BIOLOGY OF HYALURONAN-RICH MATRIX

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Hyaluronan (HA) is a widely distributed glycosaminoglycan with the simple structure of repeating disaccharide units. However, HA associates with various proteins and proteoglycans extracellularly to form a so-called "HA-rich matrix" with a variety of structures and natures, so that it affects cell proliferation and migration not only in tissue- and stage-dependent manners in embryogenesis but also in locus-specific manner in some pathological events such as wound healing and inflammation. Therefore, it may be important to learn what molecules participate in the formation of HA-rich matrix and how the assembly is regulated for each event. SHAPs (Serum-derived Hyaluronan-Associated Proteins), the heavy chains of plasma inter-alpha -trypsin inhibitor (ITI) family, are so far only the proteins that have been shown to be covalently bound to HA. The physiological significance of such a unique complex has been unknown but is of great interest because ITI is abundant in plasma, and the SHAP-HA complex is formed wherever HA meets plasma. We abolished the formation of the SHAP-HA complex in mice by targeting the gene of bikunin, the light chain of the ITI family, which is essential for the biosynthesis of ITI family and, consequently, for the SHAP-HA complex formation. The bikunin-null mutation showed a severe female infertility. Histological and biochemical studies revealed a defect in the formation of the cumulus HA-rich matrix, due to the impaired formation of the SHAP-HA complex. It is likely that the SHAP-HA complex is essential for the functional cumulus HA-rich matrix in fertilization. Liver regeneration following partial hepatectomy (PH) and ConA-induced hepatitis are well-established *in vivo* model systems to study tissue reorganization and inflammation in liver, respectively. In liver regeneration we observed the transient accumulation of HA-rich matrix along sinusoid and the synthesis of HA due to the specific increase in expression level of HA synthase1 (HAS1). The administration of ConA also induced the accumulation of HA-rich matrix, but, different from that in liver regeneration, the matrix contained the SHAP-HA complex and was formed around sublobular veins, suggesting that the HA-rich matrix in liver varies in compositions and loci so as to be functionally different and remodel the microenvironments in different and specific manners.