THE PROTECTIVE EFFECT OF ERYTHROPOIETIN ON HIGH **GLUCOSE STIMULATED ENDOTHELIAL CELL**

Yasunori Iwata, Yasuyuki Shinozaki, Haruka Yasuda, Kengo Furuichi, Norihiko Sakai, Takashi Wada.

Division of Nephrology, Kanazawa University, Kanazawa Japan

Kidney diseases cause systemic organ injury

The regulators of systemic organ damage



HG regulated the gene expression, those are related to multiple signal pathways

| # | Maps | 0 | 0.3 | 0.6 | 0.9 | 1.2 | 1.5 | 1.8 | 2.1 | 2.4 | -log(pValue) |
|---|---|---|-----|-----|-----|-----|-----|-----|-----|-----|--------------|
| 1 | Development ERK5 in cell proliferation and neuronal survival | - | | | | | | | | | |
| 2 | Transcription Transcription regulation of aminoacid metabolism | - | | | | | | | | | |
| 3 | LRRK2 in neurons in Parkinson's disease | _ | | | | | | | | | |

0 0.5 1 1.5 2 2.5 3 3.5 4

4 Signal transduction Activin A signaling regulation

Transport Clathrin-coated vesicle cycl Regulation of metabolism Role of Adiponecti

Signal transduction Calcium signaling

Transcription Role of heterochromatin protein (HP1) family in transcriptional silencing Development Osteopontin signaling in osteocl

Cell adhesion Chemokines and adhesion

Cytoskeleton remodeling TGF, WNT and

Development WNT signaling pathway. Part 1. Degradation of beta-catenin in the absence WN

Regulation of lipid metabolism Regulation of lipid metabolism via LXR, NF-Y and SREBP Regulation of metabolism Role of Adiponecti

Development Leptin signaling via PI3K-depe

Development WNT signaling pathway. Part Regulation of lipid metabolism Insulin r

regulation of metabolisn

cytoskeletal remodeling

regulation of metabolism

fatty acid methabolism Immune response IL-15 signaling Development Role of IL-8 in angiogenesis

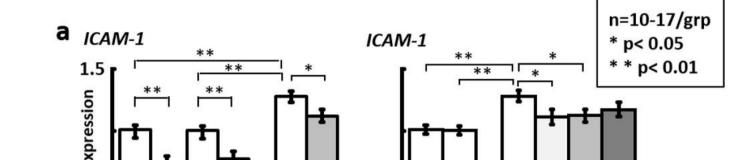
signaling

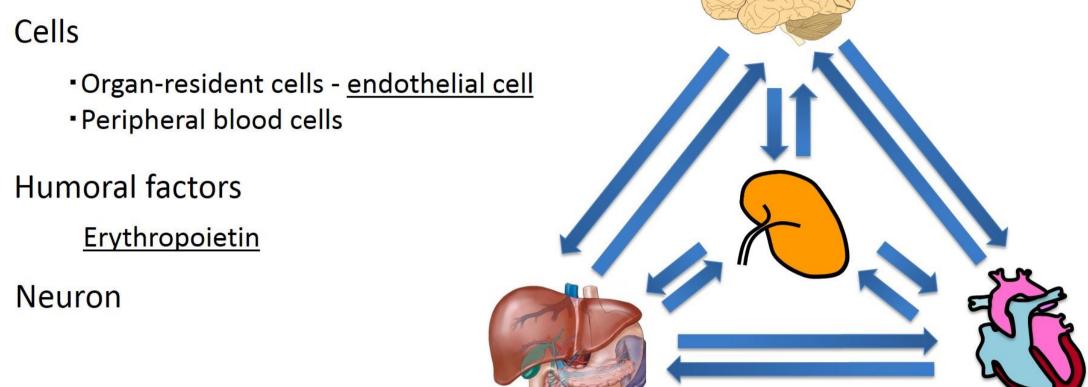
pathway

Neurophysiological process axon growth repulsion

EPO decreased the mRNA expression of

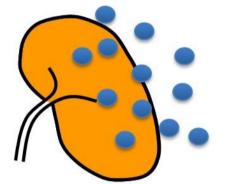
inflammatory related genes in HG stimulated HUVEC



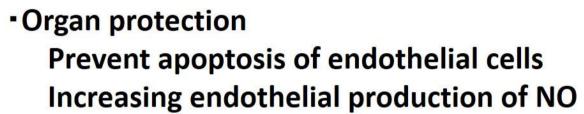


Potential role of erythropoietin in organ protection

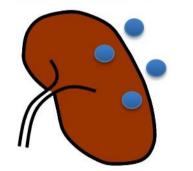
Healthy kidney



Hematopoiesis



Injured kidney

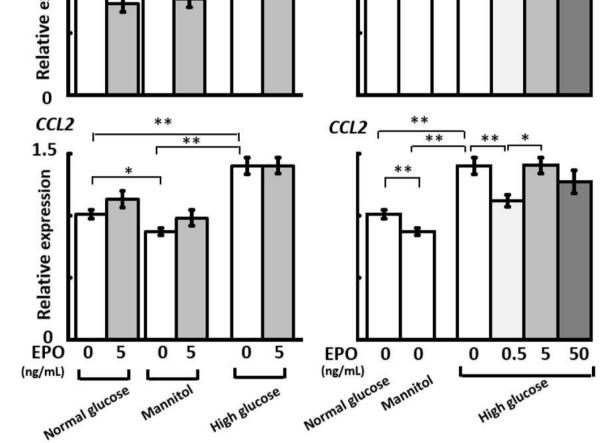


Teng R et al. Basic Res Cardiol. 2011

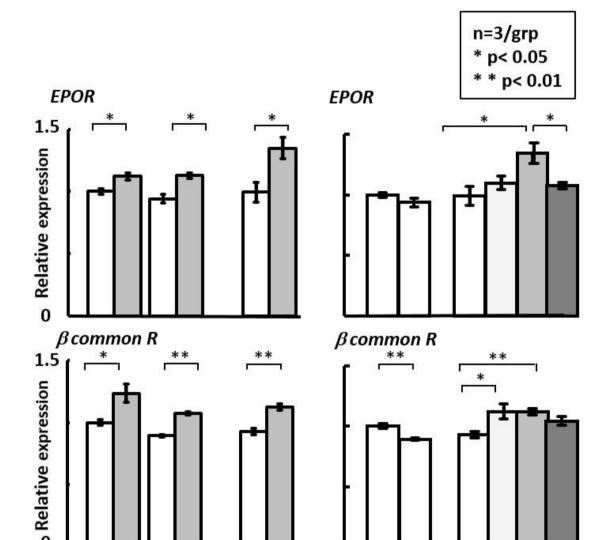
| EPO regulated the gene expression, those are |
|--|
| related to multiple signal pathways |

| # | Maps | 0 | 1 | 2 | 3 | 4 | -log(pValue) |
|----|--|---|---|---|---|----|--------------|
| 1 | Regulation of metabolism Role of Adiponectin in regulation of metabolism | - | _ | | | | |
| 2 | Regulation of lipid metabolism Regulation of lipid metabolism via LXR, NF-Y and SREBP | | _ | | _ | Č. | |
| 3 | CFTR folding and maturation (normal and CF) | - | | | | | |
| 4 | Translation Insulin regulation of translation | _ | | | | | |
| 5 | NF-AT signaling in cardiac hypertrophy | _ | _ | _ | _ | | |
| 6 | Development Ligand-independent activation of ESR1 and ESR2 | _ | _ | | | | |
| 7 | Development Membrane-bound ESR1: interaction with growth factors signaling | | | | - | | |
| 8 | Signal transduction PTEN pathway | _ | _ | _ | _ | | |
| 9 | Cytoskeleton remodeling Integrin outside-in signaling | _ | _ | _ | - | | |
| 10 | Translation Regulation of EIF4F activity | _ | | | _ | | |

| # | Maps | 0 | 0.5 | 1 | 1.5 | 2 | 2.5 | 3 | 3.5 | -log(pValue) |
|----|--|---|-----|---|-----|---|-----|---|-----|--------------|
| 1 | Cell cycle Transition and termination of DNA replication | - | | | | | | | | |
| 2 | Cell cycle Start of DNA replication in early S phase | - | | | | | _ | _ | | |
| 3 | Cell cycle Regulation of G1/S transition (part 1) | - | | | | | | | | |
| 4 | Apoptosis and survival Lymphotoxin-beta receptor signaling | - | | | | | | | - | |
| 5 | Apoptosis and survival TNFR1 signaling pathway | _ | | | | | | | | |
| 6 | Apoptosis and survival Anti-apoptotic TNFs/NF-kB/IAP pathway | - | | _ | | | | - | | |
| 7 | Development PEDF signaling | - | | | | | | | | |
| 8 | Cytoskeleton remodeling RalB regulation pathway | - | | | | | | | | |
| 9 | DNA damage Role of Brca1 and Brca2 in DNA repair | - | | | | | | | | |
| 10 | Development TGF-beta-dependent induction of EMT via SMADs | - | | | | | _ | | | |



EPO increased the mRNA expression of EPO receptors in HUVEC



Hypothesis Erythropoietin prevents endothelial

cells from high glucose induced injury

Material and Method

Human Umbilical Vein Endotherial Cell (HUVEC)



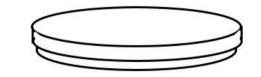
Normal glucose (5mM) 24hr

Isolate mRNA



Transcriptome with next generation sequencer

High glucose (HG) (30mM) 24hr



HG (30mM) + Erythropoietin (EPO) (5ng/ml) 24hr

EPO 0 5 0 5 0 5 EPO 0 0 0 0.5 5 50 (ng/mL)

Summary

• EPO changed the mRNA expression on HG stimulated HUVEC

•HG regulated the gene expression, those are related to multiple signal pathways

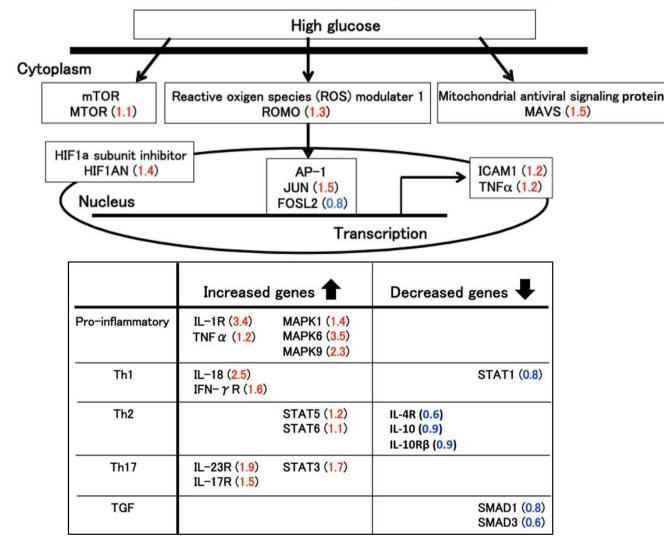
• EPO regulated the gene expression, those are related to multiple signal pathways

•HG stimulated HUVEC were skewed toward an inflammatory phenotype

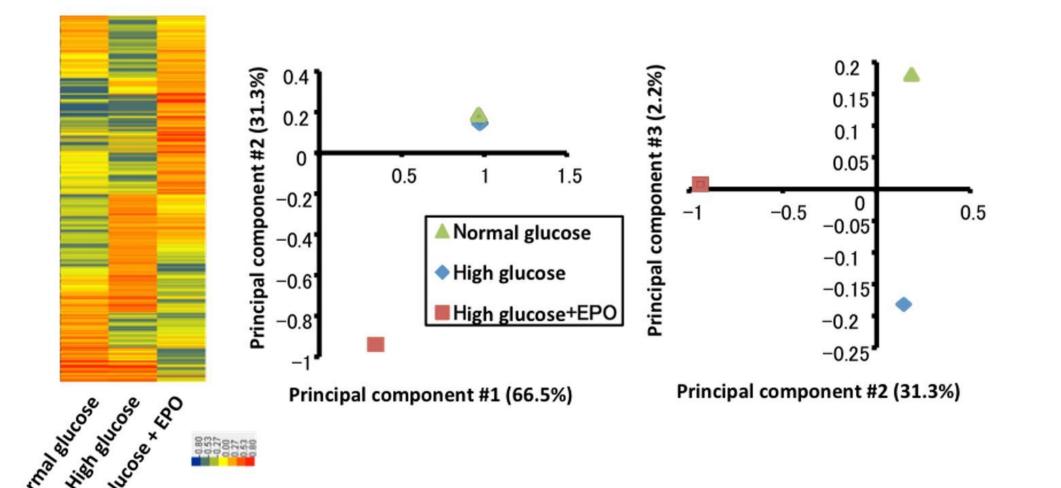
• EPO increased the mRNA expression of EPO receptors in HUVEC

HG stimulated HUVEC were skewed toward an

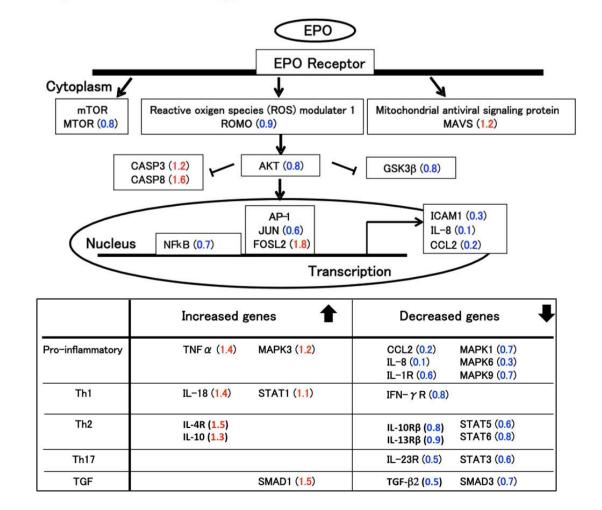
inflammatory phenotype



EPO changed the mRNA expression on HG stimulated HUVEC



EPO decreased the mRNA expression of inflammatory related genes in HG stimulated HUVEC



EPO regulated immune balance on **HG stimulated HUVEC**

