Dysregulated Pathways of Hyaluronan Degradation are Associated with IBD and May Contribute to Chronic Inflammation

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Background: Patients with IBD that undergo flares, and mice that develop colitis, exhibit increased hyaluronan (HA) deposition and altered distribution of the extracellular matrix of colon tissue compared to unaffected individuals. In animal models, HA changes precede the development of colitis, suggesting that HA contributes to the pathology. Pathological extracellular matrix HA has the ability to foster inflammatory leukocyte recruitment, and when fragmented provides damage associated molecular patterns (DAMPs) that can induce pro-inflammatory and pro-angiogenic cytokine release from multiple cell types. While over-production in the inflammatory environment is a major contributor to the HA increase, we also hypothesize that alterations in degradation pathways play a role in intestinal pathology.

Methods: To address the hypothesis, we examined two cell types relevant to the pathogenesis of IBD, platelets and fibroblasts. Platelets contain the HA degrading hyaluronidase 2 (HYAL2) enzyme, which is stored in alpha granules. Platelet HYAL2 expression was determined by immunoblot and Flow Cytometry, and enzyme function tested by HA degradation assays. We also performed comparative proteomic analysis on the extracellular matrix of mesenchymal cells isolated from colons of patients with one form of IBD (Crohn’s disease; CD) and surgical patients that did not have IBD. Immunoblot analysis and histochemistry were used to confirm protein expression, and HA degradation assays were performed to assess function.

Results: Platelets, when activated, translocate HYAL2 to their surfaces and can degrade the HA matrix from cell cultures, through a HYAL2 dependent mechanism. Platelets from IBD patients (17) carry less HYAL2 (on average 45% lower) protein than controls (13), suggesting a defect in HA degradation. In addition, the protein KIAA1199, which recently was reported to function in HA degradation, is upregulated in Crohn’s Disease fibroblasts in vitro and in vivo. Using a siRNA approach, we determined that KIAA1199 is essential in HA fragment generation by these cells. We also identified an IL6 autocrine mechanism that regulates deposition of KIAA1199 in the matrix of Crohn’s disease colon fibroblasts.

Conclusions: Together our data suggest that cells derived from IBD patients catabolize HA differently than control cells, and alterations in HA breakdown are capable of contributing to the chronic inflammation of IBD.