Understanding the Dynamics of the Extracellular Matrix Remodeling in Ventral Abdominal Wall Development

腹側腹壁の発生における細胞外マトリックス再構築の動態解明

Gabriel Opoku
Graduate School of Health Sciences, Hirohata Lab

Research Highlights

- **Ventral abdominal wall** (VAW) development requires coordinated interactions between muscle layers, connective tissue, and the **extracellular matrix** (ECM).
- **ADAMTS1** (A disintegrin and metalloproteinase with thrombospondin type 1 motifs) is an ECM protease that cleaves the proteoglycan versican; its cleavage fragment, versikine, modulates cell migration, proliferation, and tissue morphogenesis.
- ADAMTS1 knockout (KO) mouse embryos provide an in vivo model of **omphalocele** (umbilical hernia) caused by defective **ECM remodeling**.
- The study combines structural (H&E) and molecular (versican, DPEAAE, MYH3, PITX2) readouts to link proteoglycan cleavage, transcription factor localization, and muscle layer integrity

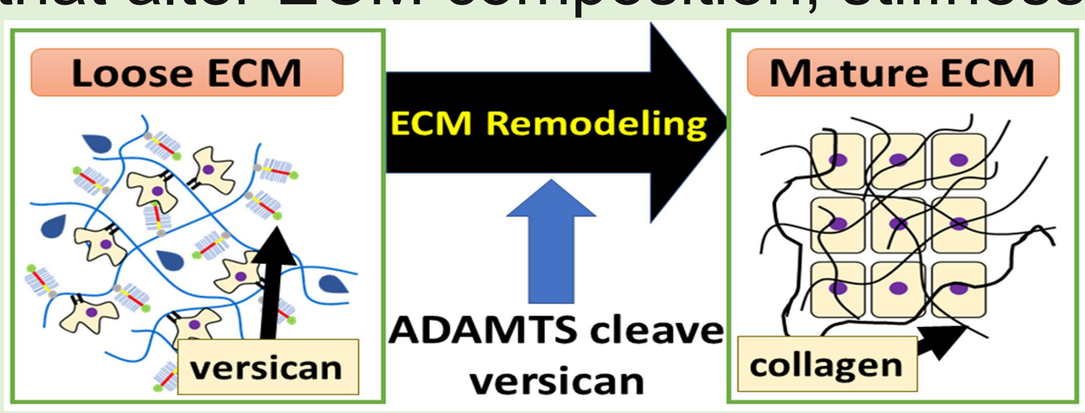
Problem Statement and Unique Features

Clinical and biological problem: Mechanistic links between ECM proteoglycan cleavage and congenital abdominal wall defects (such as omphalocele) are poorly defined.

Technical notions:

Extracellular matrix: a dynamic 3D network of proteins and proteoglycans that shapes tissue structure and cell signaling.

• **ECM remodeling**: protease-driven changes (e.g., by ADAMTS1) that alter ECM composition, stiffness, and bioactivity.

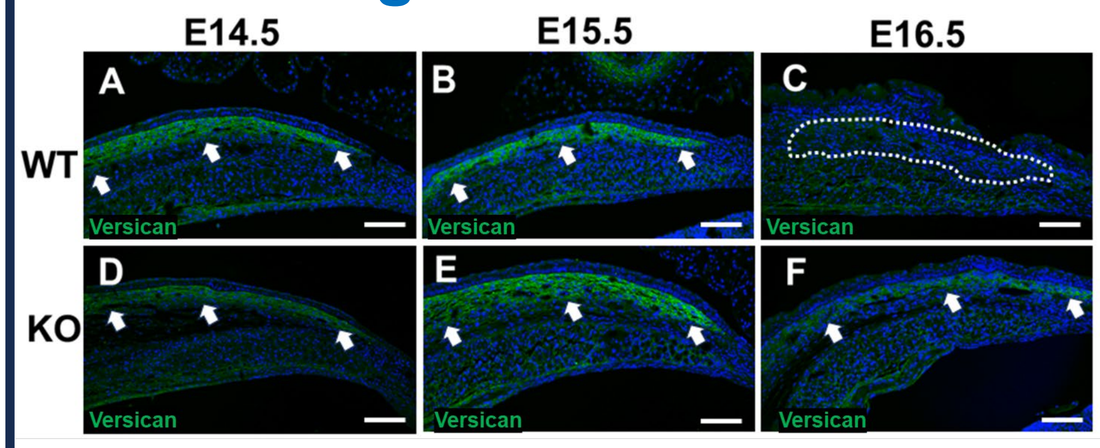


Use of DPEAAE neo-epitope as a specific readout of ADAMTS1-mediated versican cleavage in vivo.

• **Integration of ECM changes** (versican/DPEAAE), muscle architecture (MYH3, panniculus carnosus), and transcription factor dynamics (PITX2).

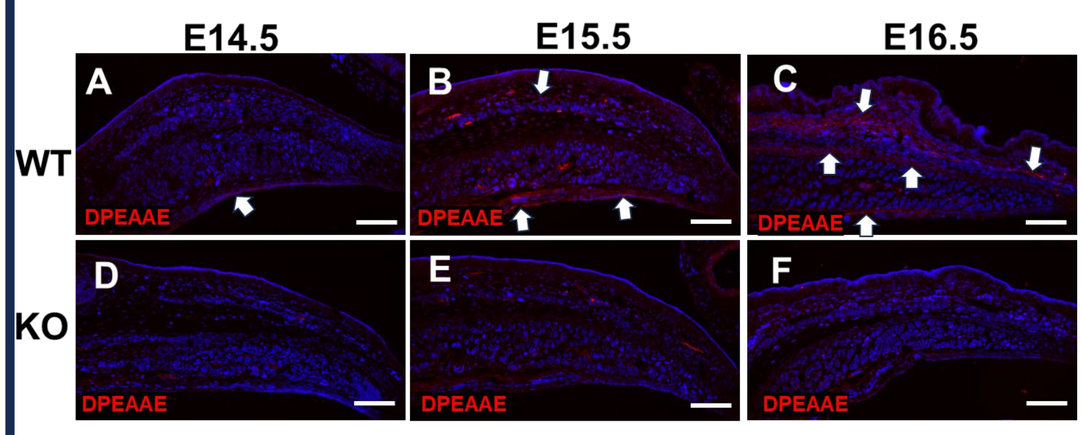
Results

ADAMTS1 deficiency is associated with enhanced versican staining



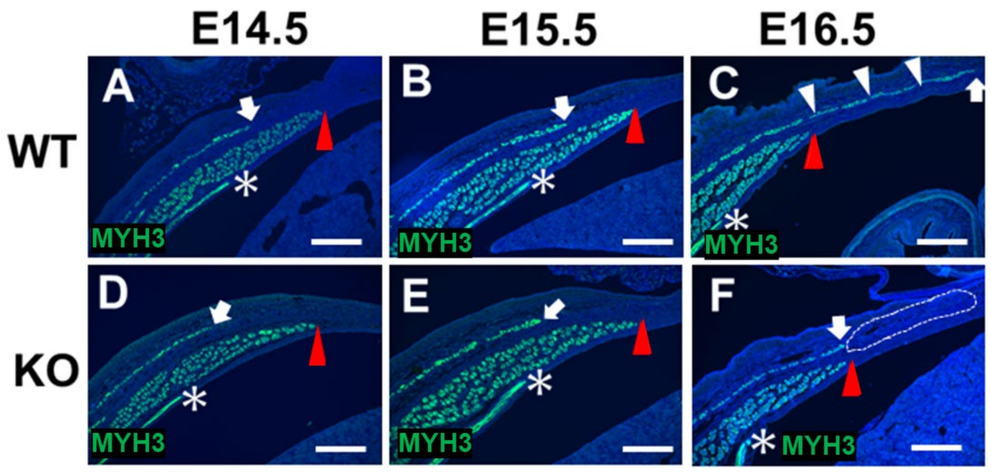
Versican staining **persisted in KO embryos** but decrease in WT by E16.5, indicating versican accumulation in the absence of ADAMTS1. Scale bars: 100μm.

Loss of ADAMTS1 abrogate versican degradation



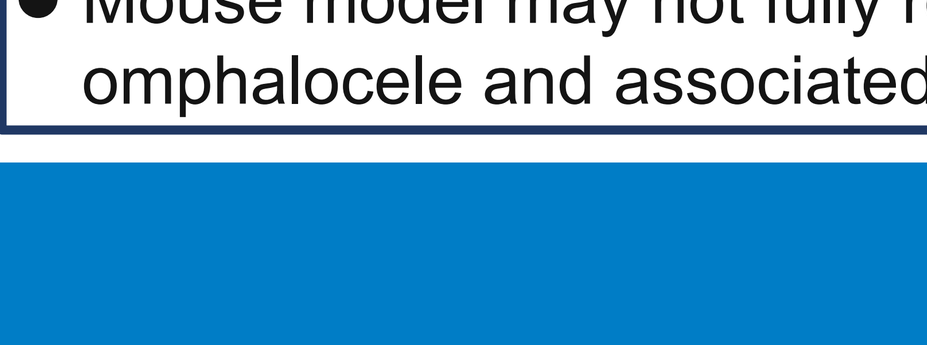
Cleaved versican (**DPEAAE, red**) increased progressively in WT embryos, indicating **active proteolysis**, while KO embryos showed minimal signals, confirming impaired versican cleavage. Scale bars: 100μm

Panniculus carnosus muscle (PC) development is impaired in *Adamts1* KO embryos



MYH3 staining revealed normal muscle organization in both genotypes up to E15.5, but at E16.5, the PC reached the umbilicus only in WT embryos, whereas KO embryos lacked PC. Scale bars: 100μm.

PITX2 staining is sustained in the absence of ADAMTS1



PITX2 expression decreased in WT by **E16.5** but remained strong in KO embryos, indicating sustained PITX2 activity. Scale bars: (A,B,D,E) 100μm, (C,F) 50μm.

Industry Appeal, Applications, and Limitations

- Establishes a mechanistically defined omphalocele model centered on ECM remodeling and proteoglycan processing.
- Identification of ECM- and transcription factor-based biomarkers for risk stratification and prognosis in abdominal wall defects.
- Mouse model may not fully recapitulate the full spectrum of human omphalocele and associated comorbidities.