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Versican proteolysis and regulation of cell plasticity

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The embryo extracellular matrix, unlike that of the adult, is of a provisional nature, consistent with the need for active extracellular matrix remodeling during morphogenesis. The proteoglycan versican is a major component of this matrix and is widely distributed throughout the embryo. In contrast to MMPs, whose inactivation in mice led to few dramatic developmental phenotypes, ADAMTS proteases are emerging as a major regulatory force during morphogenesis. Several ADAMTS proteases appear to have evolved specifically to cleave versican, and among them, significant versican-related developmental roles are known for ADAMTS1, ADAMTS5, ADAMTS9, and ADAMTS20. These include myocardial and endocardial cushion remodeling, limb development and craniofacial development (1). The mechanisms of versican proteolysis by ADAMTS proteases were recently investigated (2).

Versican and its proteolysis were previously shown to regulate the fibroblast-myofibroblast transition (3), and recent evidence strongly suggests the phenotype modulation of smooth muscle cells by ADAMTS proteolysis of versican (4). It was recently shown that versican proteolysis by ADAMTS9 in the mouse umbilical cord was essential for PDGFRβ and Shh signaling during umbilical cord vascular growth, and for the acquisition of contractile cytoskeletal proteins by umbilical vascular smooth muscle cells. Collectively, impaired smooth muscle proliferation, differentiation, and orthogonal reorientation during vascular growth in the absence of ADAMTS9, led to defective umbilical vasculature, with fetal growth restriction and death as a consequence.

ADAMTS9, acting via versican proteolysis, has emerged as a major regulator of myometrial maturation. Although the uterus develops normally, and fertility is unimpaired in the absence

of ADAMTS9, female mice with conditional deletion of myometrial ADAMTS9 are unable to complete parturition. Our studies show that the myometrial activation process, which primes it for contraction, is impaired by accumulation of a versican and fibronectin-rich ECM in the absence of ADAMTS9.

These examples illustrate how ADAMTS proteolysis of versican serves crucial roles in morphogenesis and reproductive biology, with significant implications for matrix remodeling in adult diseases.

References:

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