Regulatory effects of EphB2 signaling on stem cell aging and Nrf2-mediated antioxidative mechanism

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Dean, College of Vet. Medicine, Seoul National University

Presentation for Keiichiro Maeda Memorial Ise Award Lecture, 20210924

Introduction

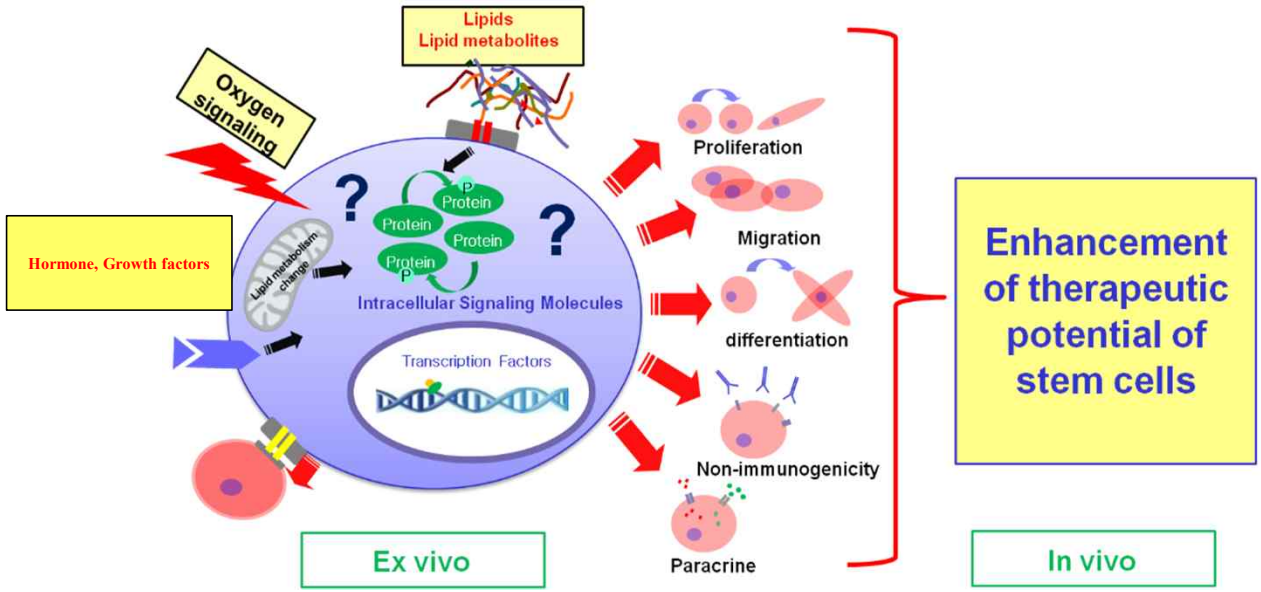
Academic career

2007-2013 College of Veterinary Medicine, Kyungpook National University, Daegu, Korea

2013-2021 College of Veterinary Medicine, Seoul National University, Seoul, Korea.

Research of interest

Identifying the molecular mechanism of stem cell aging and the antioxidative mechanism of extracellular bioactive molecules, such as nutrients, growth factors, hormone, and cytokines.



Major achievements

Lee HJ*, **Jung YH***, Choi GE, Kim JS, Chae CW, Lim JR, Kim SY, Yoon JH, Cho JH, Lee SJ, Han HJ. Urolithin A suppresses high glucose-induced neuronal amyloidogenesis by modulating TGM2-dependent ER-mitochondria contacts and calcium homeostasis. *Cell Death Differ*. 2021 Jan;28(1):184-202. *Co-first author. IF : 15.828

Jung YH, Lee HJ, Kim JS, Lee SJ, Han HJ. EphB2 signaling-mediated Sirt3 expression reduces MSC senescence by maintaining mitochondrial ROS homeostasis. *Free Radic Biol Med*. 2017 Sep;110:368-380. IF: 7.376

Jung YH, Lee SJ, Oh SY, Lee HJ, Ryu JM, Han HJ. Oleic acid enhances the motility of umbilical cord blood derived mesenchymal stem cells through EphB2-dependent F-actin formation. *Biochim Biophys Acta*. 2015 Aug;1853(8):1905-17. IF: 4.739

Kim JS*, **Jung YH***, Lee HJ, Chae CW, Choi GE, Lim JR, Kim SY, Lee JE, Han HJ. Melatonin activates ABCA1 via the BiP/NRF1 pathway to suppress high-cholesterol-induced apoptosis of mesenchymal stem cells. *Stem Cell Res Ther*. 2021 Feb 5;12(1):114. *Co-first author. IF: 6.832

Lee HJ*, **Jung YH***, Choi GE, Kim JS, Chae CW, Lim JR, Kim SY, Lee JE, Park MC, Yoon JH, Choi MJ, Kim KS, Han HJ. O-cyclic phytosphingosine-1-phosphate stimulates HIF1α-dependent glycolytic reprogramming to enhance the therapeutic potential of mesenchymal stem cells. *Cell Death Dis*. 2019 Aug 5;10(8):590. *Co-first author. IF: 8.460


Contents lists available at ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Original article

EphB2 signaling-mediated Sirt3 expression reduces MSC senescence by maintaining mitochondrial ROS homeostasis

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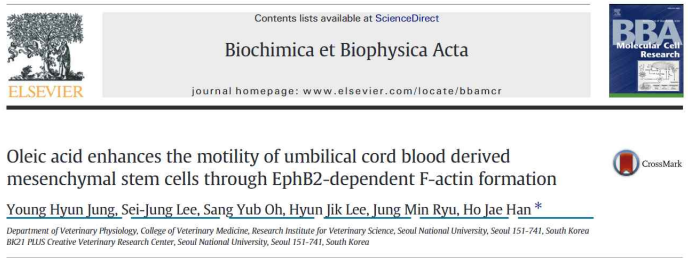
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Biochimica et Biophysica Acta

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Oleic acid enhances the motility of umbilical cord blood derived mesenchymal stem cells through EphB2-dependent F-actin formation

Young Hyun Jung, Sei-Jung Lee, Sang Yub Oh, Hyun Jik Lee, Jung Min Ryu, Ho Jae Han *

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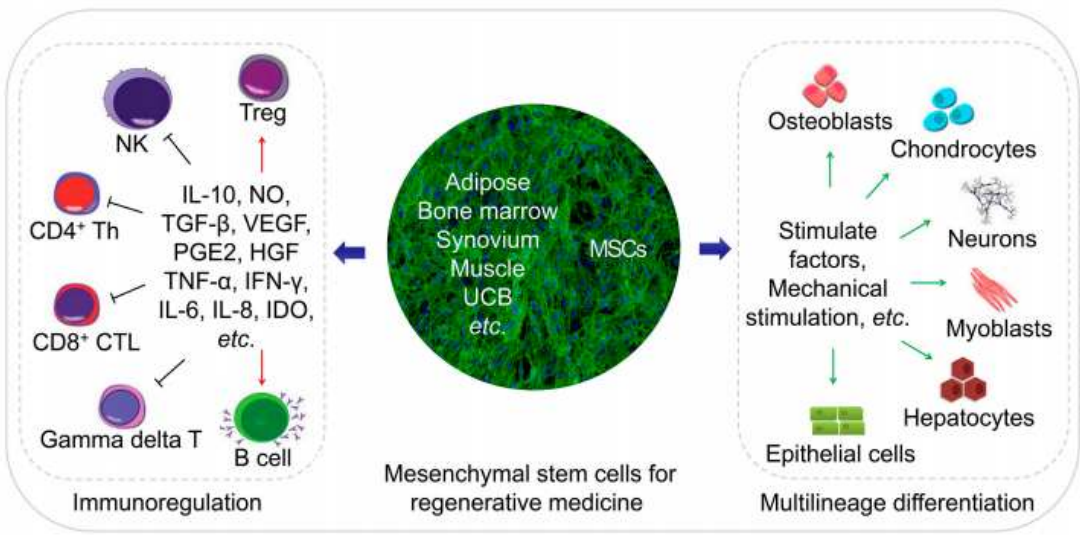
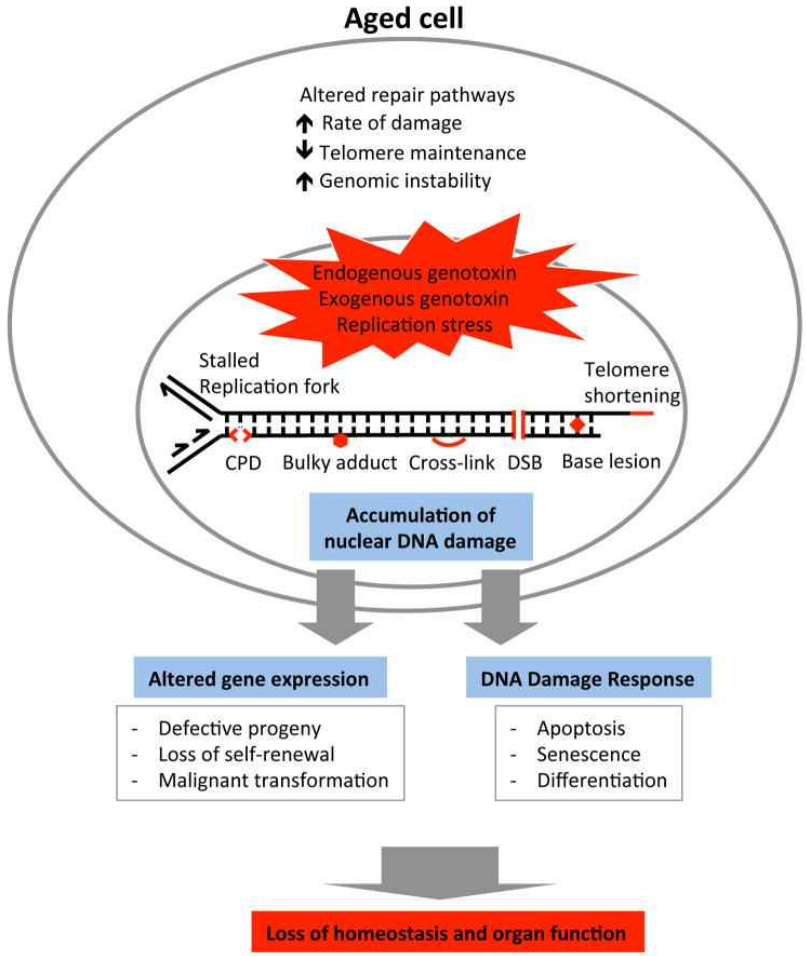
Mesenchymal stem cells and aging



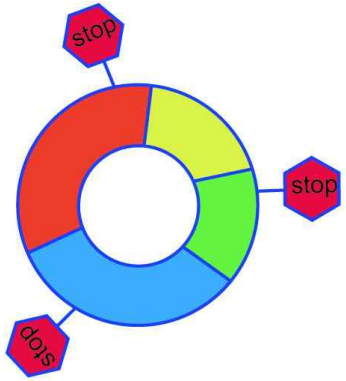
(Han et al., Cells, 2017)



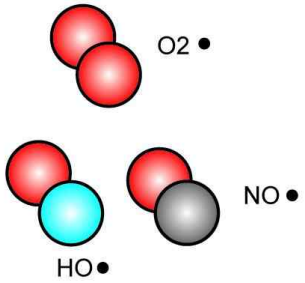
Good but could be aged,
Can stem cells are reversed from aging?

(Oh et al., Nat Med, 2015)

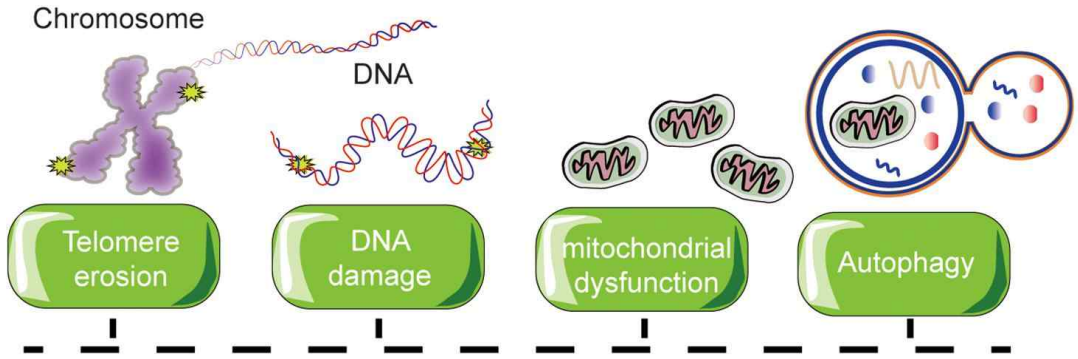
MSCs and senescence

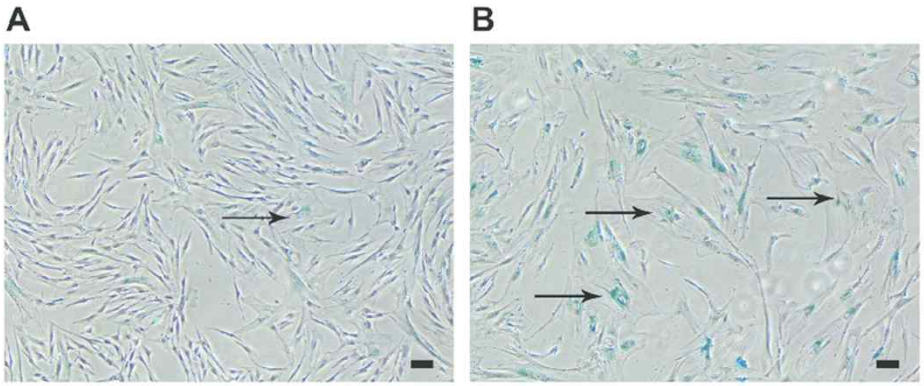


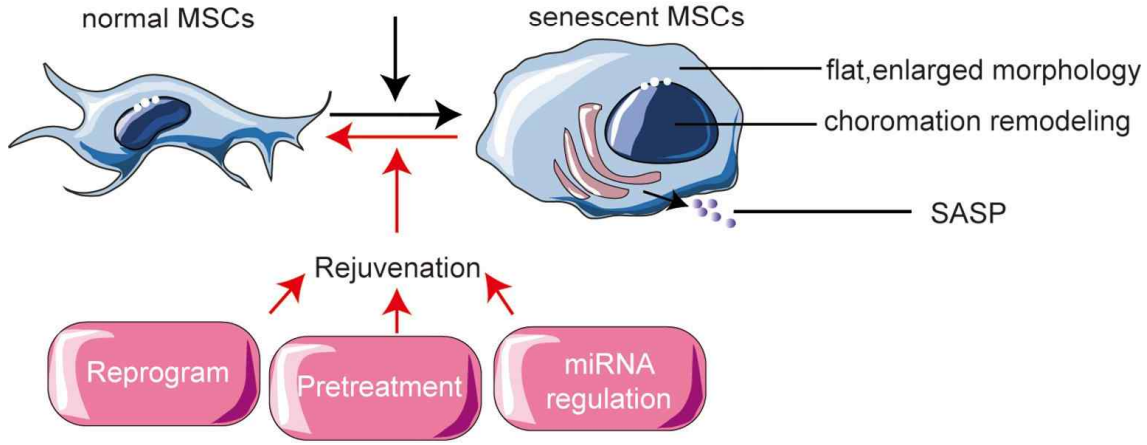
Replicative senescence



Stress-induced senescence



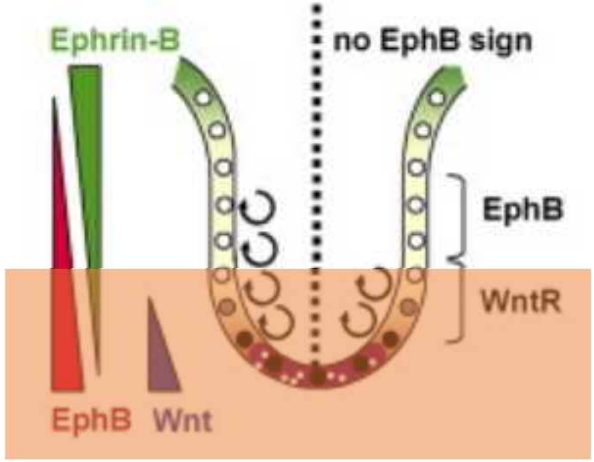




Proliferative but not infinite, Viable but not normal,
What to do?

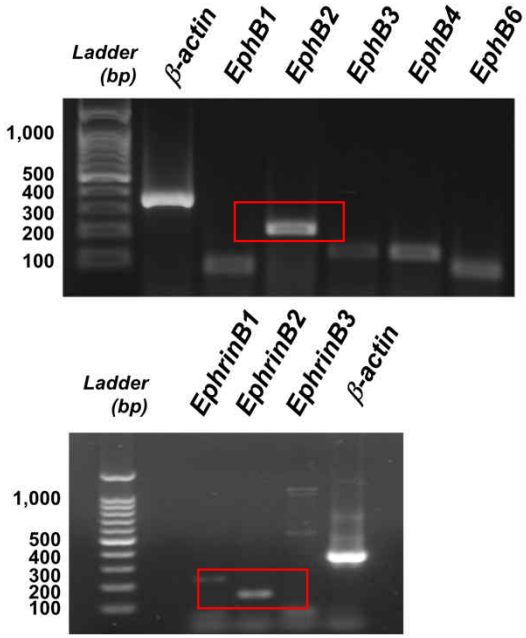
(Zhou et al., Front. Cell Dev. Biol. 2020)

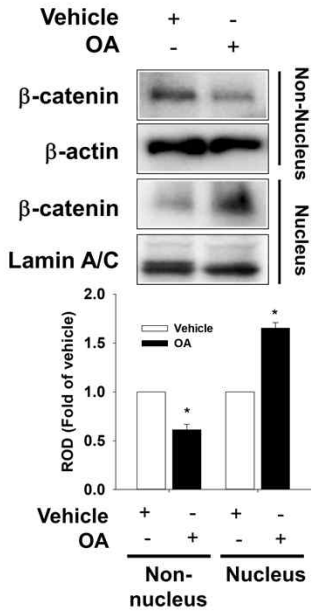
EphB2 expression in MSCs

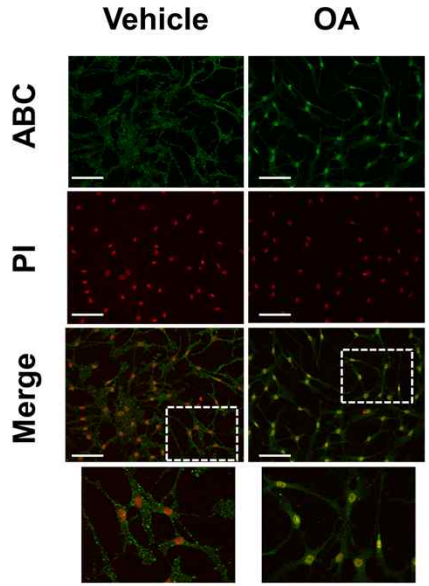


EphB2 expression is high in intestinal stem cell niche (Proliferative and migratory)

Which EphBs expression in UCB-MSCs?

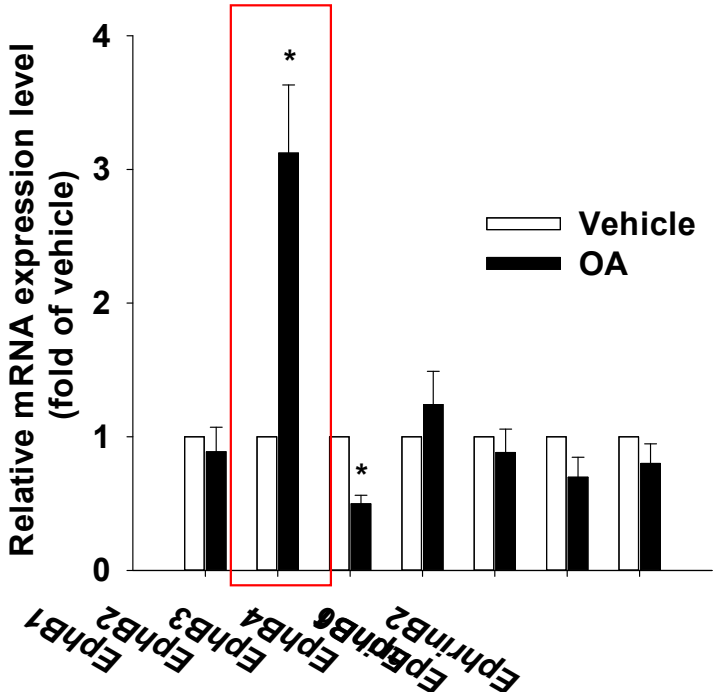


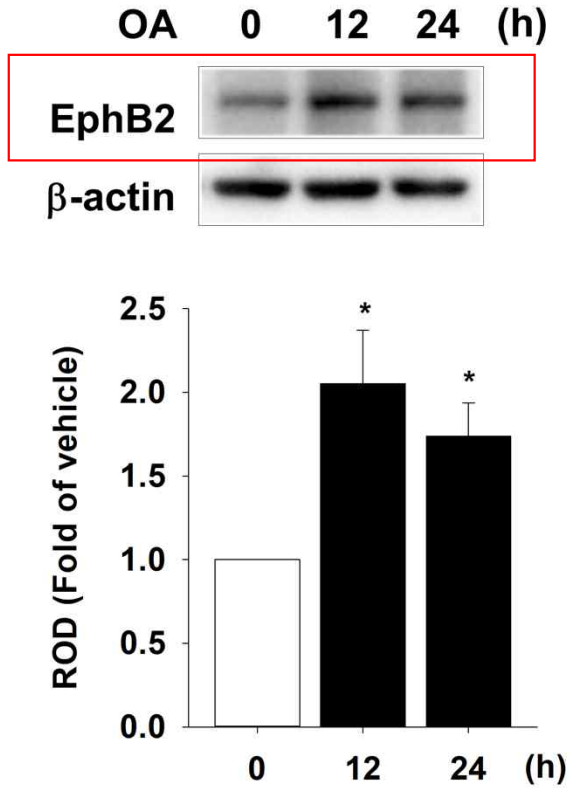




Oleic acid induces Wnt/β-catenin signaling

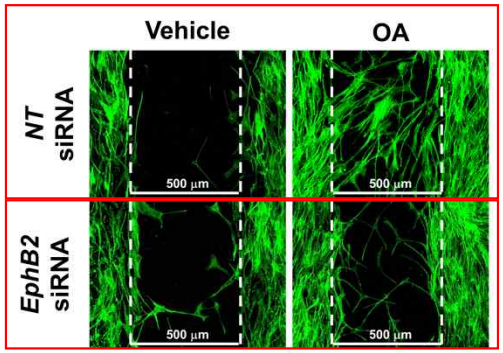
EphB2 expression in MSCs

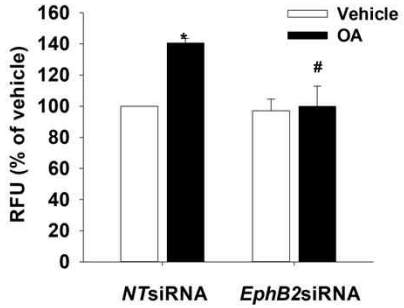


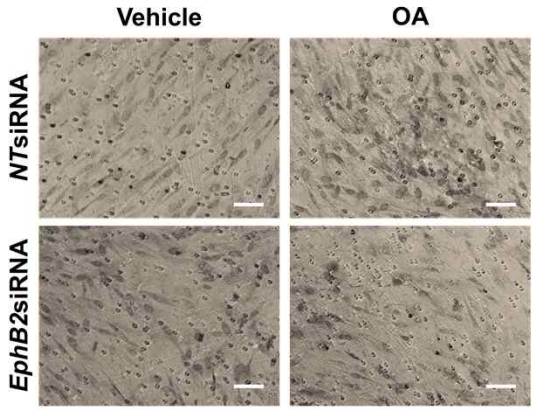


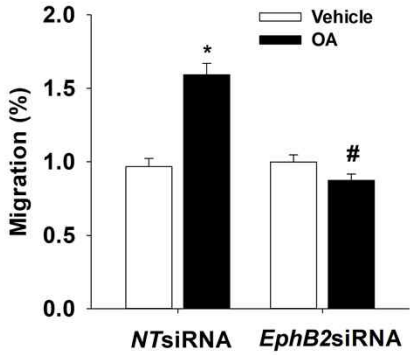
Oleic acid increased EphB2 expression

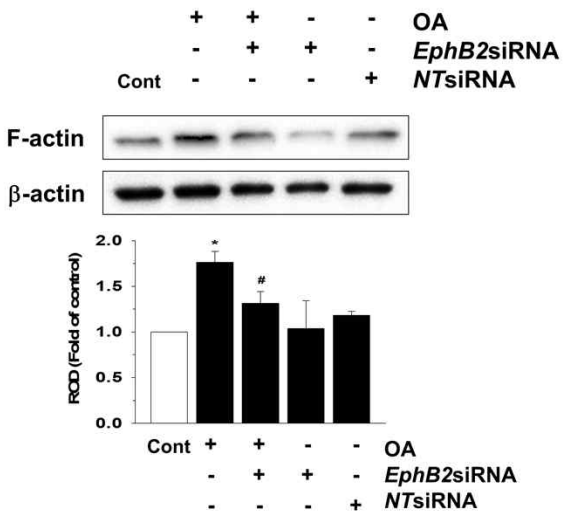
EphB2 expression is regulator of stem cell migration

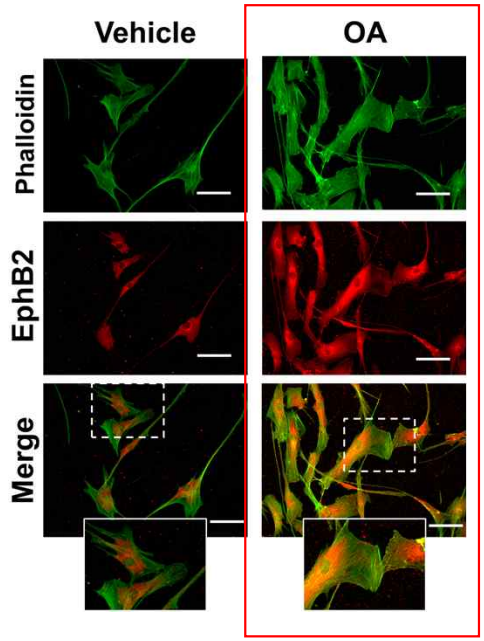








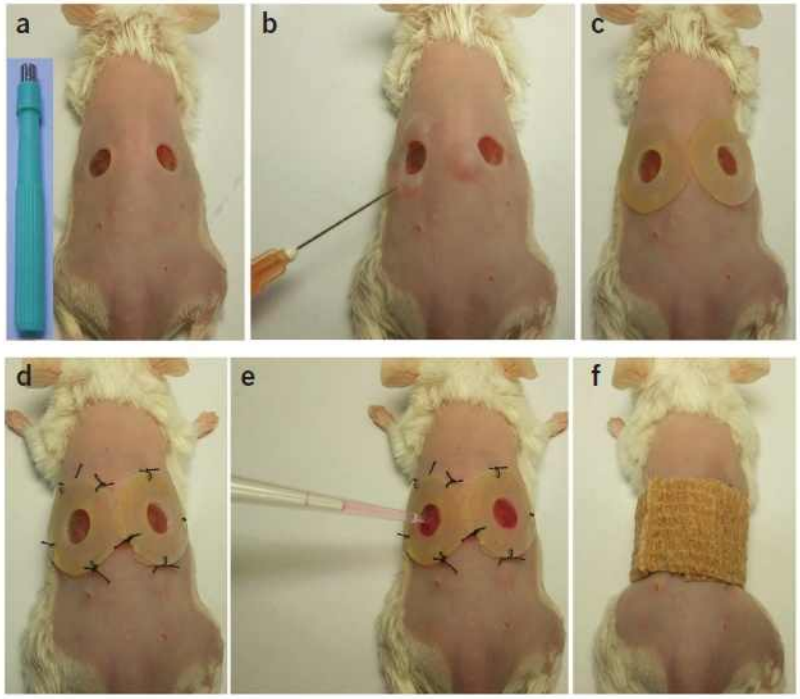




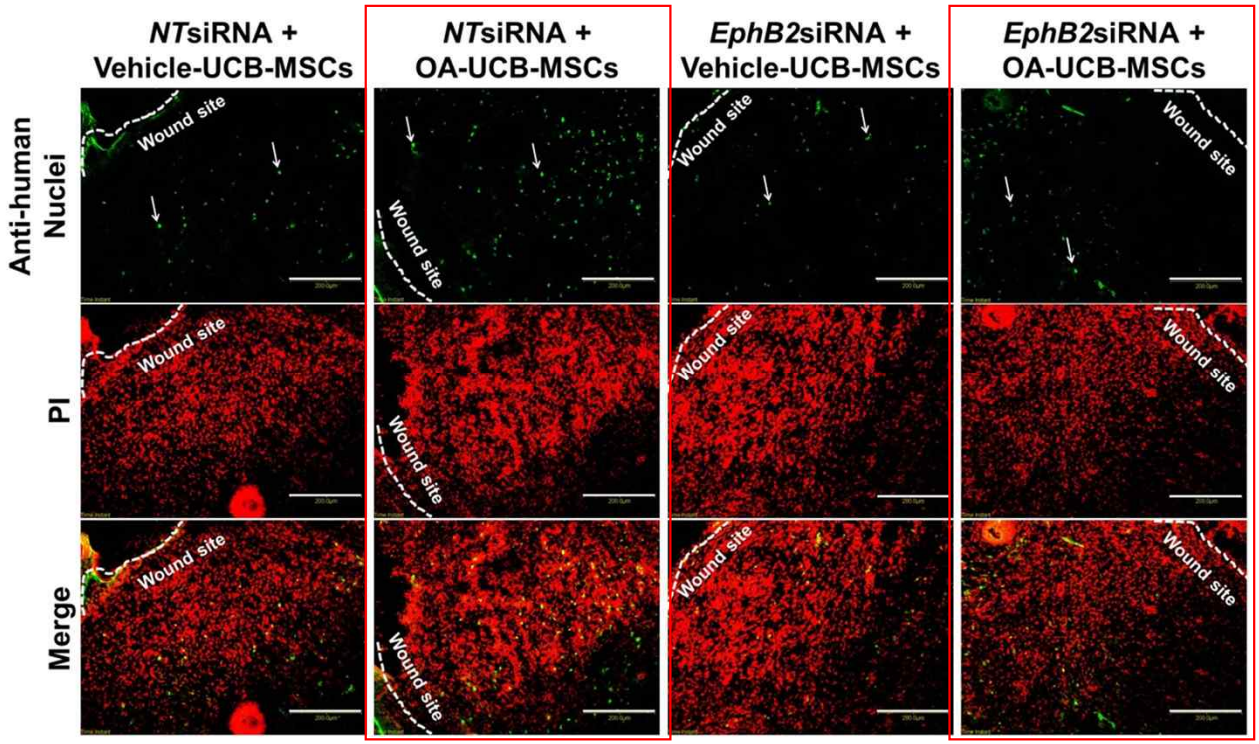
EphB2 expression ↓
→ slow migration

EphB2 expression ↑
→ Filamentous actin ↑

In vivo skin wound healing analysis



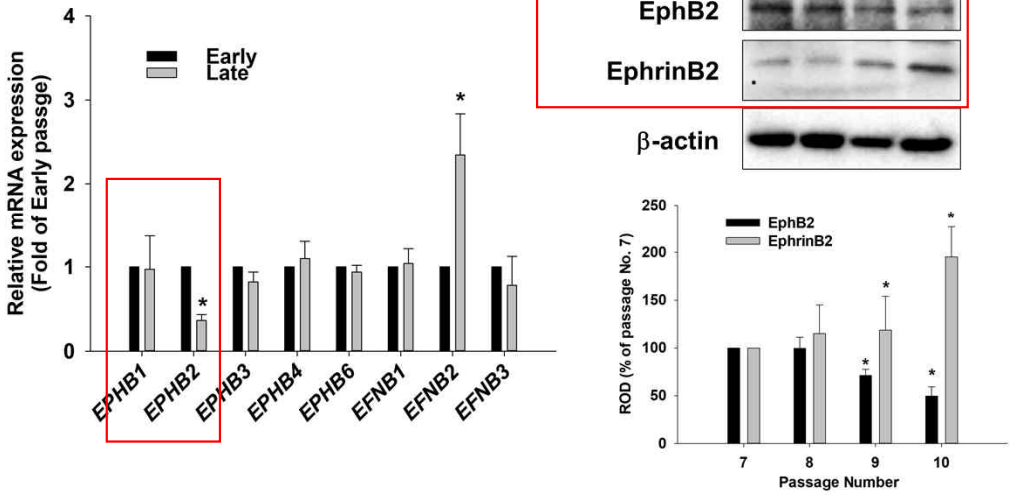
Injection of MSC around would sites

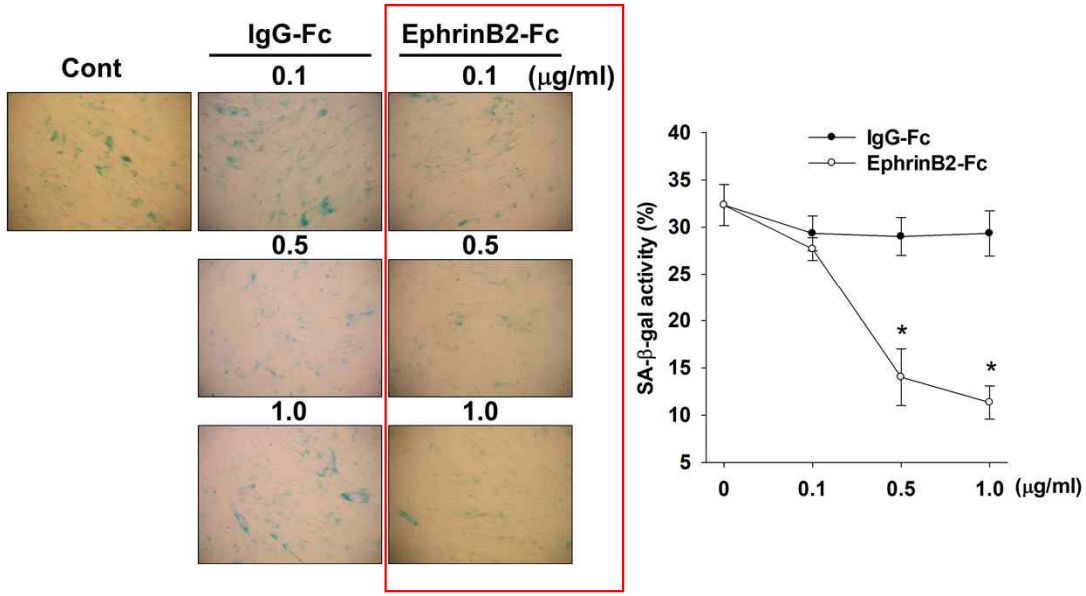


EphB2 expression ↑
→ Fast migration in skin wound sites

Differential expression levels of Ephrin/Ephs in MSCs

How about the change of EphBs expression in senescent MSCs?

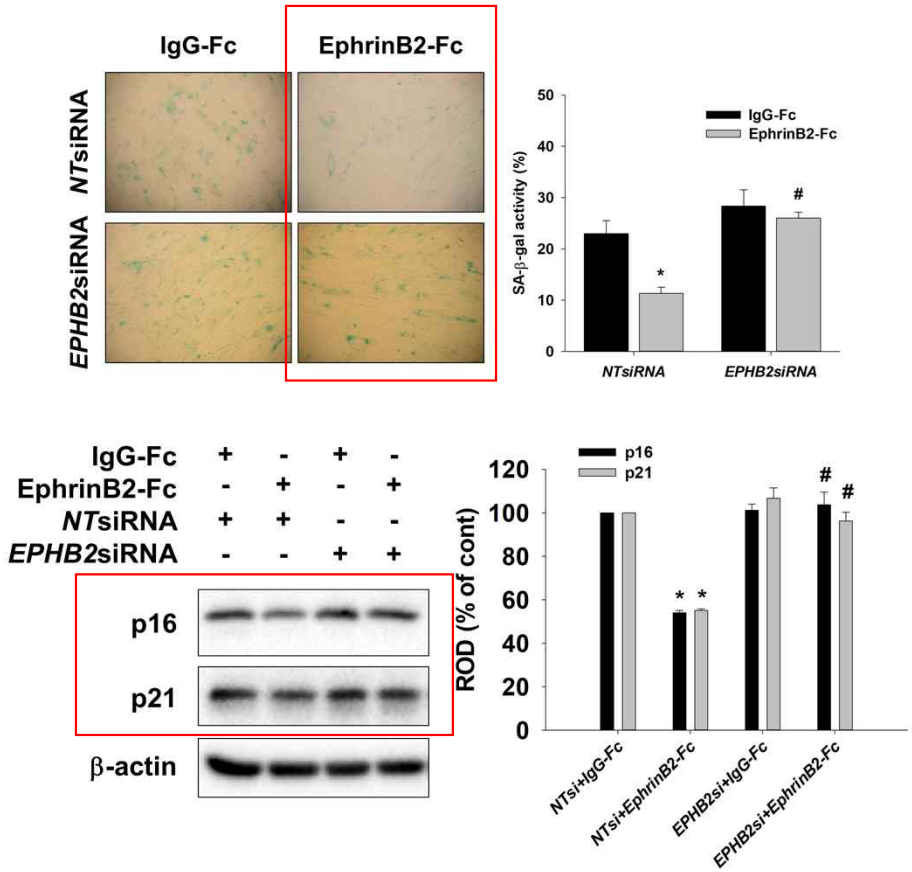




Passage ↑ →
EphB2 ↓, EphrinB2 ↑

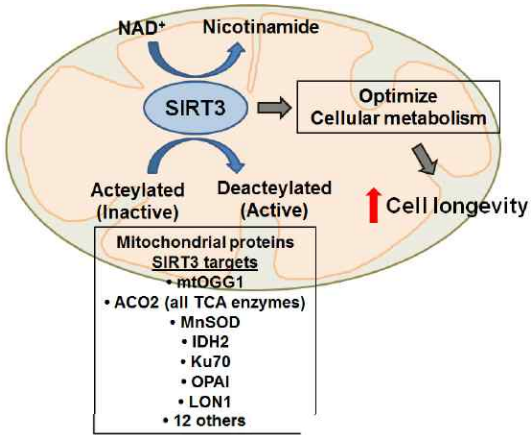
EphB2 activation
→ Slow senescence

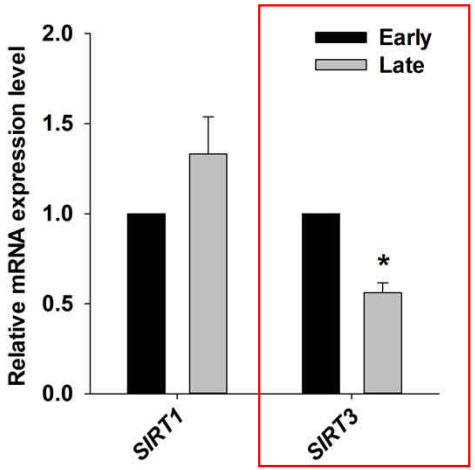
Effect of EphB2 signaling in anti-senescence of MSCs

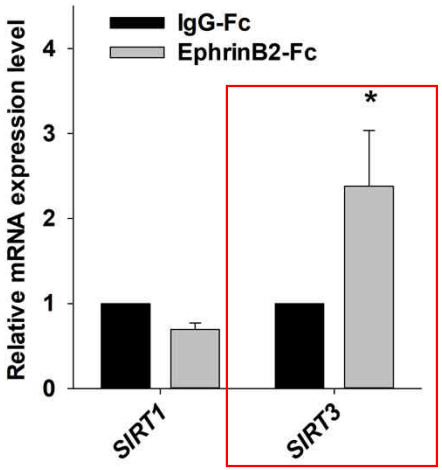


EphB2 expression ↓
→ Stem cell senescence ↑

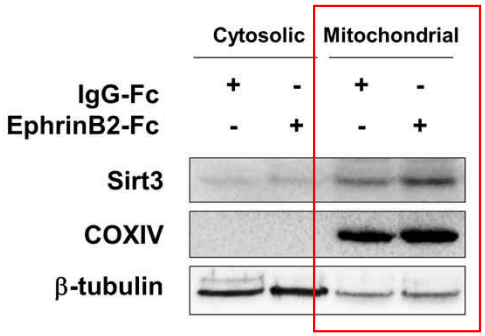
Effect of EphB2 signaling in sirt3 expression

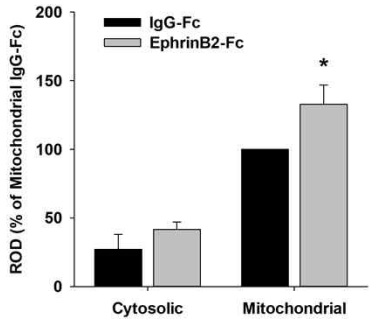


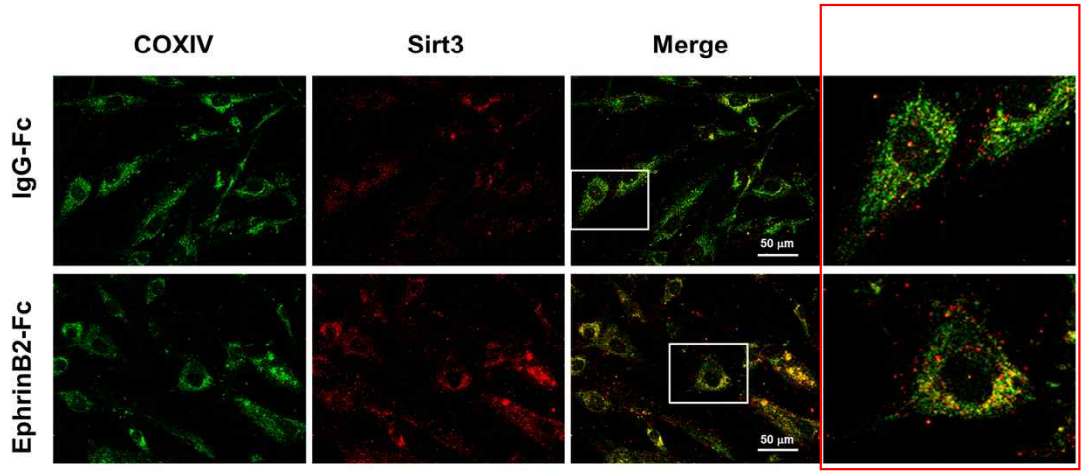




Stem cell senescence
→ Sirt3 expression ↓

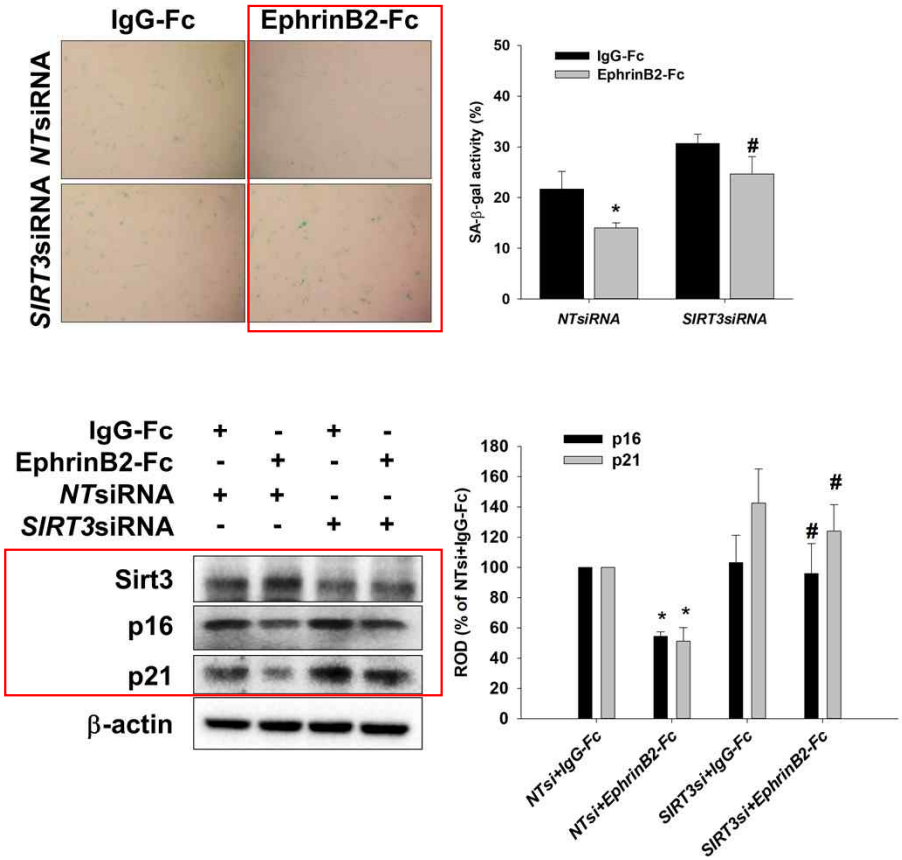






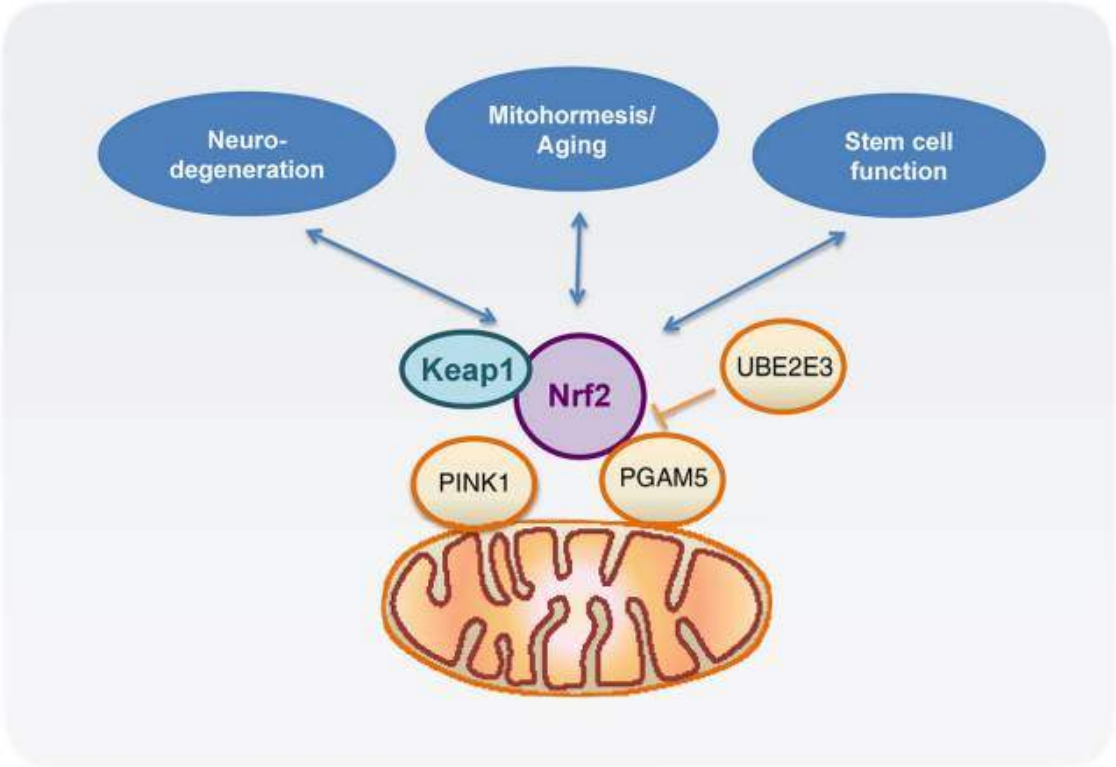
EphB2 activation
→ Mitochondrial Sirt3 ↑

Effect of EphB2 signaling in sirt3 expression

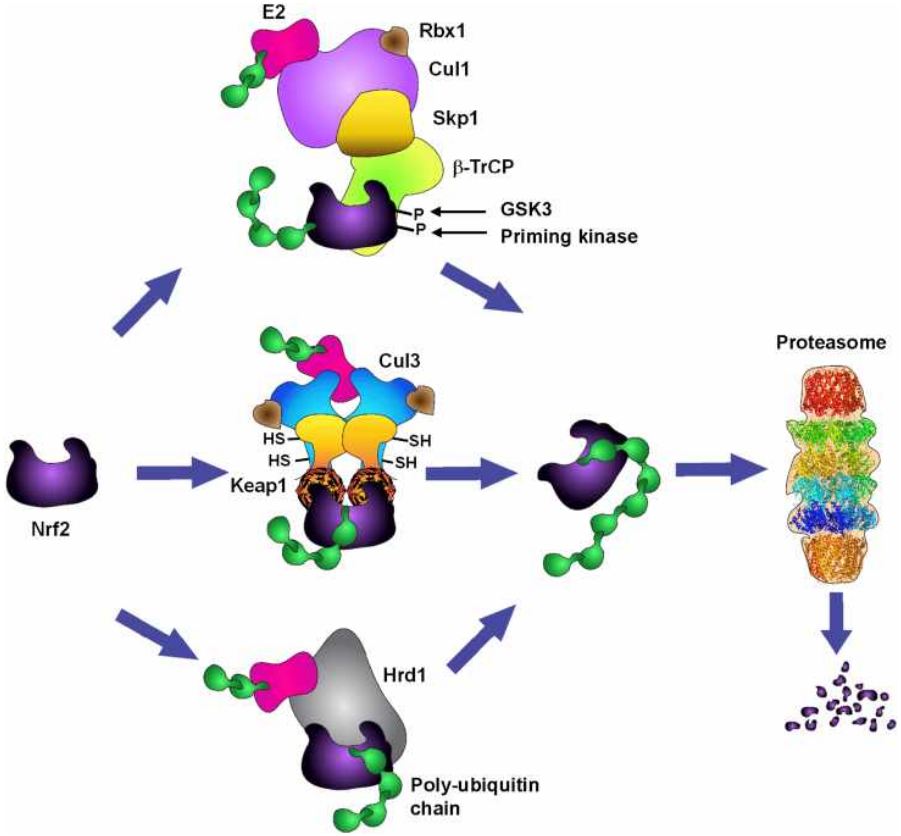


Sirt3 expression ↓
→ Stem cell senescence

Mitochondrial dysfunctions and Nrf2



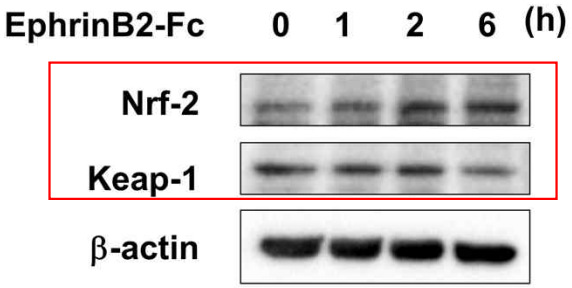
Nrf2, a master regulator of cellular redox homeostasis

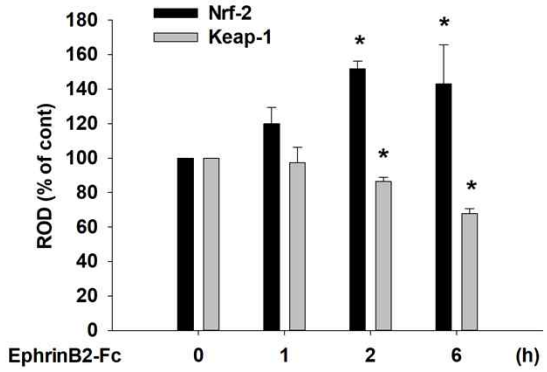


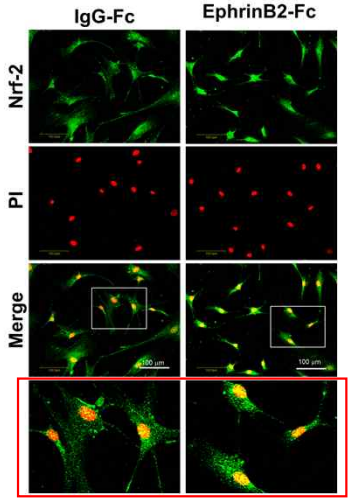
Nrf2 regulation mechanism

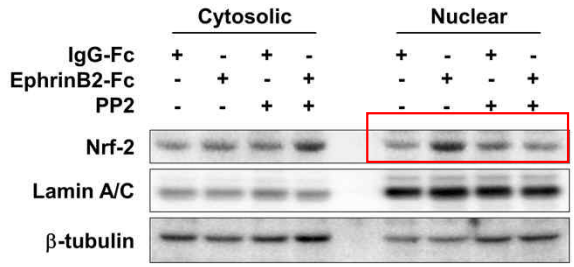
(Holmström et al., Curr Opin Toxicol. 2016)

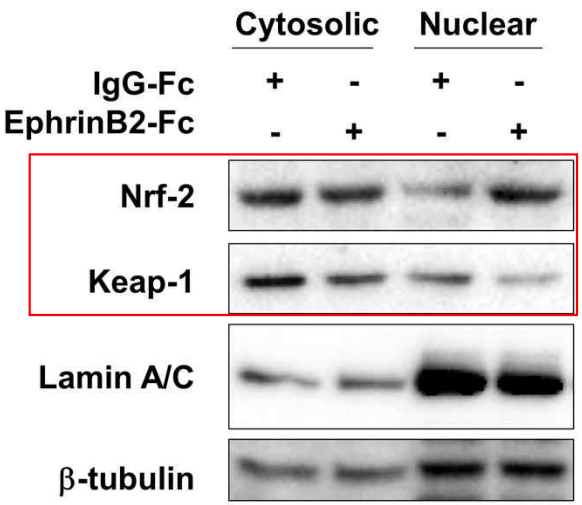
Effect of EphB2 signaling in NRF-2 nuclear translocation

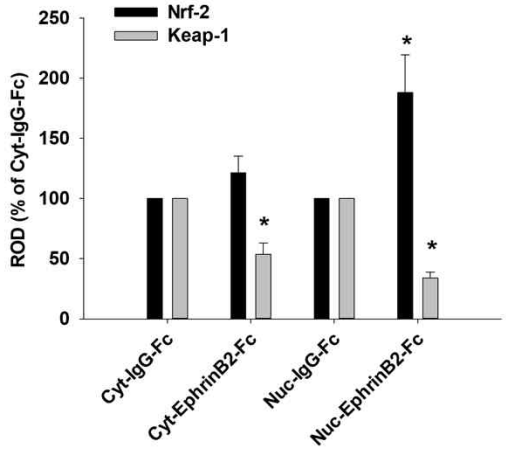


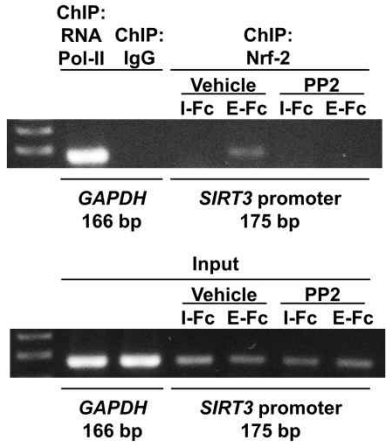


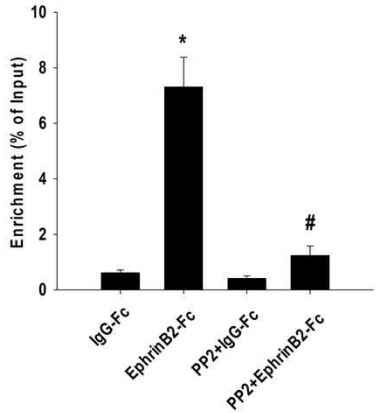






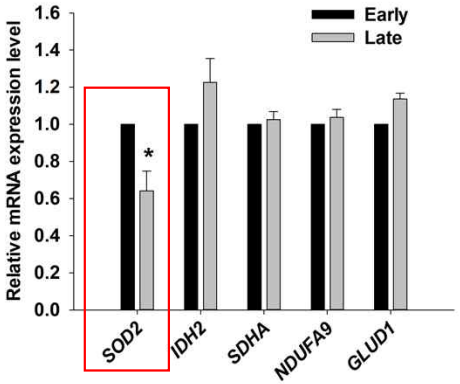


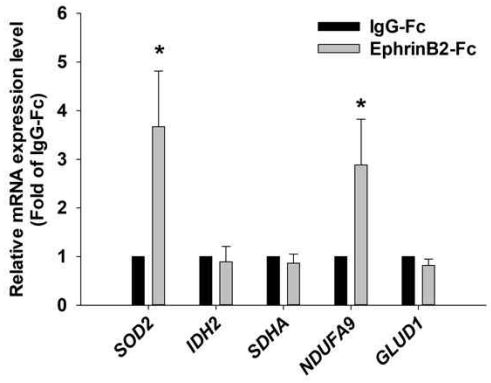


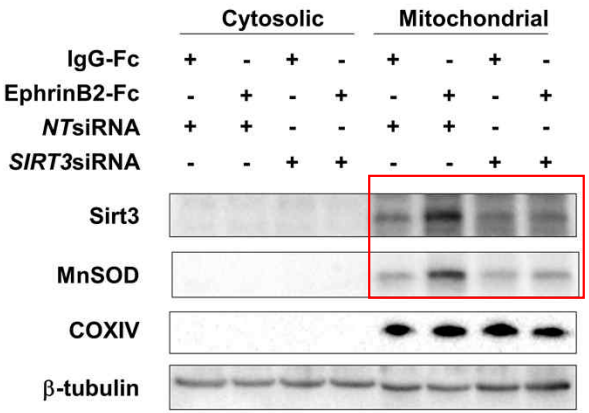


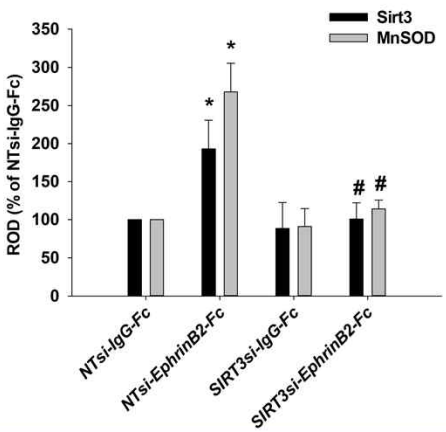
EphB2 → Nrf2 nuclear translocation

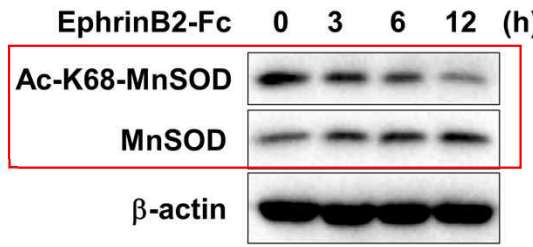
Effect of EphB2 signaling in regulation of MnSOD

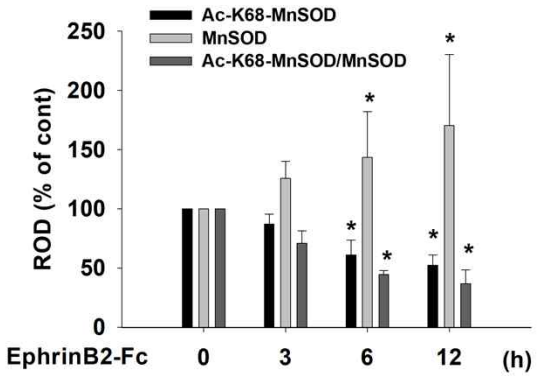








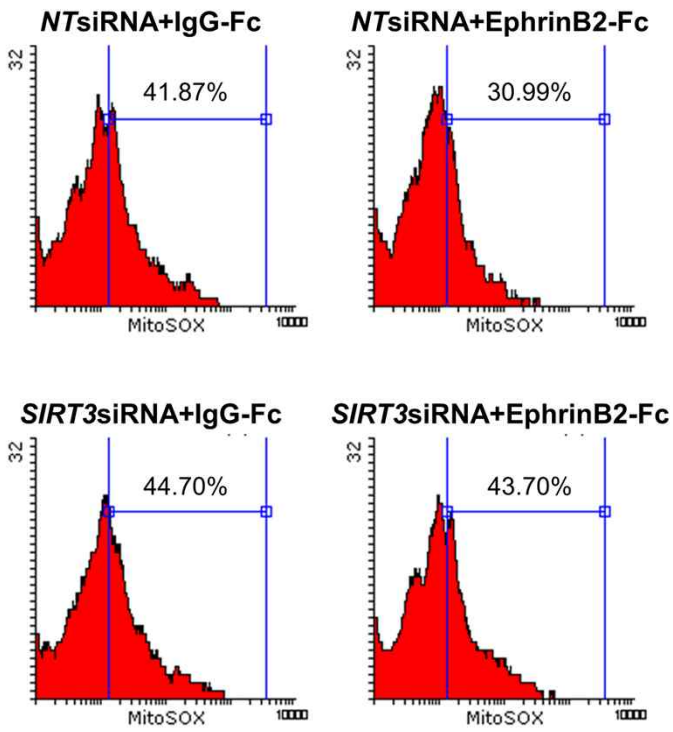


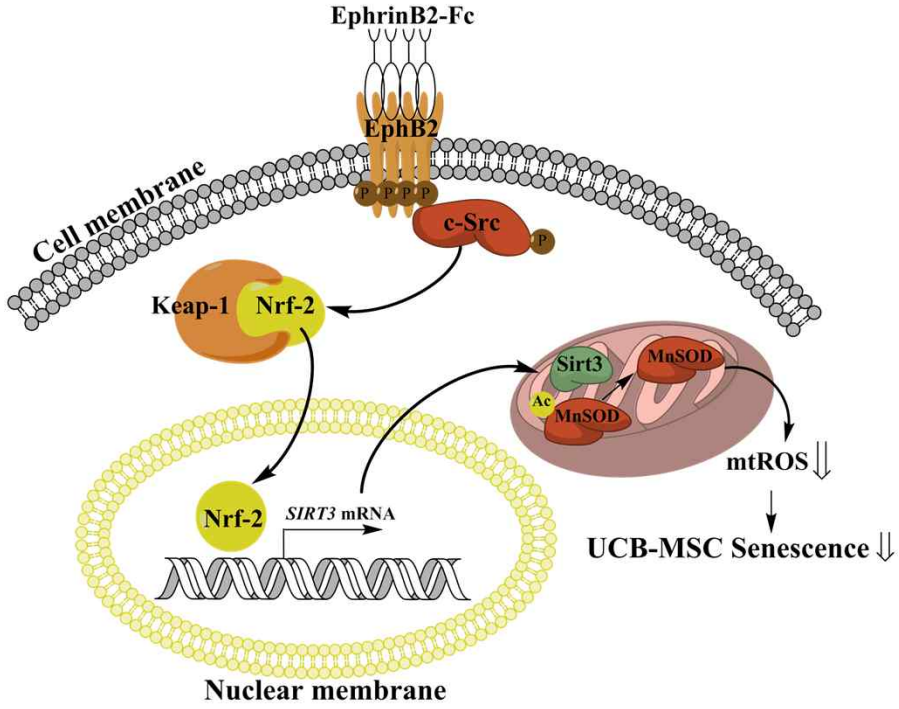


EphB2 activation
→ MnSOD expression ↑

EphB2 activation
→ MnSOD activity ↑

Effect of Sirt3 expression on increasing MnSOD activity





EphB2 activation → mitochondrial ROS ↓

Conclusion

- **OA enhances UCB-MSC motility through EphB2-dependent F-actin formation. (Jung et al., *BBA Mol Cell Res*, 2015)**
- **Priming EphB2 signaling could be a strategy for enhancing the replicative capacity of UCB-MSCs in an *in vitro* culture and for increasing the therapeutic efficacy of UCB-MSCs in clinical use by preserving mtROS homeostasis. (Jung et al., *FRBM*, 2017)**

Thank you for your attention

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