Smad2-dependent PN-1 overexpression differentiates progressive aneurysms from acute dissections of human ascending aorta

Inserm U698, Xavier Bichat Hospital, Paris.

Delphine Gomez & Jean-Baptiste Michel
Common pathology
Plasminogen convection and plasmine activation in TAA

Plasminogen convection and plasmine activation in TAA
Fibronectin turnover

[Fibronectin turnover graph]

[Control and TAA groups compared]
Overexpression of antiproteases in TAA
Plasminogen activators and Smad2 expression

Smad2 mRNA (aortic tissue)

Smad2 mRNA (cultured VSMC)
Epigenetic control of antiprotease overexpression in TAA

**PN-1 mRNA level**

- Control VSMC
- TAA VSMC

**PAI-1 mRNA level**

- Control VSMC
- TAA VSMC

**PN-1 mRNA level**

- Control siRNA
- Smad2 siRNA

**PAI-1 mRNA level**

- Control siRNA
- Smad2 siRNA

Legend:
- * p < 0.05 compared to control
- # p < 0.05 compared to TGF-β1+TRAP
Epigenetic control of antiprotease overexpression in TAA

**Smad2 enrichment on the PN-1 promoter**

<table>
<thead>
<tr>
<th>Gene</th>
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<th>position</th>
<th>strand</th>
</tr>
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<tbody>
<tr>
<td>PN-1</td>
<td>CGTCTGCCT</td>
<td>-834</td>
<td>+</td>
</tr>
<tr>
<td>PAI-1</td>
<td>GTCTGTGT</td>
<td>-903</td>
<td>+</td>
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<td>AGCCAGACA</td>
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<td></td>
<td>AGACAGACA</td>
<td>-281</td>
<td>-</td>
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**Smad2 enrichment on the PAI-1 promoter**

**PUTATIVE SMAD BINDING SITES**

- PN-1 CGTCTGCCT -834 +
- GTCTGTGT -903 +
- AGCCAGACA -734 -
- AGTCTGGAC -686 +
- AGACAGACA -585 -
- AGACAGACA -281 -

- Smad consensus binding site

**Smad2 binding (IP/INPUT)**

**PN-1 Promoter**

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**Smad2 binding (IP/INPUT)**

- Control
- TAA

**Smad2 enrichment**

- Control
- TAA

**Epigenetic control of antiprotease overexpression in TAA**
VSMC consequences

Plasminogen activation at VSMC surface

Pericellular plasmin inhibition by VSMCs

VSMC detachment induced by plasminogen

Plasmin activity (/s)

Non-treated Control VSMCs
TGF-β1 Control VSMCs
Non-treated aneurysmal VSMCs
TGF-β1 aneurysmal VSMCs
VSMC consequences

A: Control VSMCs

<table>
<thead>
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<th>Plasmin</th>
<th>Plasmin + Ab PN-1</th>
<th>Plasmin + control Ab</th>
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<td>DAPI</td>
<td></td>
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B: TAA VSMCs

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TGF-β1
Epigenetic reprogramming of antiproteases expression

Intrinsic defect (monogenic diseases)

Extrinsic injuries (blood-borne protease overload)

Enhanced sensitivity to extrinsic injuries

VSMC

Epigenetic reprogramming of antiproteases expression

Progressive dilatation

Aneurysm

NO reprogramming

Acute rupture

Dissection

Conclusion