

ADAMTS4 is a crucial proteolytic enzyme for versican cleavage in the amnion at parturition

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Hyalactan cleavage may play an important role in extracellular matrix remodeling. However, the proteolytic enzyme responsible for hyalactan degradation for fetal membrane rupture at parturition remains unknown. Here, we revealed that versican (VCAN) was the major hyalactan in the amnion, where its cleavage increased at parturition with spontaneous rupture of membrane. We further revealed that ADAMTS4 was a crucial proteolytic enzyme for VCAN cleavage in the amnion. Inflammatory factors may enhance VCAN cleavage by inducing ADAMTS4 expression and inhibiting ADAMTS4 endocytosis in amnion fibroblasts. In turn, versikine, the VCAN cleavage product, induced inflammatory factors in amnion fibroblasts, thereby forming a feedforward loop between inflammation and VCAN degradation. Mouse studies showed that intra-amniotic injection of ADAMTS4 induced preterm birth along with increased VCAN degradation and proinflammatory factor abundance in the fetal membranes. Conclusively, there is enhanced VCAN cleavage by ADAMTS4 in the amnion at parturition, which can be reenforced by inflammation.