Progranulin Regulation of Autophagy Contributes to Its Chondroprotective Effect in Osteoarthritis

Fengjin Guo^{1,2}, Aubryanna Hettinghouse², Eric Strauss², Chuan-Ju Liu^{2*}

1. Department of Cell Biology and Genetics, Core Facility of Development Biology, Chongqing Medical University, Chongqing 400016, China
2. Departments of Orthopaedic Surgery, New York University School of Medicine, New York, NY10003, USA

Osteoarthritis

The most common arthritis, Joint degenerative disease ,

Symptoms and signs

- Pain
- Tenderness
- Bony swelling
- Cartilage degradation
- Osteophytes
- Bone sclerosis and attrition
- Synovium inflammation
- Muscle atrophy
- Single- or multiple-joint osteoarthritis

Progranulin is a growth factor with multiple functions

Guo Fengjin ; Yongjie Lai; Qingyun Tian; Li Kong; Edward A. Lin;Chuan-ju Liu, Granulin-Epithelin Precursor (GEP) Binds Directly to ADAMTS-7 and ADAMTS-12 and Inhibits Their Degradation of Cartilage Oligomeric Matrix Protein, ***Arthritis and Rheumatism***, 2010.6, 62(7): 2023~2036.

Zhao YP, Tian QY, Wei JL, Richbough B, Liu CJ. Progranulin protects against osteoarthritis through interacting with TNF- α and β -Catenin signalling. ***Ann Rheum Dis***. 2015;74(12):2244-2253.

Jian J, Zhao S, Tian QY, Liu H, Zhao Y, Chen WC, Grunig G, Torres PA, Wang BC, Zeng B, Pastores G, Tang W, Sun Y, Grabowski GA, Kong MX, Wang G, Chen Y, Liang F, Overkleeft HS, Saunders-Pullman R, Chan GL, Liu CJ. Association Between Progranulin and Gaucher Disease.

EBioMedicine. 2016;11:127-137.

Jian, J., Hettinghouse, A. Grunig, G.; Zhang, W.; Setchell, K.D.R; Overkleeft, H.S.; Chan, G.L; and Liu, C.J. Progranulin Recruits HSP70 to Glucocerebrosidase and Is Therapeutic Against Gaucher Disease.

EBioMedicine. 2016 ;13:212-224.

Caramés B., Hasegawa, A., Taniguchi, N., Miyaki, S., Blanco, F.J., and Lotz, M. *Autophagy activation by rapamycin reduces severity of experimental osteoarthritis.* **Ann Rheum Dis**, 2012;71(4):575-81.

Caramés B., Olmer, M., Kiosses, W.B., and Lotz, M. *The relationship of autophagy defects to cartilage damage during joint aging in a mouse model.* **Arthritis & rheumatology**, 2015;67(6):1568-76.

Objective

To determine whether PGRN also regulates chondrocyte autophagy and if so, whether PGRN regulation of autophagy is important for PGRN's protective role in OA.

Autophagy-associated molecules are elevated in OA chondrocytes

Expression of PGRN, ATG5, ATG12 and LC3 α/β in OA and normal chondrocytes.

PGRN is required for chondrocyte autophagy

PGRN^{-/-} chondrocyte (C28I2)

PGRN is required for chondrocyte autophagy

PGRN is required for IL-1 β triggered chondrocyte autophagy

A

B

	Sample name	Subset name	Mean
	No treatment(WT)	Ungated	33.62
	IL-1 β (WT)	Ungated	167.85
	No treatment(KO)	Ungated	142.59
	IL-1 β (KO)	Ungated	145.38

C

Local delivery of recombinant PGRN attenuated OA development in a surgically induced model

Autophagy is important for PGRN's protective role in chondrocytes and OA

A

human OA joints

B

Mouse DMM OA model

Autophagy is important for PGRN's protective role in chondrocytes and OA

PGRN interacts with ATG5-ATG12 conjugate in chondrocytes and cartilage

Granulin E and G domains of PGRN are important for its association with ATG5-ATG12

Summary

a) Progranulin-mediated autophagy is important for its chondroprotective effect in OA.

b) PGRN regulates autophagy in chondrocytes and OA through, at least partially, the interactions between Granulin E and G domains of PGRN and ATG5-ATG12 conjugate.

THANK YOU!!

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