The Abnormal Accumulation of Heparan Sulfate in Patients with Mucopolysaccharidosis Prevents the Elastolytic Activity of Cathepsin V

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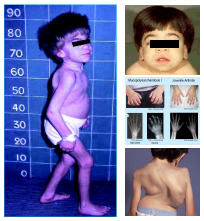
Introduction: Mucopolysaccharidosis (MPS) types I, II, and III represent a group of rare inherited lysosomal storage diseases characterized by accumulation of glycosaminoglycans, in particular heparan sulfate (HS). Patients exhibit progressive multi-visceral dysfunction and shortened lifespan mainly due to a severe cardiac/respiratory decline. According to collagen and elastin afford essential support for the parenchymal portions of the lungs, there may be a relationship between the altered collagen/elastin metabolism and reduced lung function in MPS. Cathepsin V (CatV) is a potent elastolytic protease (elastin degradation) implicated in extracellular matrix (ECM) remodeling.

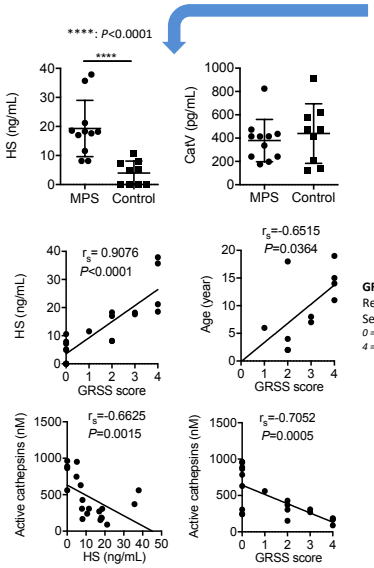
Aim: Whether levels and activity of CatV are altered by HS in lungs from MPS (I, II, III) patients remained unknown.



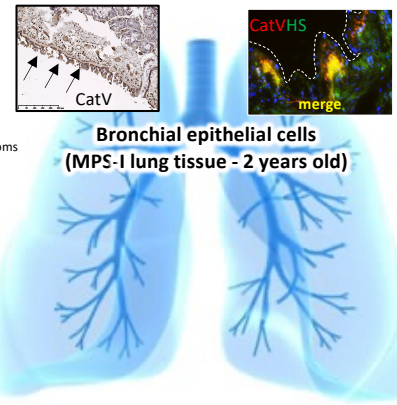
RESULTS

CatV inhibition by HS *ex vivo*

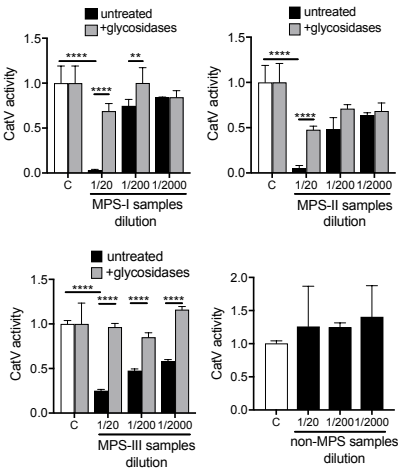
Sputum, expectoration from young patients:
-MPS I (n=2), II (n=5), III (n=4)
-Non-MPS (control, n=9)



GRSS score (Global Respiratory Symptoms Severity): **0-4**
0 = no symptom
4 = severe symptoms



Bronchial epithelial cells
(MPS-I lung tissue - 2 years old)

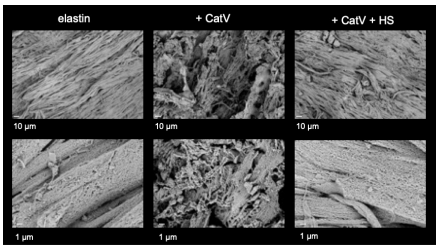


HS level and cathepsins activity are associated with the onset of respiratory-related disorders

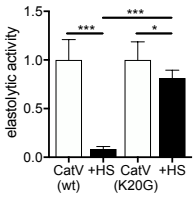
Accumulation of HS in MPS patients impairs CatV activity.

CatV inhibition by HS *in vitro* (Ki= 11.4±3 µM): Lys20 is crucial

Scanning Electron Microscope

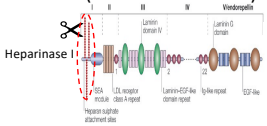


Site-directed mutagenesis in the active site of CatV (mutant CatV K20G)

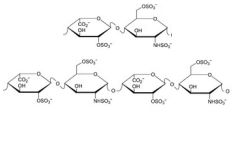


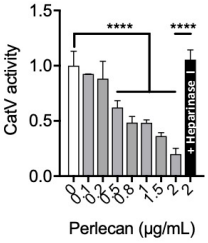
HS-related glycosaminoglycans are potent inhibitors of CatV

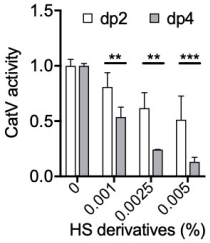
Heparan sulfate Proteoglycan 2 (Perlecan: 400 kDa)



di- and tetra-saccharides (dp2, dp4)

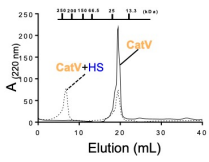




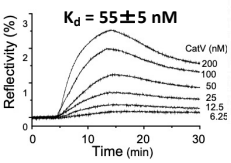


Complex formation between CatV and HS

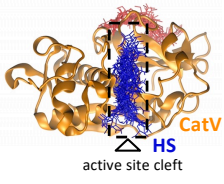
Size exclusion chromatography



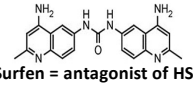
SPRi



MD simulations



SURFEN restores CatV activity (*in vitro*, MPS samples)



Surfen = antagonist of HS