Role of GAG synthesizing enzymes as targets for the prevention of atherosclerosis

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Presentation overview

- Cardiovascular disease/Atherosclerosis
- Imatinib & PG/LDL binding *in vivo* and *in vitro*
- Proteoglycan structure
- GAG synthesising enzymes
- Emerging data
- Future directions
Human coronary artery disease

“Normal” acute proximal lesion

Coronary artery atherosclerosis

Coronary angiograms courtesy of Dr Archer Broughton, Cardiology, Alfred Health
Imatinib inhibits lipid binding and atherosclerosis

Imatinib inhibits GAG hyperelongation in VSMC

Proteoglycans

Glycosaminoglycan chain

“Natural” or basal chain

Hyperelongation

Core Protein

Linkage region

Glycosaminoglycan chain

Xyl  GlcA  Gal  GalNAc

GlcA  GalNAc

Hyperelongation

LDL Particles

TGF-β (ng/ml)

kDa

220

97

Biglycan

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Chondroitin sulfate GAG synthesising enzymes

Progression of atherosclerosis in mouse aorta

Expression of GAG synthesising enzymes in mouse aorta

TβR-I mediates GAG hyperelongation

Smad and p38 MAP kinase-mediated signaling of proteoglycan synthesis in vascular smooth muscle. Dadlani et al. JBC (2007)
Temporal expression of GAG synthesising enzymes

Linkage region

“Natural” or basal chain

Hyperelongation

XT-1

GalNAcT-2, ChSy-1

C4ST-1

Xyl

GlcA

Gal

GalNAc

XYT-1

CHSY1

C4ST1

Xylosyltransferase-1

Chondroitin sulfate synthase-1

Chondroitin 4-O-sulfotransferase-1

Xylosyltransferase-1 mRNA expression (Fold change)

Chondroitin sulfate synthase-1 mRNA expression (Fold change)

Chondroitin 4-O-sulfotransferase-1 mRNA expression (Fold change)
Future plans

With our ability to measure the expression of mRNA for enzyme causing GAG hyperelongation, we wish to:

*In vitro or cell studies:*

– Use selective knockdown techniques (siRNA) to silence individual genes and identify which are associated with GAG elongation.

*Animal studies for atherosclerosis:*

– Extend studies of GAG synthesising enzymes from vascular smooth muscle cells to **blood vessels**.

– Assess the regulation of individual GAG synthesising enzymes in blood vessels in animal studies of atherosclerosis and its prevention by drugs such as imatinib.