (TCR) activation and almost exclusively mediated by HA synthase 3 (HAS3). TCR activation also resulted in the upregulation of HA receptors CD44, hyaluronan-mediated motility receptor (HMMR), and layilin (LAYN), although kinetics and strength of expression varied greatly between subjects. The HA-degrading enzymes HYAL1 and HYAL2 were detected at low levels and induced by cell activation in some individuals. Interestingly, expression of HAS3, HA receptors, and hyaluronidases were modulated by the proinflammatory cytokines IL-6 and IL-1bβ in most subjects. To assess the functional role of HA in CD8 T cells, we performed carboxyfluorescein succinimidyl ester (CFSE) based proliferation assays and cytokine analysis in the presence of the HA inhibitor 4- Methylumbelliferone (4-MU). Despite significant inter-individual variation with regard to the effective dose, 4-MU resulted in the inhibition of CD8 T cell proliferation and reduced release of TNF-α and IFN-γ. Collectively, these data demonstrate that human CD8 T cells respond to TCR stimulation with a synthesis of HA and expression of HA-related genes. They further suggest that HA inhibition may be helpful in interfering with pathogenic T cell activation in human disease.

Keywords : CD8 T cells, extracellular matrix, hyaluronan, hyaluronan synthase 3
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