β-Catenin Is a Central Mediator In Systemic Sclerosis

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Wnt/β-catenin-pathway

- Wnt-2 and SFRP4 are increased in Tsk mouse skin (Bayle et al. J Invest Dermatol 2008;128:871-881)
- Wnt-10b is increased in the bleomycin model and in lesional SSc tissue (Wei et al. Arthritis Rheum 2011;63:1707-1717 & Distler et al. Nat Comm in press, abstract)
- Inhibition of GSK-β induces fibrosis (Bergmann et al., Arthritis 2011 Aug 25; abstract)
- Dkk-1 is decreased in SSc (Distler et al. Nat Comm in press, abstract)
- TGF-β decreases Dkk-1 expression and stimulates Wnt/β-catenin signaling (Distler et al. Nat Comm in press, abstract)
- β-catenin is the central integrator of canonical Wnt signaling

Wnt-signaling in SSc

- Wnt-2 and SFRP4 are increased in Tsk mouse skin (Bayle et al. J Invest Dermatol 2008;128:871-881)
- Wnt-10b is increased in the bleomycin model and in lesional SSc tissue (Wei et al. Arthritis Rheum 2011;63:1707-1717 & Distler et al. Nat Comm in press, abstract)
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- Dkk-1 is decreased in SSc (Distler et al. Nat Comm in press, abstract)
- TGF-β decreases Dkk-1 expression and stimulates Wnt/β-catenin signaling (Distler et al. Nat Comm in press, abstract)
- β-catenin is the central integrator of canonical Wnt signaling

Stabilization of β-catenin in SSc

- β-catenin is the central integrator of canonical Wnt signaling

Is β-catenin a key player of fibrosis?
Stabilization of β-catenin in SSc

Overexpression of Wnts leads to β-catenin stabilization

Fibroblast-specific targeting of β-catenin in vivo

ΔEx3 β-catenin

fibroblast-specific stabilization
**Fibroblast-specific targeting of β-catenin in vivo**

Col1a2; Cre-ER

![Diagram](image1)

**Fibroblast-specific targeting of β-catenin in vivo**

ΔEx3 β-catenin

β-catenin

fibroblast-specific stabilization

fibroblast-specific deletion

**Stabilization of β-catenin drives fibrosis**

Skin thickness

2 weeks 4 weeks 8 weeks

![Graph](image2)

**Stabilization of β-catenin drives fibrosis**

![Graph](image3)

**Deletion of β-catenin inhibits experimental fibrosis**

Skin thickness

2 weeks 4 weeks 8 weeks

![Graph](image4)

**Deletion of β-catenin inhibits experimental fibrosis**

![Graph](image5)

**Summary**

- β-catenin is stabilized by Wnt-1 and -10b in SSc
- Fibroblast-specific stabilization of β-catenin drives progressive skin fibrosis
- Fibroblast-specific deletion of β-catenin inhibits bleomycin-induced skin fibrosis

→ Wnt/β-catenin signaling is a potential molecular target for the treatment of fibrosis in SSc
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