Hyaluronan Drives Asymmetric Gut and Vascular Development

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Embryonic Development

- Organogenesis
- Primordial gut tube development
Packaging of Small Intestines
Medical Applications

Normal rotation

Mal-rotation occurs in 1:500 babies
Dorsal Mesentery

- Pathway to the gut for blood vessels and lymphatic vessels
90 degree Counterclockwise Rotation Initiates Intestinal Looping

Cross-section

Dorsal Mesentery

Gut tube

Leftward tilt
Left Mesenchyme Condenses Right Mesenchyme Expands
Dorsal Mesentery Exhibits Vascular Asymmetries
Pitx2 Drives Asymmetry

- High expression of the Pitx2 transcription factor on the left DM is attributed to left-right asymmetric development
Vascular Asymmetry

HH17
HH18
HH19

L R L R L R

Tie1-YFP

Mahadevan et al., Dev. Cell, 2014
Mesenchymal Expansion

- The expansion of the right DM coincides with the disappearance of vasculature
Extra-Cellular Matrix Responsible for Expansion
Extracellular Asymmetries

Alcian Blue

Hyaluronan

Proteoglycans

Hyaluronan
Presence of Hyaluronan

Fold change

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<th>HH17</th>
<th>HH17.5</th>
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<th>HH18.5</th>
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Is Hyaluronan Regulating Vascular Exclusion?

- Inhibiting HA synthesis using 4-methylumbelliferone-β-D xyloside (MU-xyloside)

HH16

WT

L

DA

R

R: DMSO

L

R: MU-Xyl

WT
HA depletion rescues vasculature in right DM

- Targeted degradation of HA using Hyal2
Summary

1. Vascular asymmetries initiated by right DM

2. Cellular asymmetries in the DM are spatially and temporally coordinated with vascular asymmetries
Summary

1. Vascular asymmetries initiated by right DM

2. Cellular asymmetries in the DM are spatially and temporally coordinated with vascular asymmetries

3. Pronounced asymmetries at the level of ECM coincide with vascular asymmetries.

4. Hyaluronan is necessary for vascular asymmetries
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