

## **Hyaluronan-based Matrices in Inflammation**

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In 1998, Carol de la Motte showed that colon smooth muscle cells exposed to viral stimuli synthesize and organize a hyaluronan-based matrix to which monocytes selectively adhere (1). This discovery uncovered a potent biological defense mechanism in which cells undergoing certain kinds of stress synthesize and deposit a matrix with structural information that localizes the infiltrating inflammatory cell responses. The priority of monocytes and macrophages that interact with this matrix is to remove it. A key molecule in the essential phagocytic response is CD44, the cell surface receptor with a classic hyaluronan-binding motif (the link module). Teder et al. (2) showed that the continuous accumulation of this matrix during bleomycin-induced inflammation in CD44 null mice is fatal. Alana Majors showed that reagents that induce endoplasmic reticulum stress (unfolded protein response) initiate synthesis of this matrix, thereby identifying one major underlying mechanism (3). Aimin Wang showed that mesangial cells exposed to hyperglycemia during mitosis also synthesize this matrix, thereby identifying a second mechanism (4). Milinkovic et al. (5) showed that lymphocytes adhere to hyaluronan matrices adjacent to vascular endothelial cells in sections of skin from patients with graft versus host disease but do not adhere to hyaluronan matrices in the adjacent papillary dermis. This clearly shows that the hyaluronan-based matrix synthesized by the cells undergoing attack (the vascular endothelial cells) by the graft inflammatory cells has structural information that is absent in the adjacent normal hyaluronan-based matrix. One underlying biochemical reaction that characterizes the matrix is the transfer of heavy chains from chondroitin sulfate on inter-alpha-trypsin inhibitor (ITI) to hyaluronan (6). ITI is normally present in serum, but will enter tissues during inflammation. The heavy chain transfer is mediated by tumor necrosis factor stimulated gene 6 (TSG-6) (7), a molecule with a link module that is often up-regulated in inflammations (8). The emerging model from these studies (reviewed in 9) is defining a critical role for the hyaluronan-based matrix synthesized by cells undergoing various forms of inflammatory stress in modulating the inflammatory response. The balance between synthesis of the abnormal hyaluronan matrix (the stress response for localizing the problem) and its removal in the acute phase of inflammation (the restoration of tissue function) will likely impact on understanding the extent of inflammation in a variety of pathologies, including asthma, inflammatory bowel diseases, diabetic nephropathy, and inherited disorders involving endoplasmic reticulum stress, such as Marfan's disease and cystic fibrosis.

References: 1) de la Motte et al. *J. Biol. Chem.* 274:30747-30755, 1999. 2) Teder et al. *Science* 296:155-158, 2002. 3) Majors et al. *J. Biol. Chem.* 278:47223-47231, 2003. 4) Wang and Hascall *J. Biol. Chem.* 279:10279-10285, 2004. 5) Milinkovic et al. *Blood* 103:740-742, 2004. 6) de la Motte et al. *Am. J. Path.* 163:121-133, 2003. 7) Rugg et al. *J. Biol. Chem.* 280:in press, 2005. 8) Zhuo et al. *J. Biol. Chem.* 279:39079-38082, 2004. 9) Hascall et al. *Biochim. Biophys. Acta* 1673:3-12, 2004.