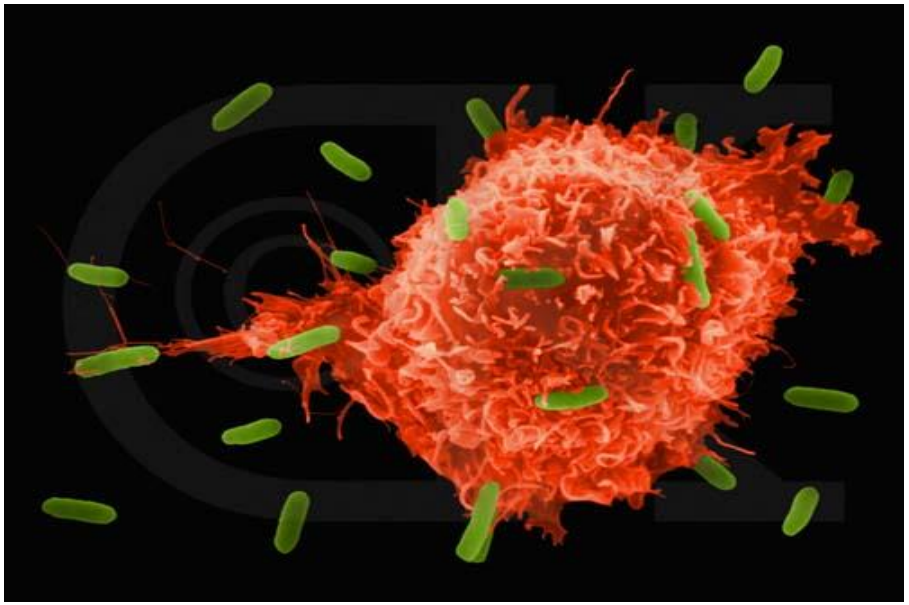
보건복지부 질환극복기술개발 심혈관계 융합연구센터
한국연구재단 줄기세포 Niche의 조절과 생체 이식 최적화를 통한 줄기세포의 실용화 기술개발
보건복지부 성체줄기세포의 심근경색 치료 효능 극대화기술 개발
보건복지부 저분자 분화조절제를 이용한 환자 자가유래 iPSCs의 생산과 심근 경색 세포 치료에의 적용
한국연구재단 원천기술개발사업 바이오·의료기술개발사업 심혈관질환 분자시스템생물학 연구

Emerging Role of Macrophages in Cardiovascular Disease:

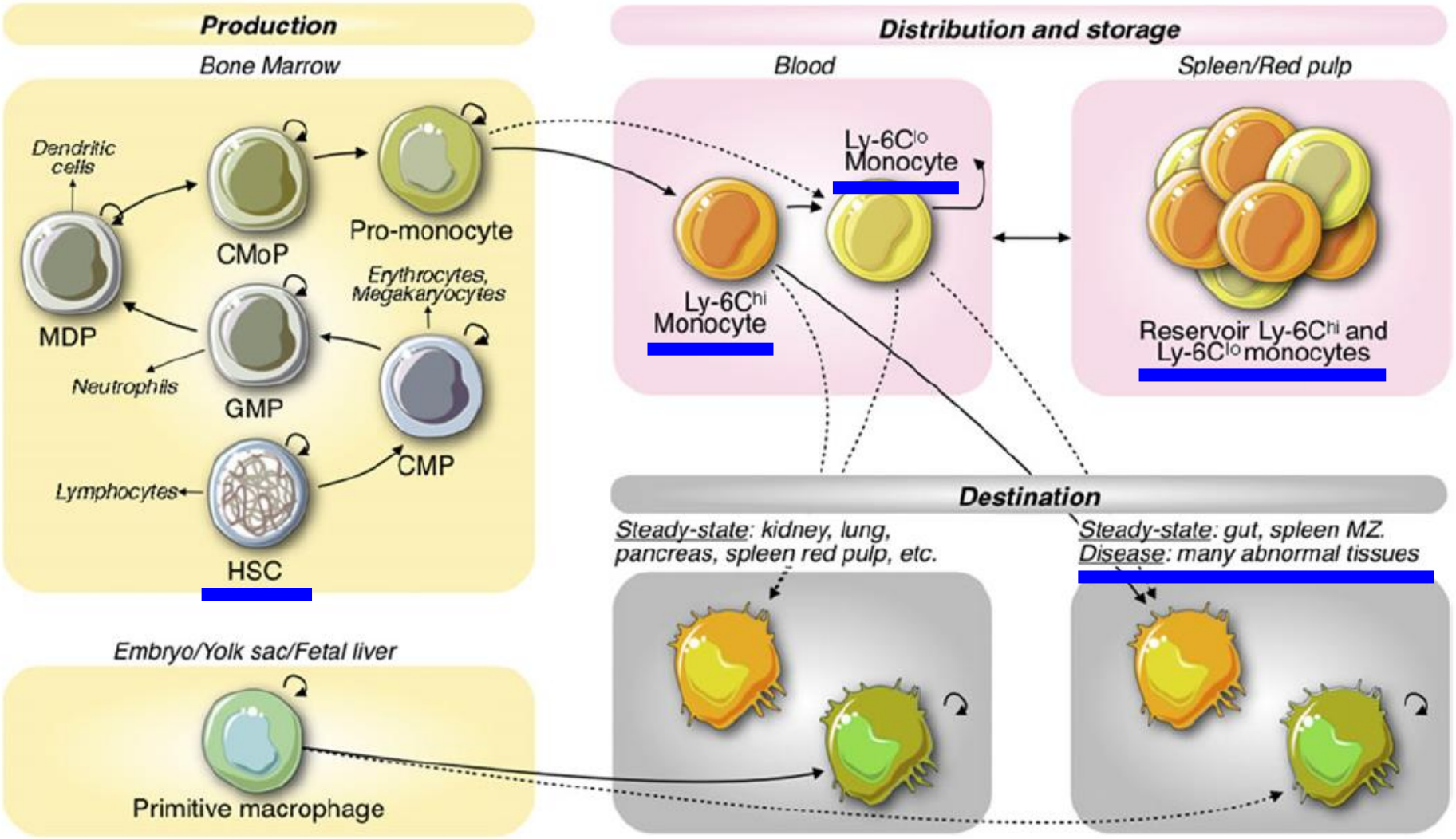
The Change of Macrophage Phenotype in Myocardium



Youngkeun Ahn, MD, PhD

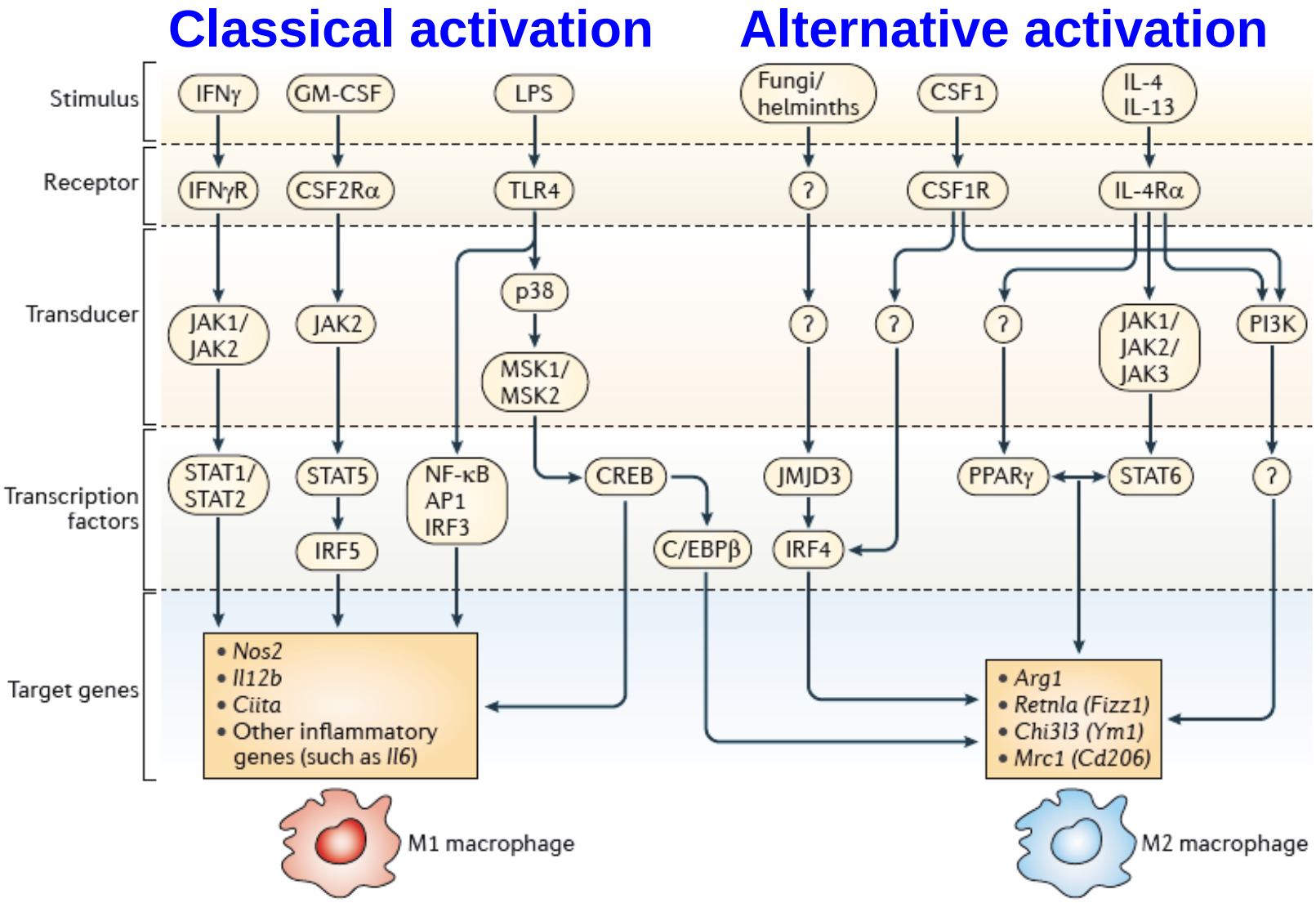
Department of Cardiology
Cardiovascular Center
Chonnam National University Hospital

The Journey from progenitors to macrophages



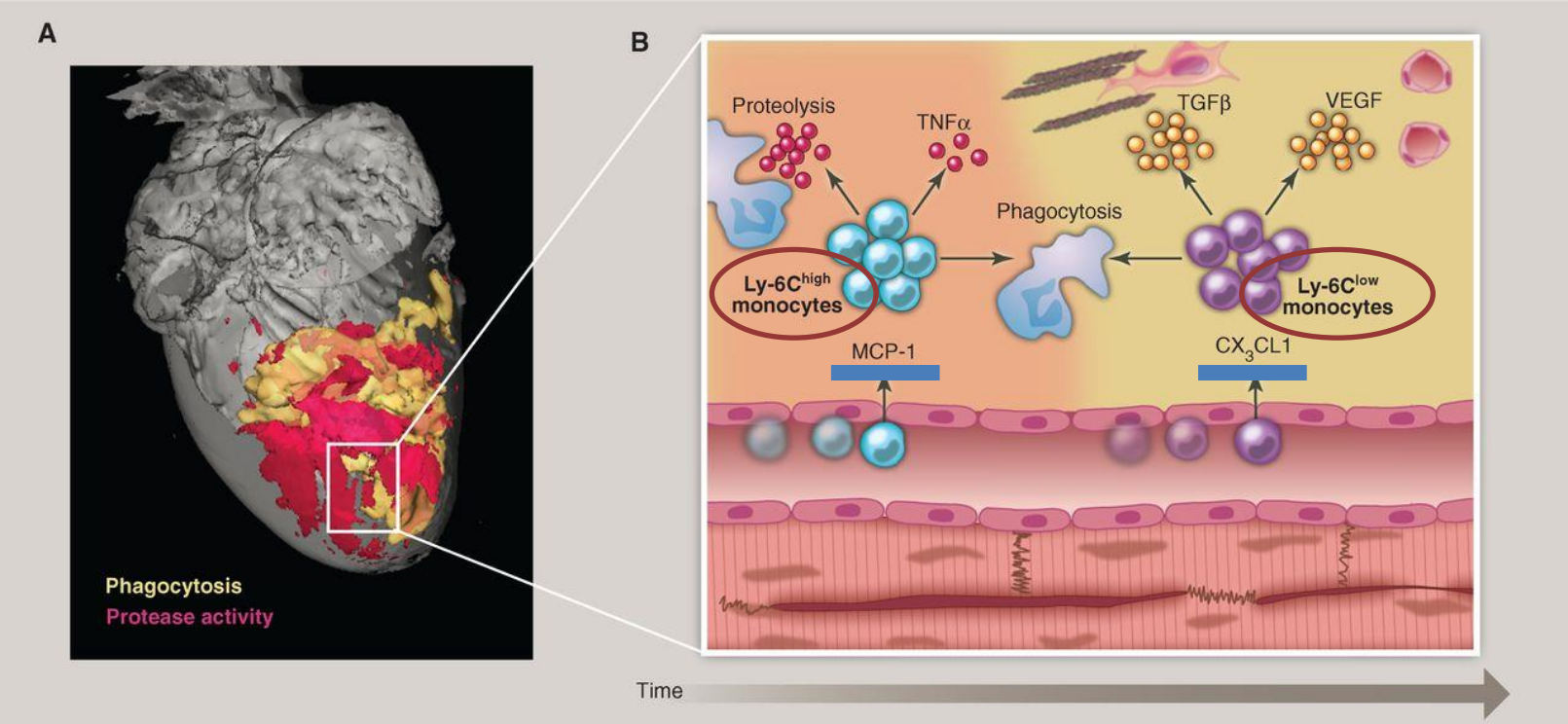
Ann. N. Y. Acad. Sci., 2014;1-18

Signal transduction pathways to M1 and M2 macrophage polarization



Nature. 2011;11:750-761

Biphasic monocyte response during early myocardial remodeling



Optical projection tomography of a murine heart with MI after injection of MIR for major function of myeloid cells, including protease activity and phagocytic activity.

Biphasic monocyte subset activity in the infarct

SCIENCE. 2013;339:161-166

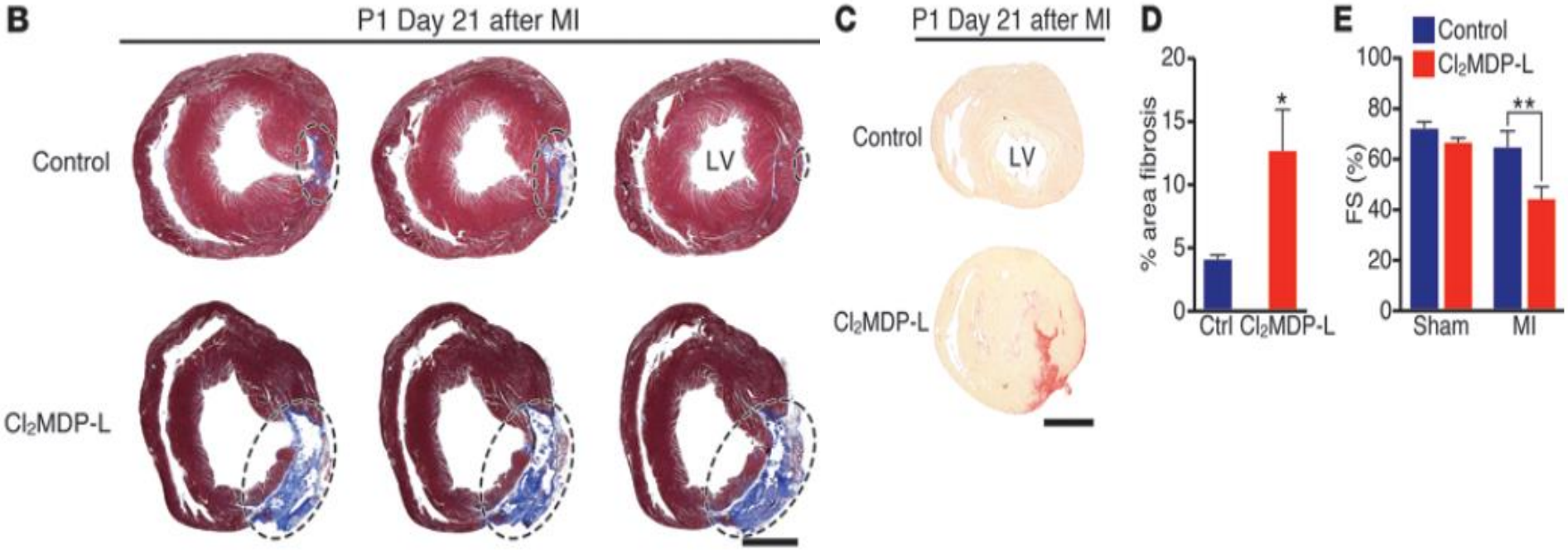
Research article

Macrophages are required for neonatal heart regeneration

Arin B. Aurora,[1] Enzo R. Porrello,[1] Wei Tan,[1] Ahmed I. Mahmoud,[2] Joseph A. Hill,[2]
Rhonda Bassel-Duby,[1] Hesham A. Sadek,[2] and Eric N. Olson[1]

[1]Department of Molecular Biology and [2]Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

J Clin Invest. 2014;124:1382-92.

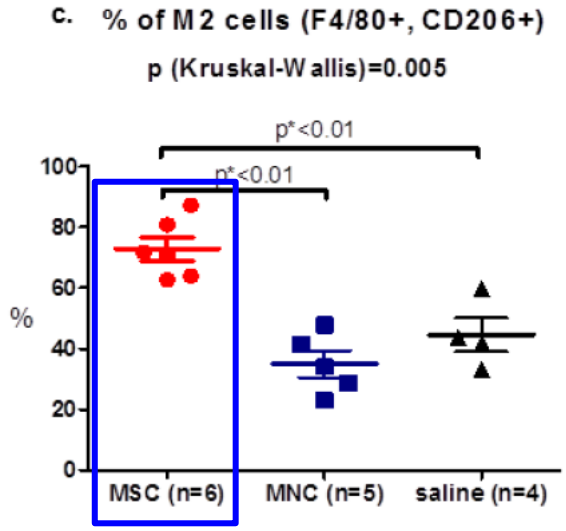


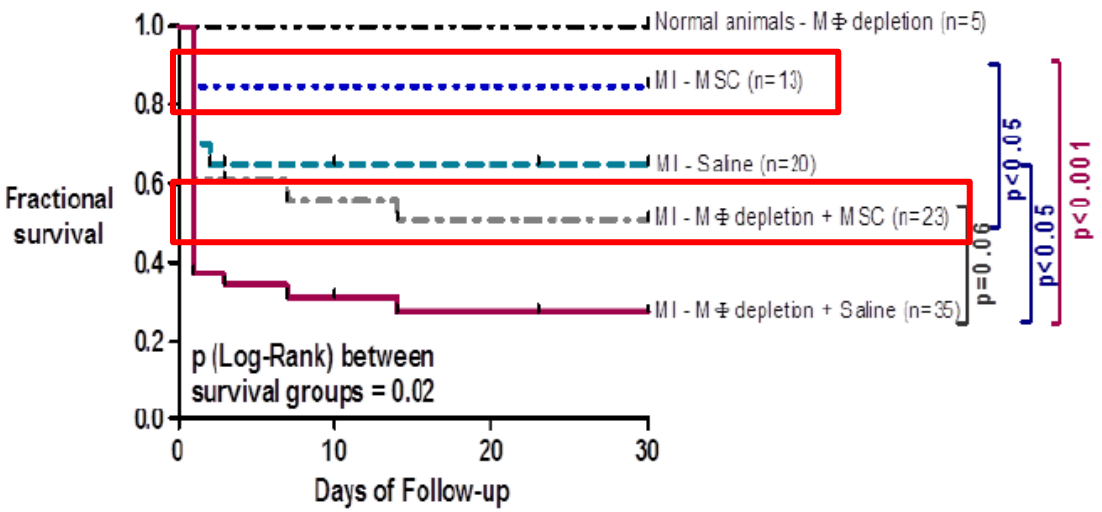
clodronate liposomes

J Am Coll Cardiol. 2013 Aug 12.

Macrophage Subpopulations are Essential for Infarct Repair with and without Stem Cell Therapy.

Ben-Mordechai T, Holbova R, Landa-Rouben N, Harel-Adar T, Feinberg MS, Elrahman IA, Blum G, Epstein F, Silman Z, Cohen S, Leor J.





MSCs increased M2 macrophage percentage at day 3 after MI.

Macrophage depletion increased mortality with and without MSCs.

Induction of MI in mice and allocated them to bone marrow MSCs, MNCs, or saline injection into the infarct, with and without early (4 h before MI) and late (3 days after MI) macrophage depletion. Balb/C mice, clodronate liposomes 0.1 mL iv

I. Regulation of Infiltrated Macrophages in Infarcted Myocardium by Stem Cells

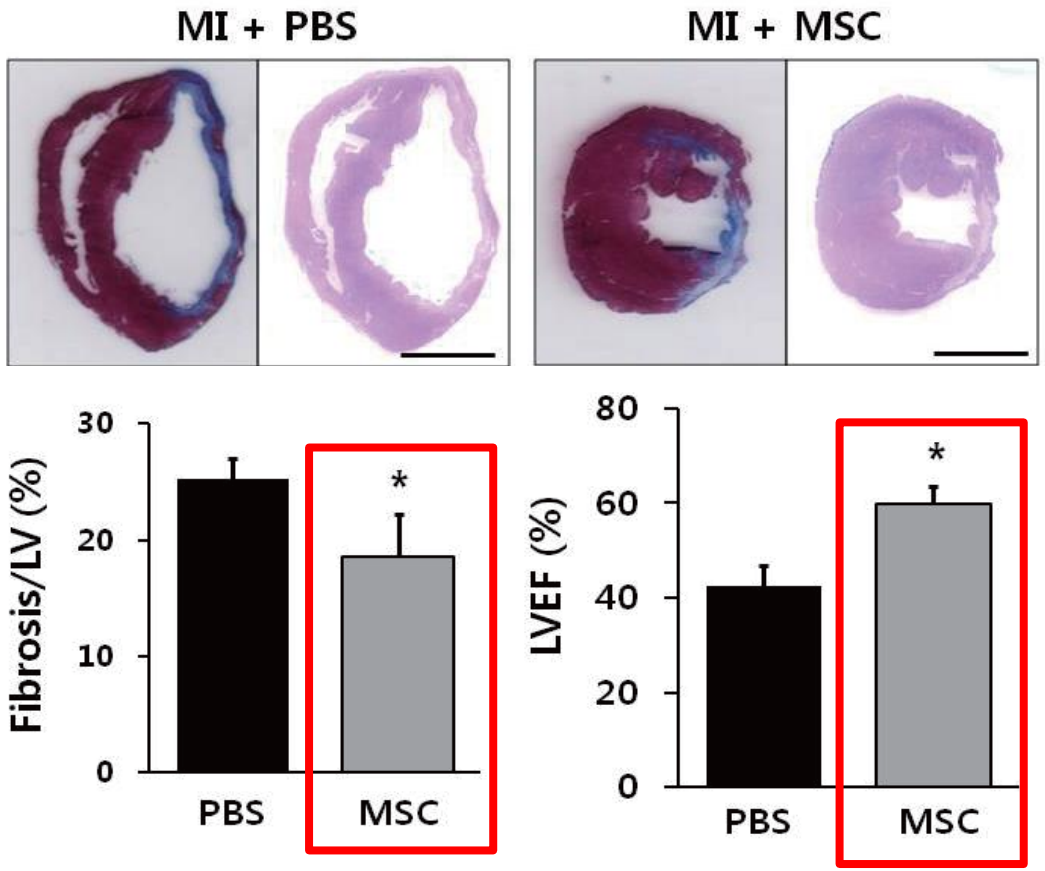
ORIGINAL ARTICLE

Experimental & Molecular Medicine (2013) 45, e00; doi:10.1038/emm.2013.135

www.nature.com/emm

Mesenchymal stem cells reciprocally regulate the M1/M2 balance in mouse bone marrow-derived macrophages

Dong-Im Cho[1], Mi Ra Kim[1], Hye-yun Jeong[1], Hae Chang Jeong[2], Myung Ho Jeong[2,3], Sung Ho Yoon[4], Yong Sook Kim[1,3] and Youngkeun Ahn[2,3]



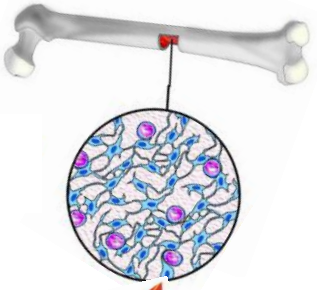
14 days after MSC injection

*P<0.05

The isolation of mouse bone marrow derived macrophages (BMDMs)/MSCs and co-culturing of BMDMs and MSCs

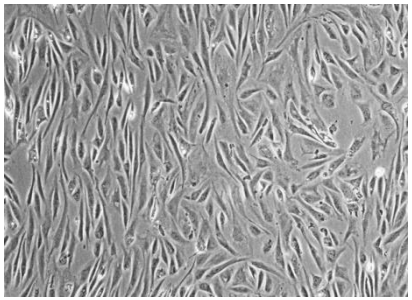
Balb/C, 8w

Bone marrow isolation



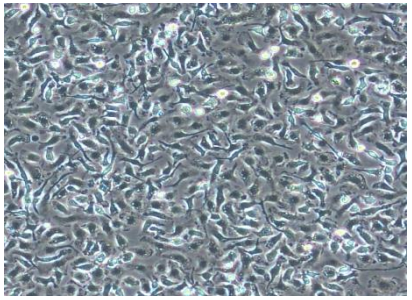
Bone marrow progenitor cells

BM-MSCs



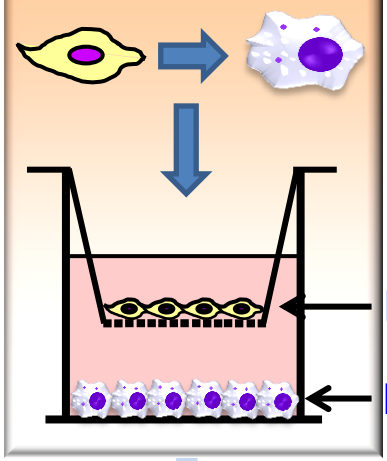
Culture in MSC medium for 3-4 days (passage 3)

BMDMs



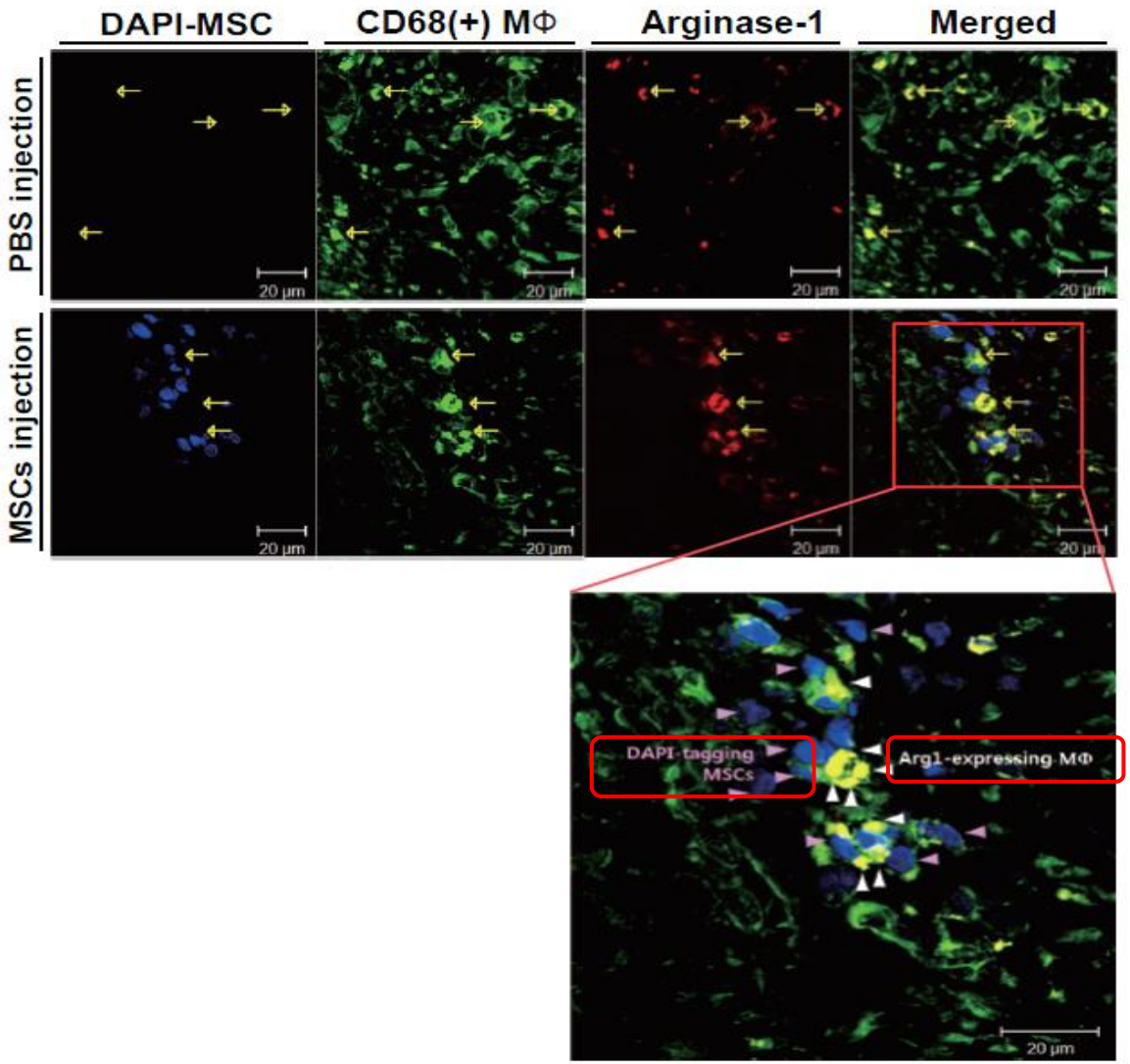
Differentiation in Macrophage complete medium(MCSF) for 7days

Transwell co-culture



M1/M2 markers profile assay

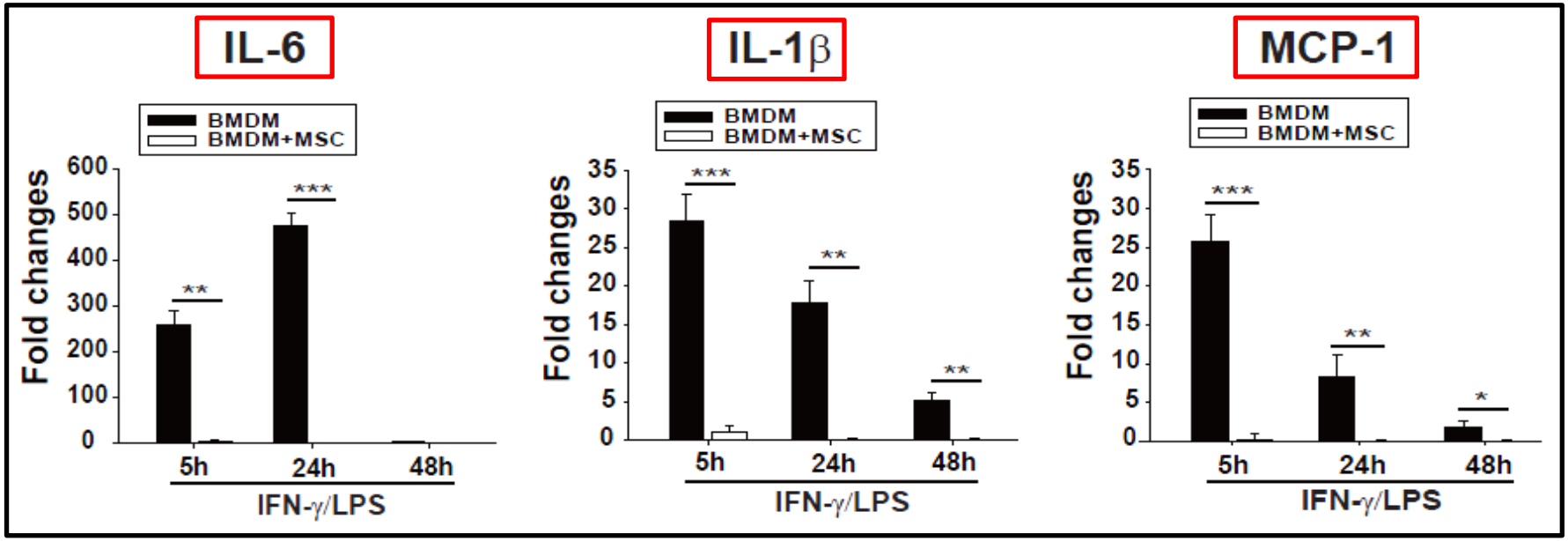
The identification of arginase-1 expressing macrophages in infarct myocardium



7 days after MSC injection

The modulatory effect of MSCs on the phenotype of BMDM at the transcriptional level (I)

M1

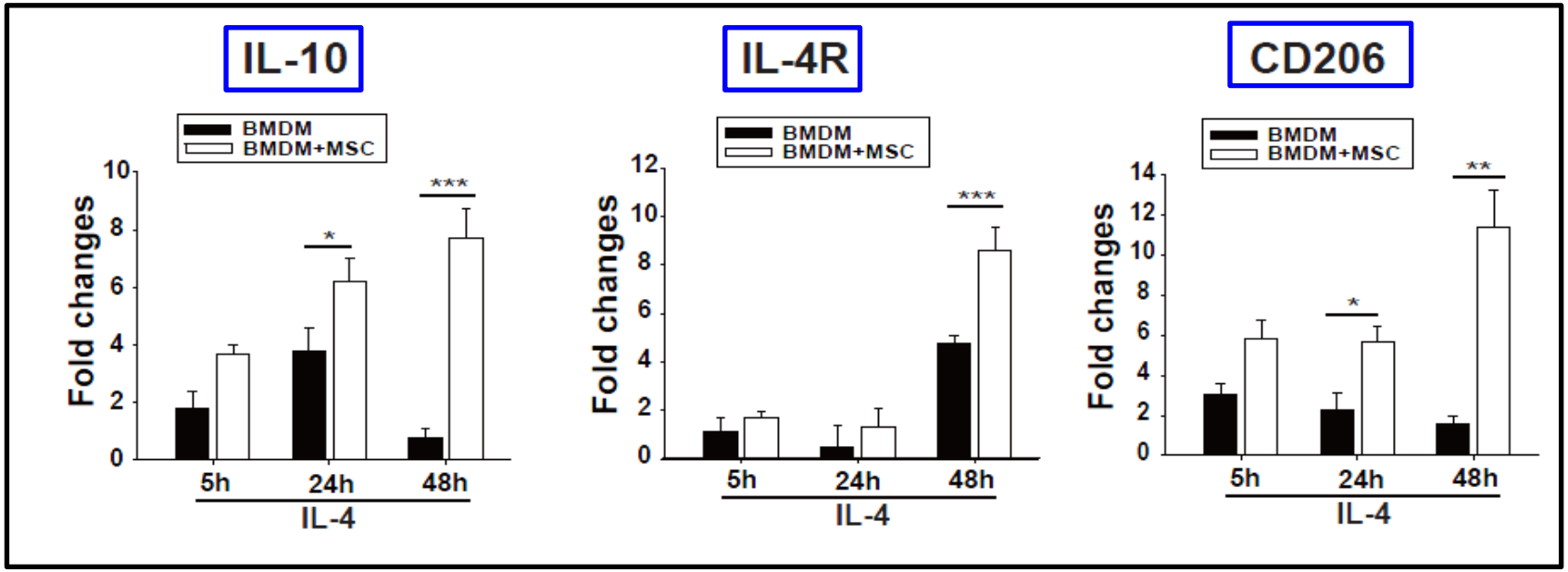


LPS 100 ng/mL + IFN-γ 30 ng/mL or IL-4 (20 ng/mL).

**p<0.05, **p<0.01, ***p<0.001*

The modulatory effect of MSCs on the phenotype of BMDM at the transcriptional level (II)

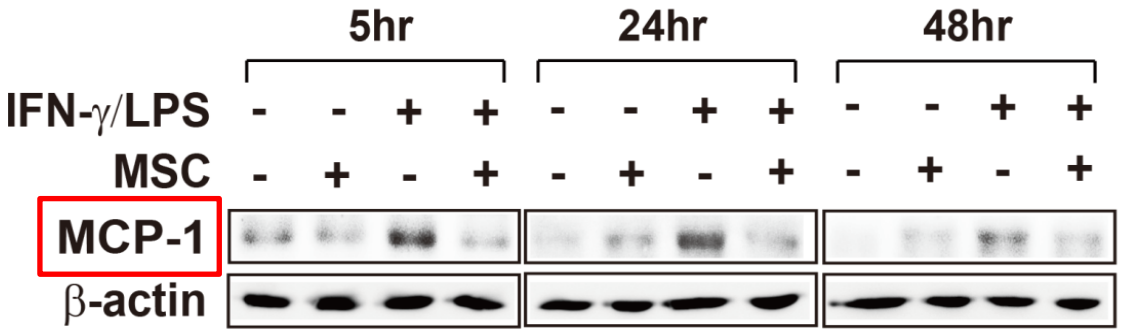
M2

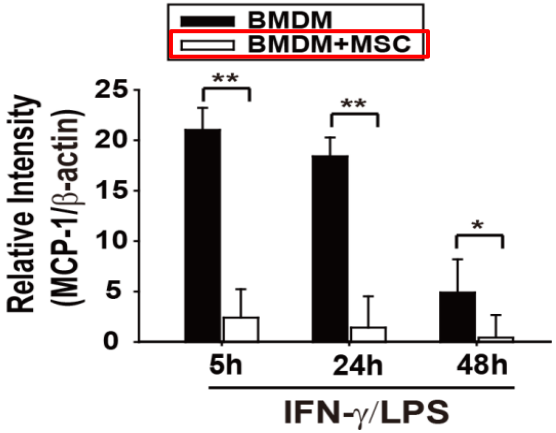


LPS 100 ng/mL + IFN-γ 30 ng/mL or IL-4 (20 ng/mL).

*$p<0.05$, **$p<0.01$, ***$p<0.001$

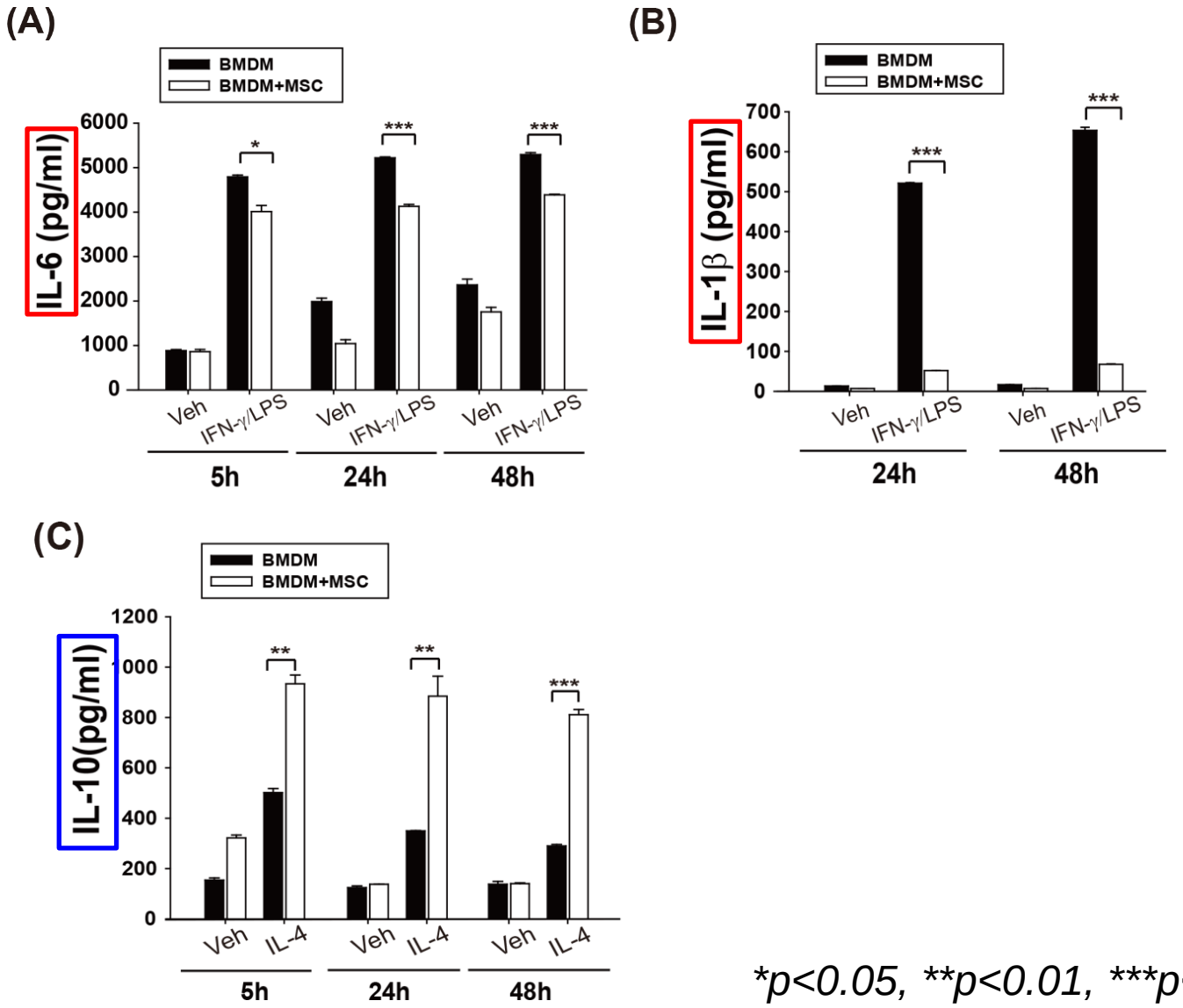
The modulatory effect of MSCs on the phenotype of BMDMs at the translational level (I)





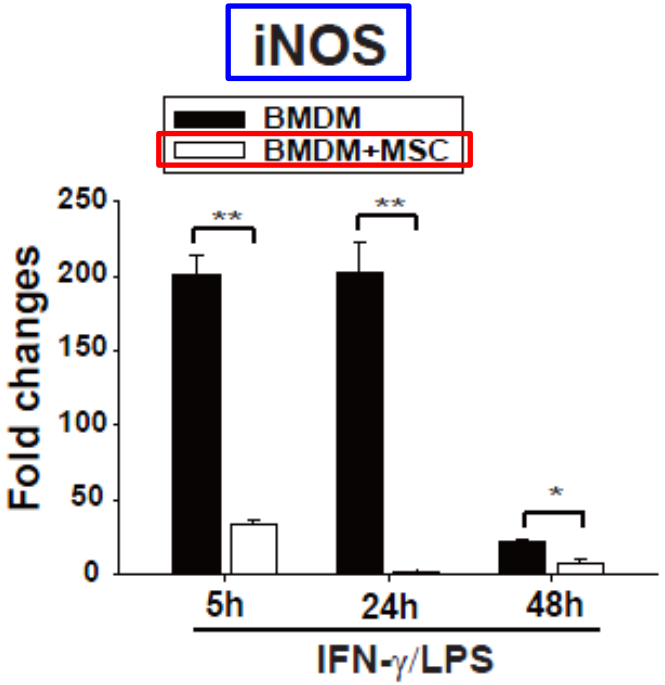
*p<0.05, **p<0.01

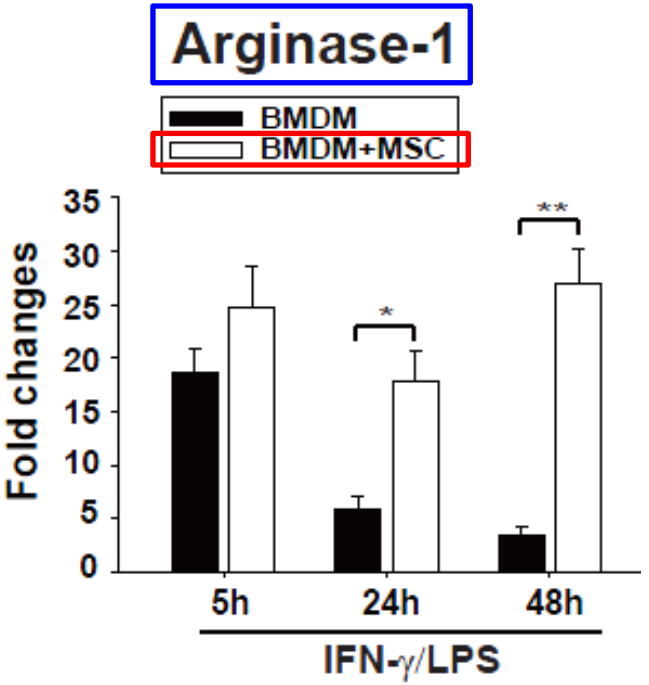
The modulatory effect of MSCs on the phenotype of BMDMs at the translational level (II)



*p<0.05, **p<0.01, ***p<0.001

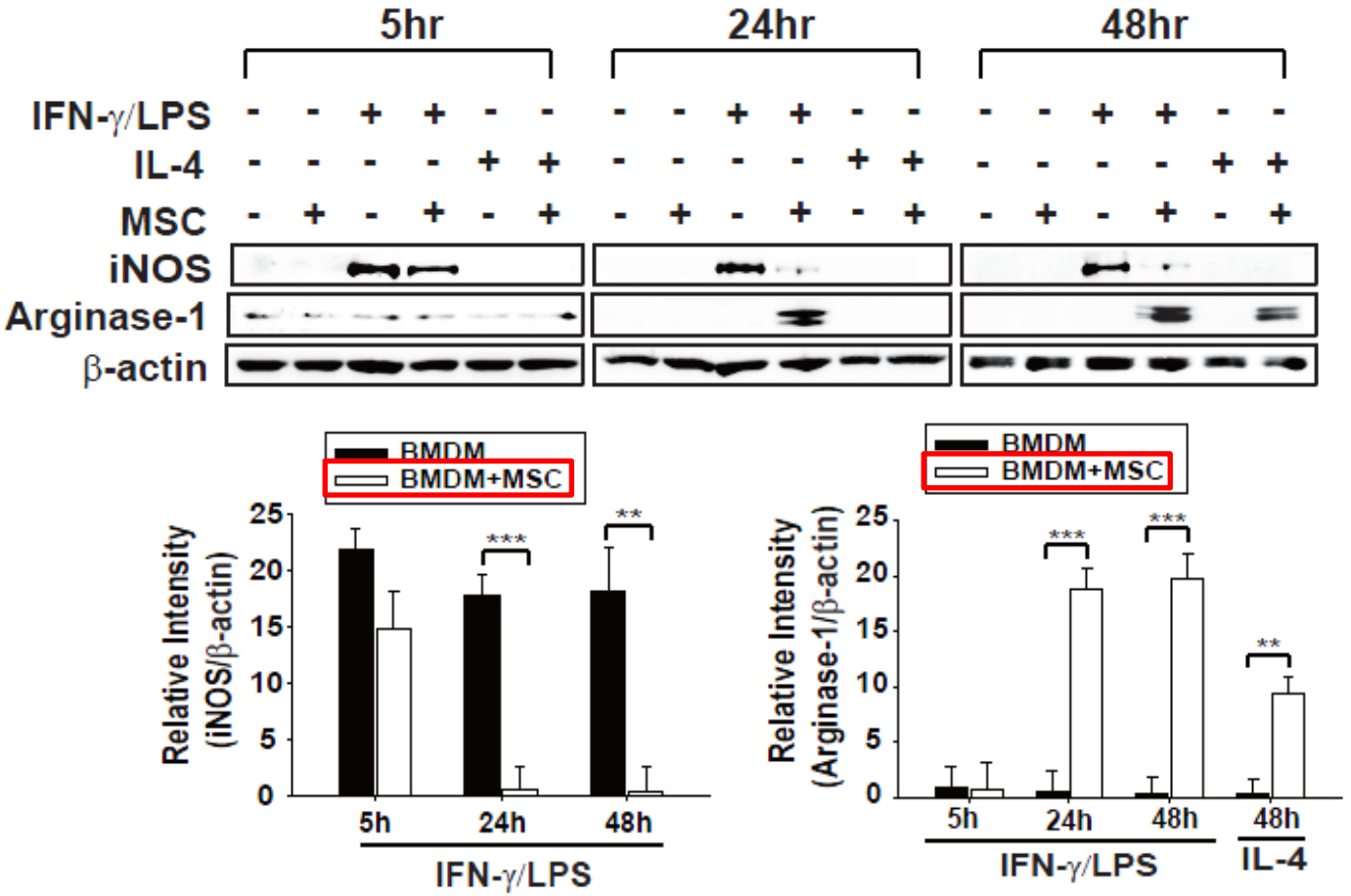
MSCs co-culturing skewed the BMDM phenotype to M2 by decreasing the ratio of iNOS to Arg-1





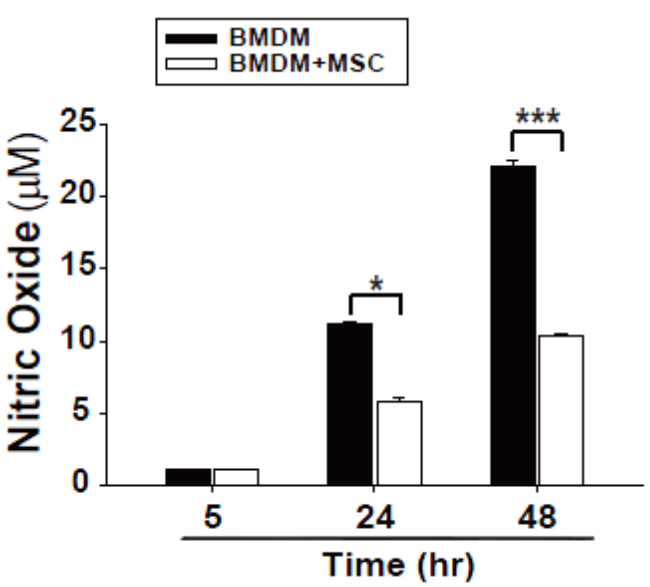
*p<0.05, **p<0.01

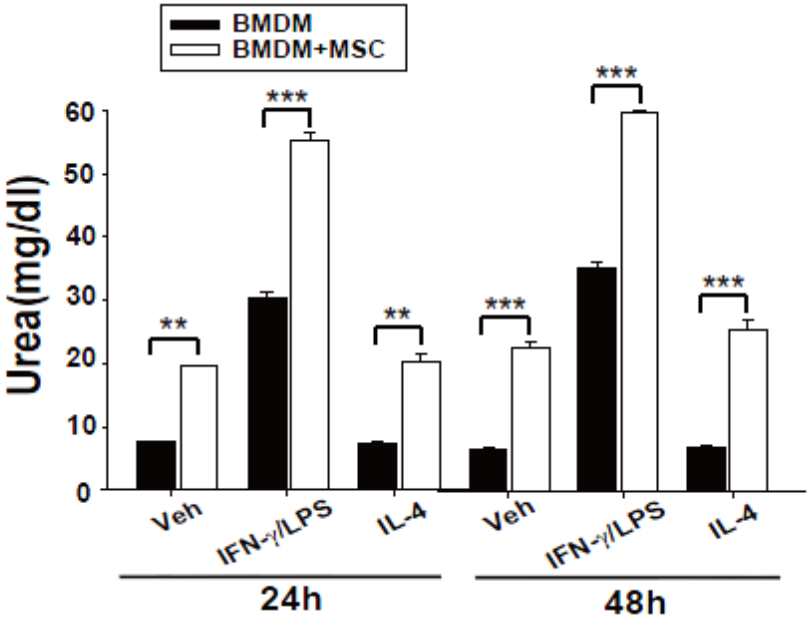
MSCs co-culturing skewed the BMDM phenotype to M2 by decreasing the ratio of iNOS to Arg-1



*p<0.05, **p<0.01, ***<0.001

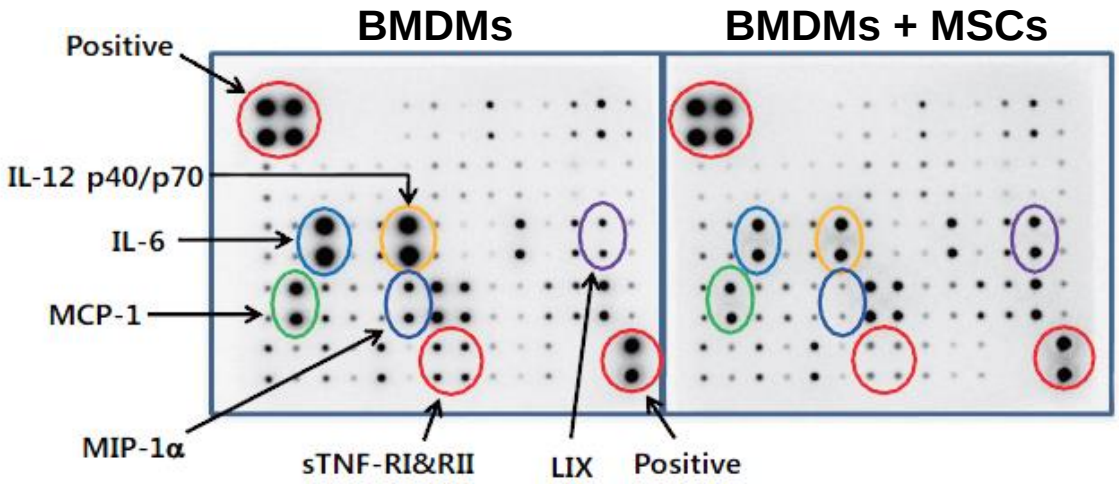
The enzymatic activities of iNOS and arginase-1

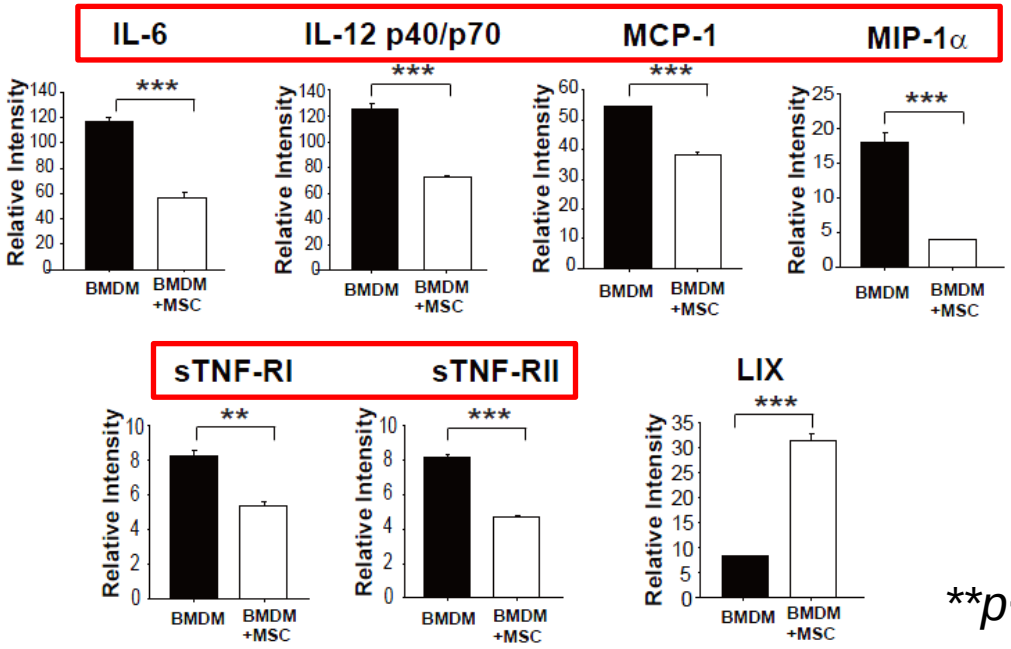




*p<0.05, **p<0.01, ***<0.001

MSCs regulated inflammatory cytokines





**p<0.01, ***p<0.001

These results suggest that the preferential shift of macrophage phenotype from M1 to M2 may be related to the immune-modulating characteristics of MSC which contribute to cardiac repair.

Ongoing study: Application to human macrophages and human MSCs

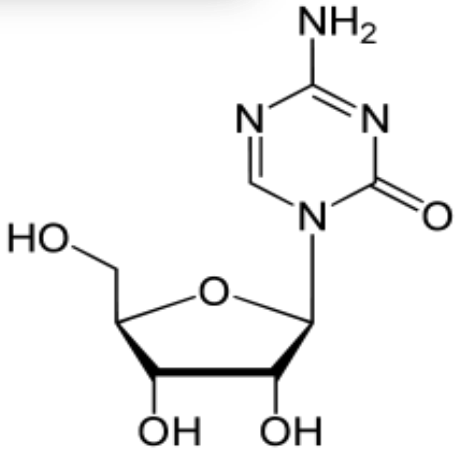
II. Regulation of Infiltrated Macrophages in Infarcted Myocardium by 5-azacytidine

J. Cell. Mol. Med. Vol XX, No X, 2014 pp. 1-10

Protective role of 5-azacytidine on myocardial infarction is associated with modulation of macrophage phenotype and inhibition of fibrosis

Yong Sook Kim [a], Wan Seok Kang [b, c], Jin Sook Kwon [a], Moon Hwa Hong [b], Hye-yun Jeong [b, c], Hae Chang Jeong [d], Myung Ho Jeong [a, d], Youngkeun Ahn [a, b, d, *]

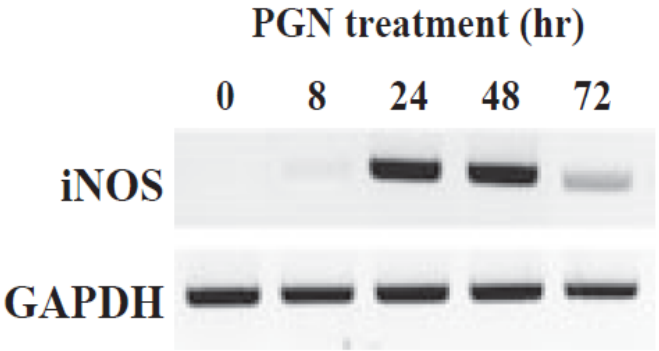
5-Azacytidine (5AZ)

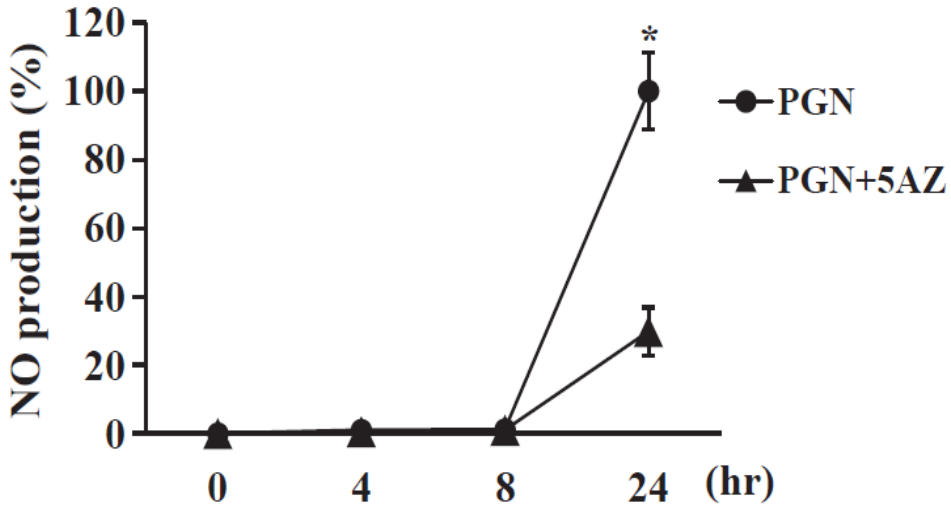


- ◆Chemical analogue of cytidine
- ◆DNA methylation inhibitor
- ◆Treatment of myelodysplastic syndrome, acute myeloid leukemia
- ◆Induction of cell transdifferentiation

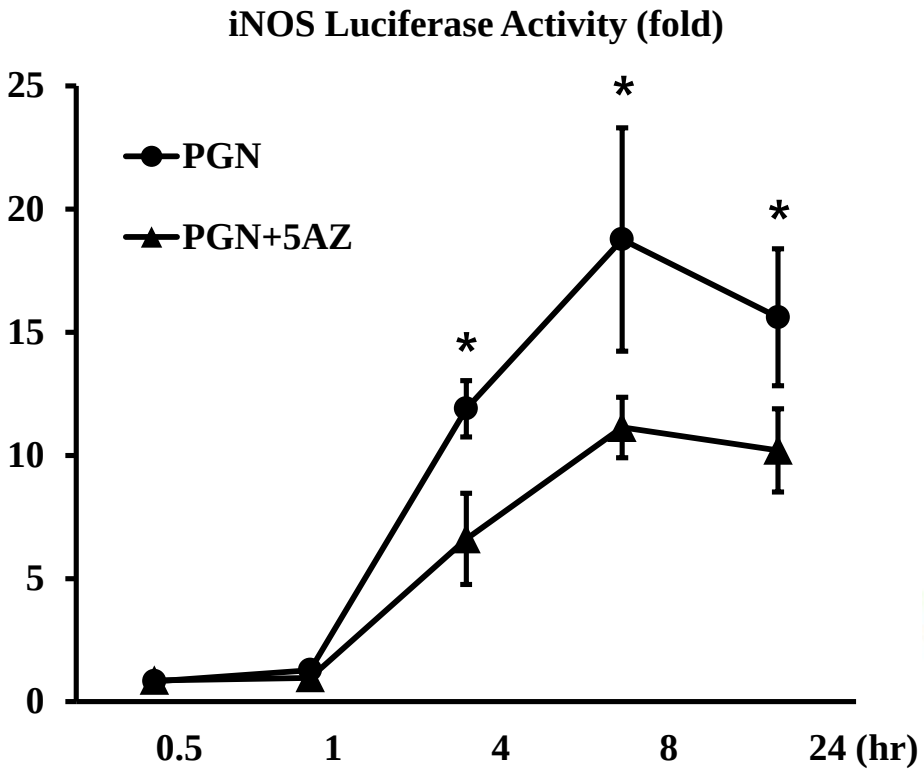
Effect of 5AZ on fibrosis in iNOS-induced NO generation

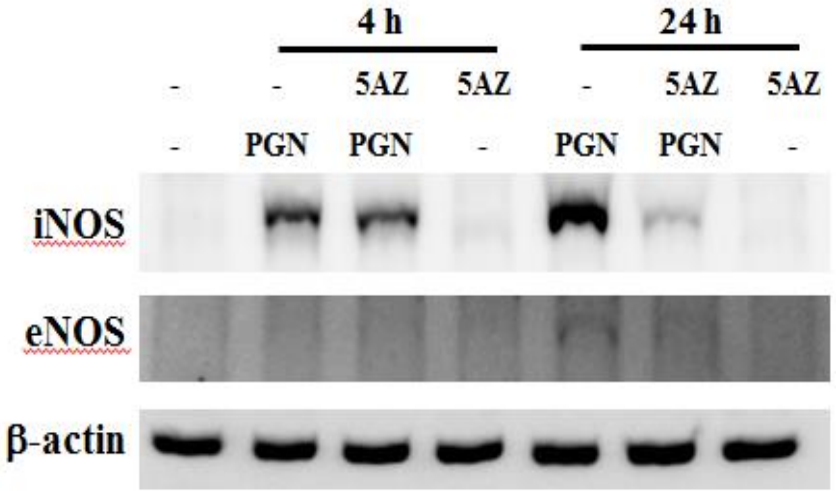
- **RAW264.7 murine macrophage cell line**
- **Stimulant: Peptidoglycan (PGN, 10 μg/mL)**
- **Effector: 5AZ (10 μM)**
- **Target: Inducible nitric oxide synthase (iNOS)**



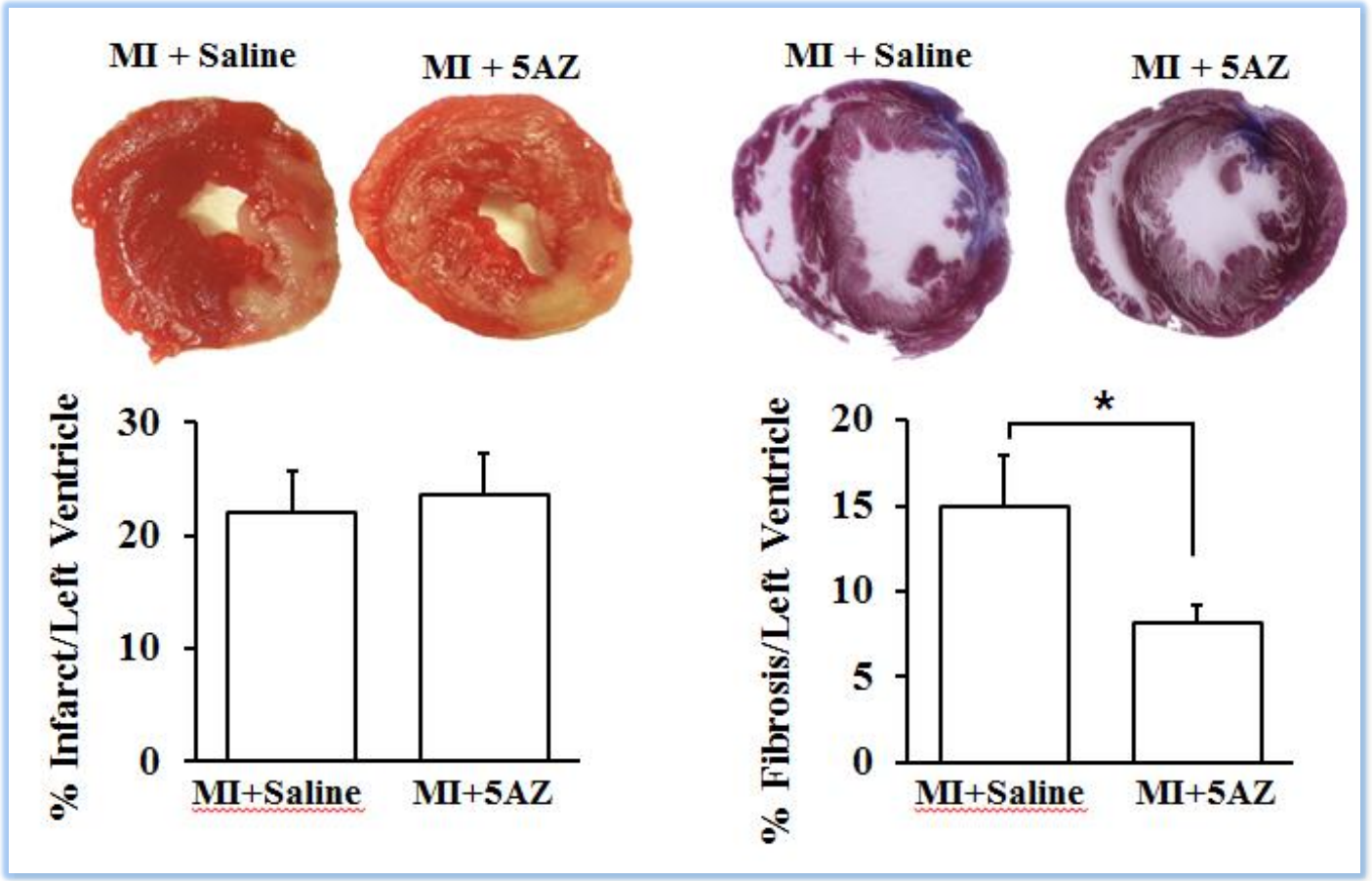


Effect of 5AZ administration on iNOS transcriptional activity and translational activity

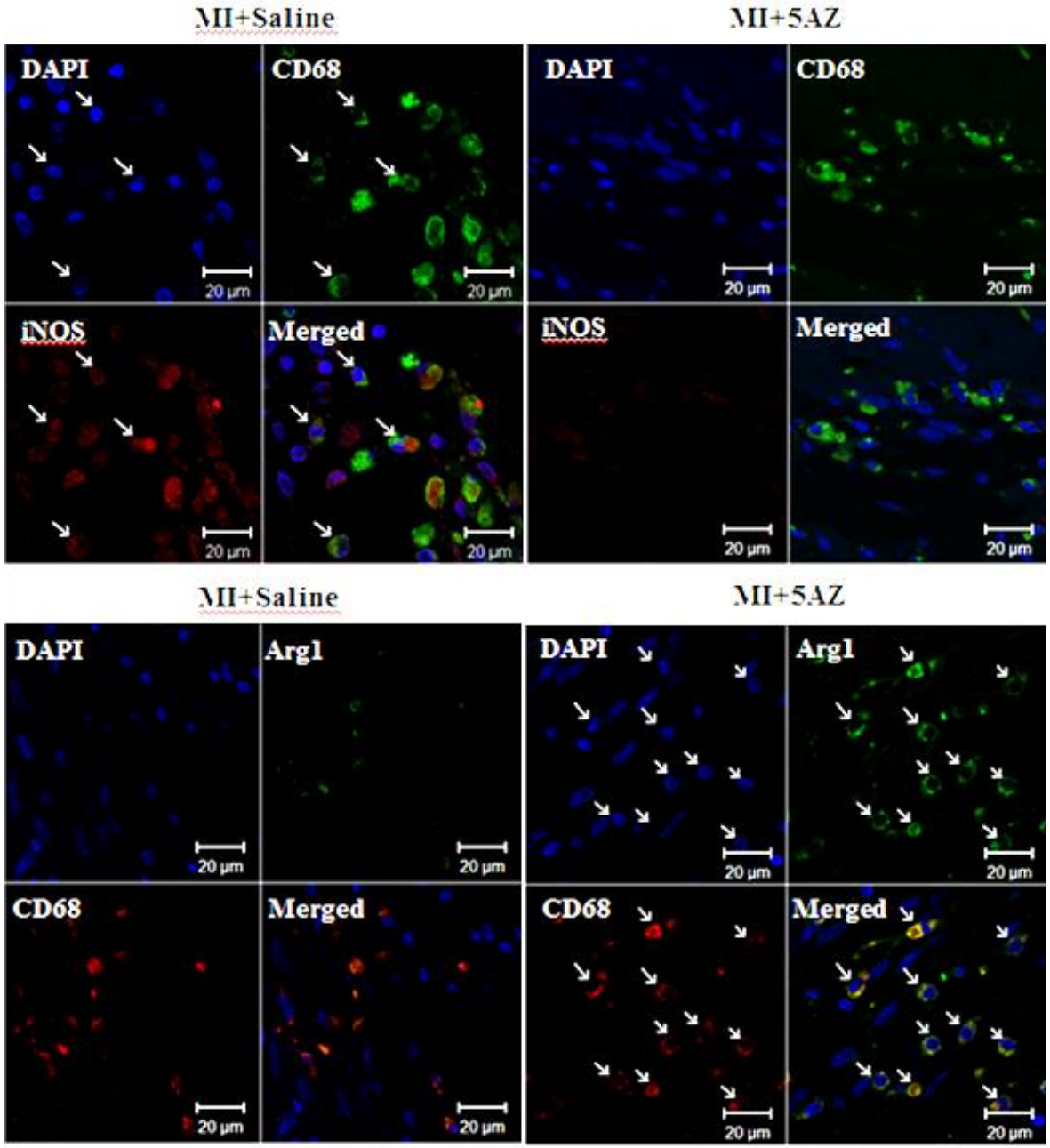


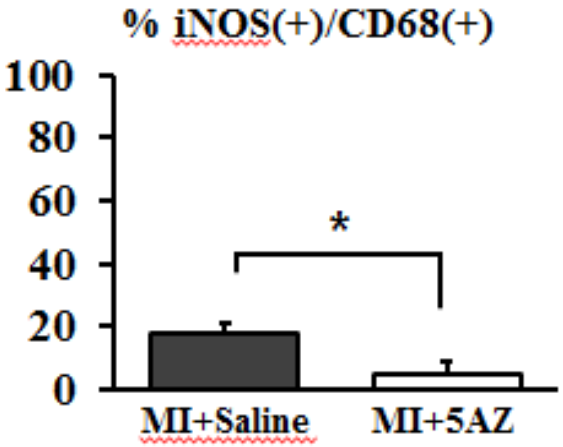


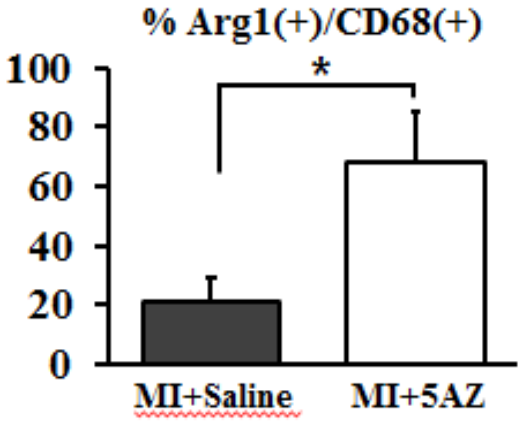
Effect of 5AZ administration on fibrosis in infarcted myocardium.



After 1 day of MI, treatment was performed every other day via ip for 2 weeks.


MI+Saline
MI+5AZ
DAPI
CD68
iNOS
Merged
Arg1
20 μm

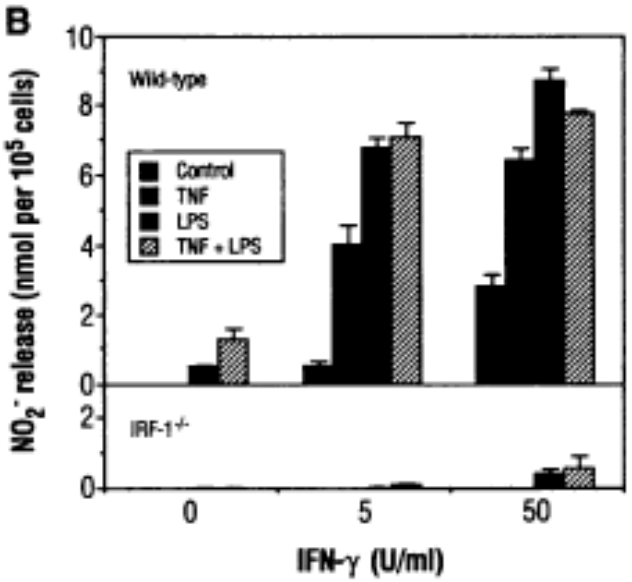

% iNOS(+)/CD68(+)
100
80
60
40
20
0
*
MI+Saline
MI+5AZ

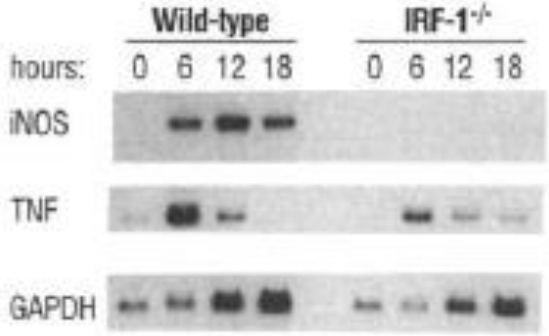

% Arg1(+)/CD68(+)
100
80
60
40
20
0
*
MI+Saline
MI+5AZ

III. IRF-1 as an Effector of 5-azacytidine in Activated Macrophages

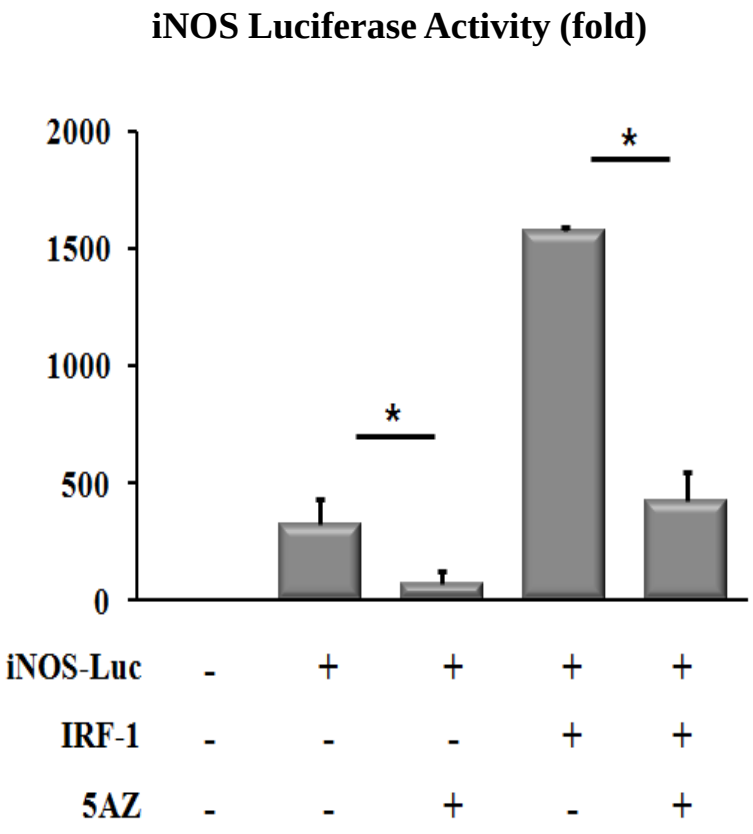
Requirement for Transcription Factor IRF-1 in NO Synthase Induction in Macrophages

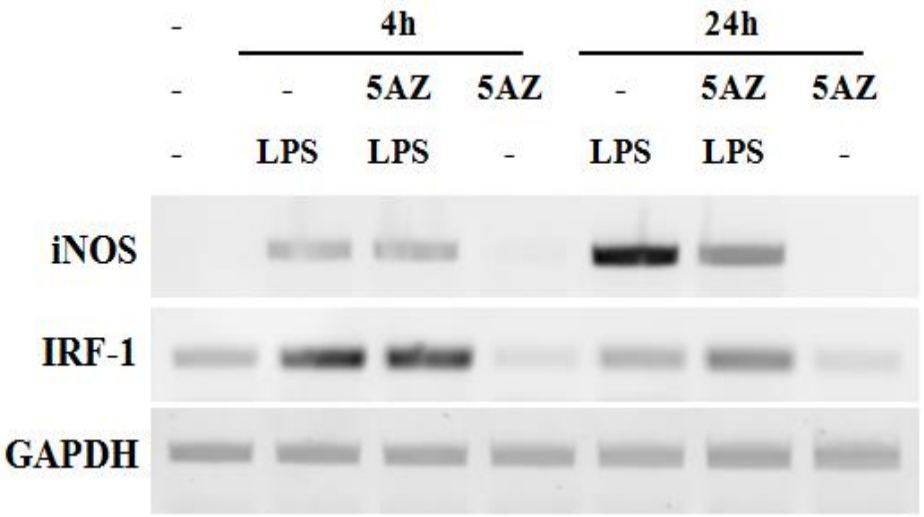
R. Kamijo,* H. Harada, T. Matsuyama, M. Bosland, J. Gerecitano, D. Shapiro, J. Le, S. I. Koh, T. Kimura, S. J. Green, T. W. Mak, T. Taniguchi, J. Vilček†





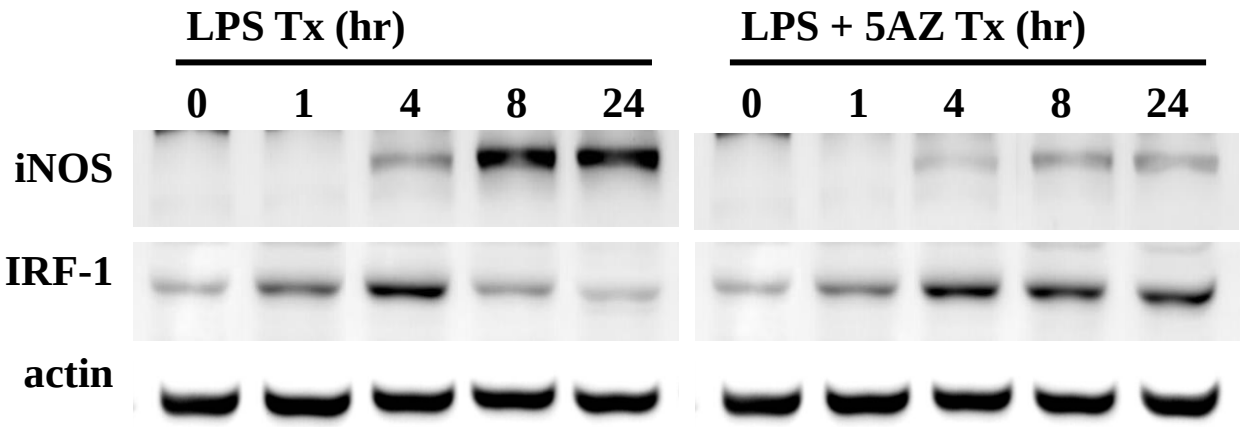
5AZ inhibited iNOS activity and expression in LPS-activated RAW264.7 cells

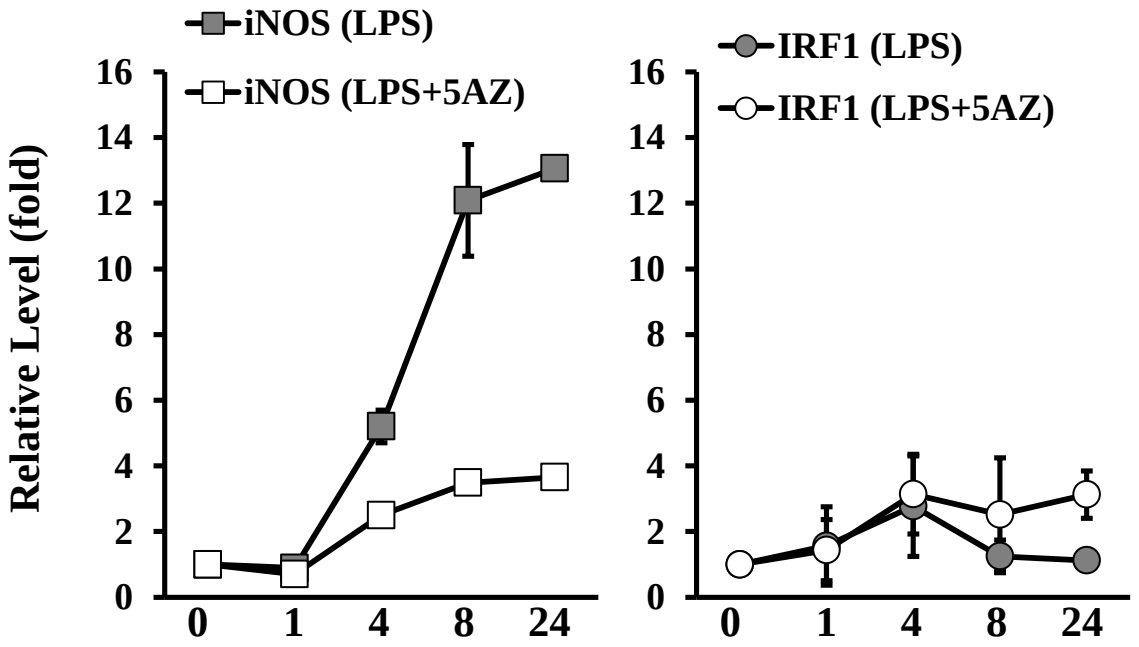


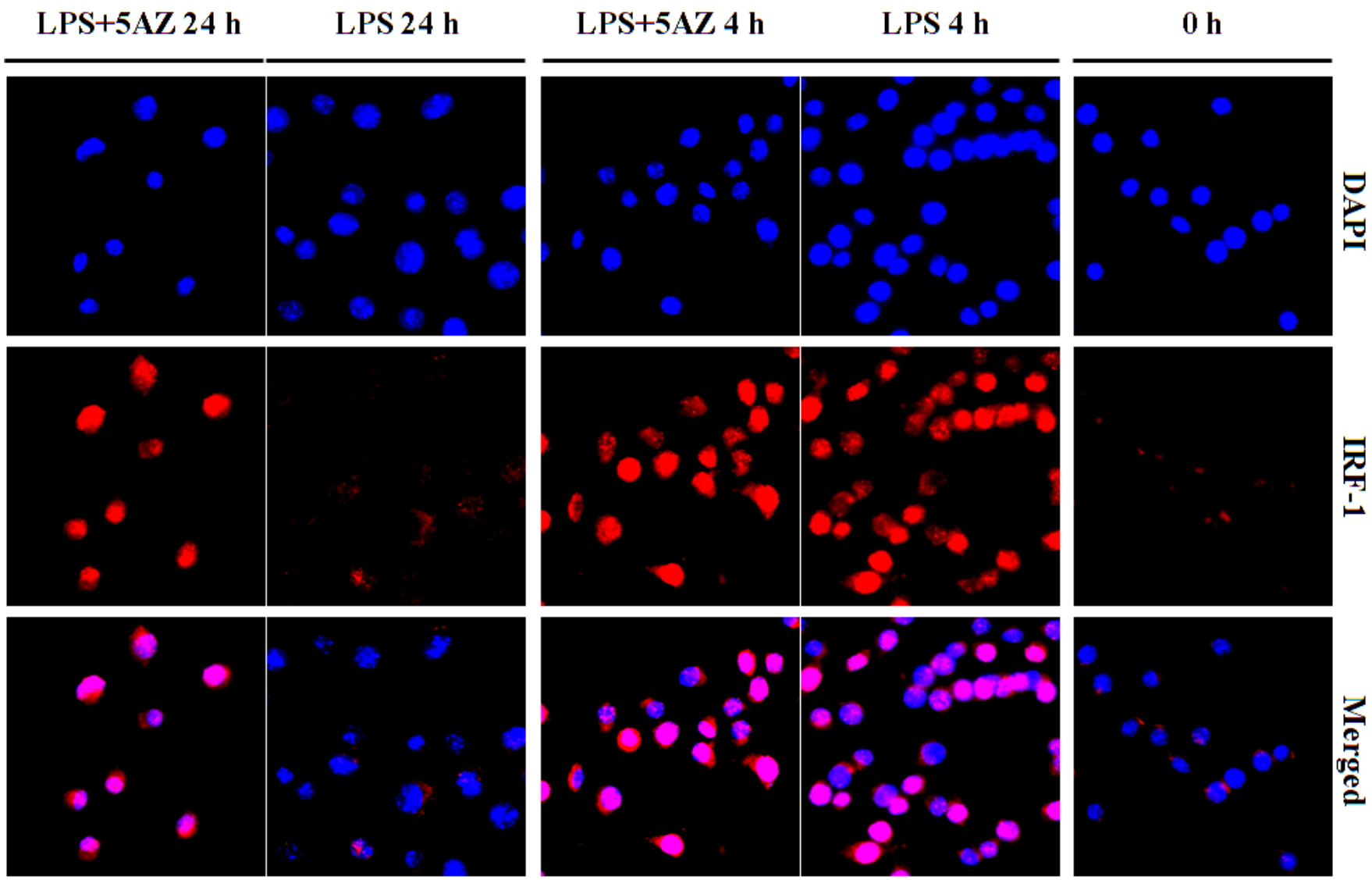


LPS for 24 hours

Altered kinetics of iNOS and IRF-1 by 5AZ






LPS+5AZ 24 h
LPS 24 h
LPS+5AZ 4 h
LPS 4 h
0 h
DAPI
IRF-1
Merged

IV. Application of a Novel Macrophage-Specific Promoter for the Change of Phenotype of M2 Macrophage

OPEN

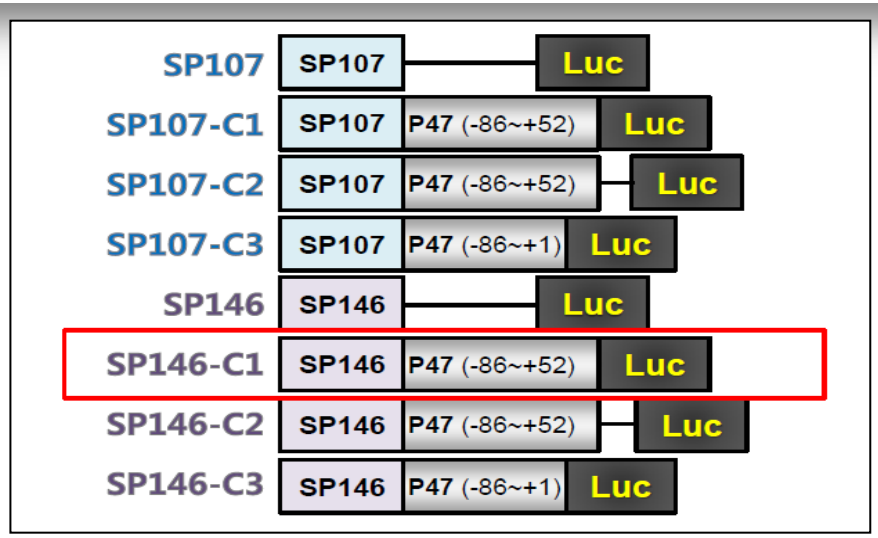
Gene Therapy (2014), 1–10

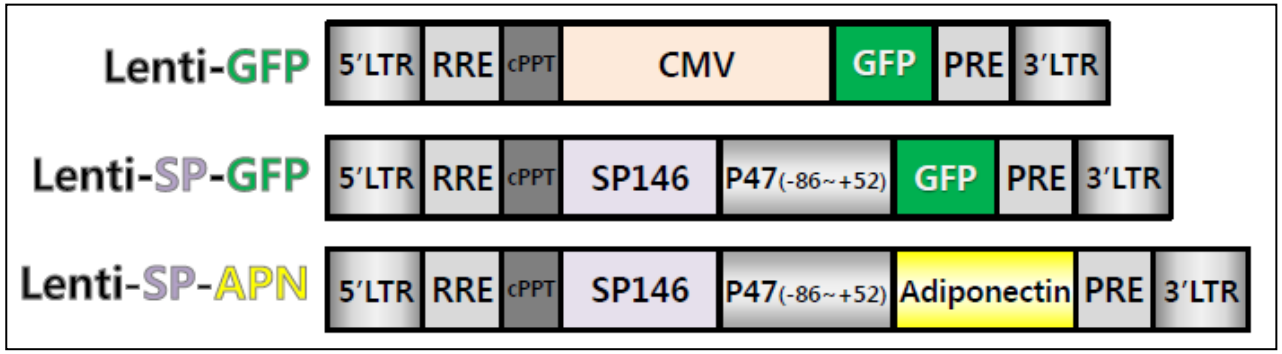
www.nature.com/gt

ORIGINAL ARTICLE

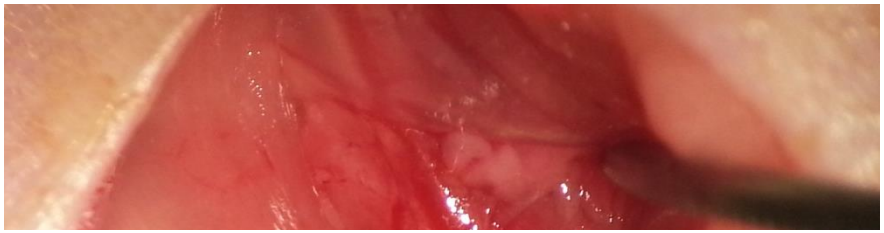
A macrophage-specific synthetic promoter for therapeutic application of adiponectin

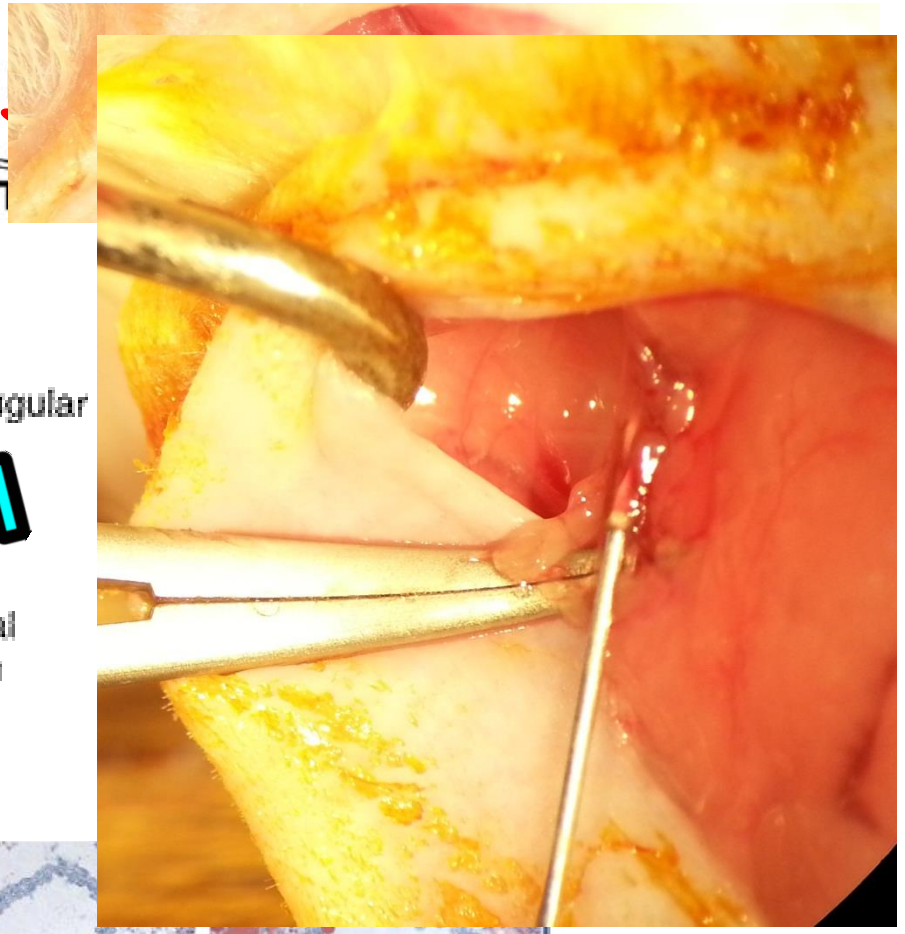
WS Kang[1,2,5], JS Kwon[1,3,5], HB Kim[1], H-y Jeong[1], HJ Kang[1], MH Jeong[3,4], JG Cho[4], JC Park[4], YS Kim[1,3] and Y Ahn[1,3,4]

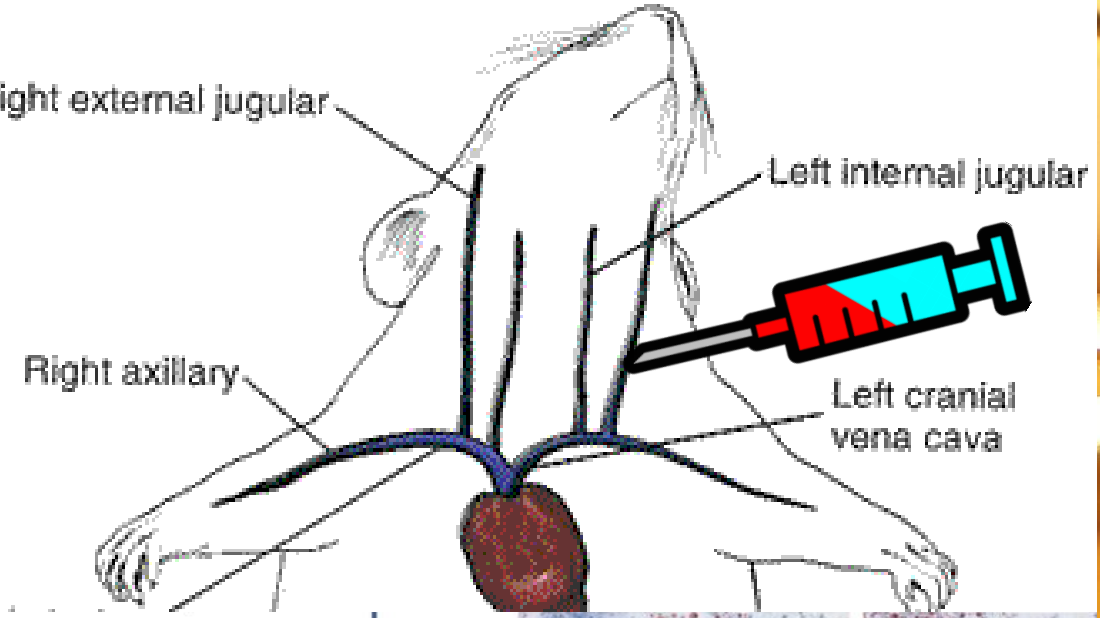


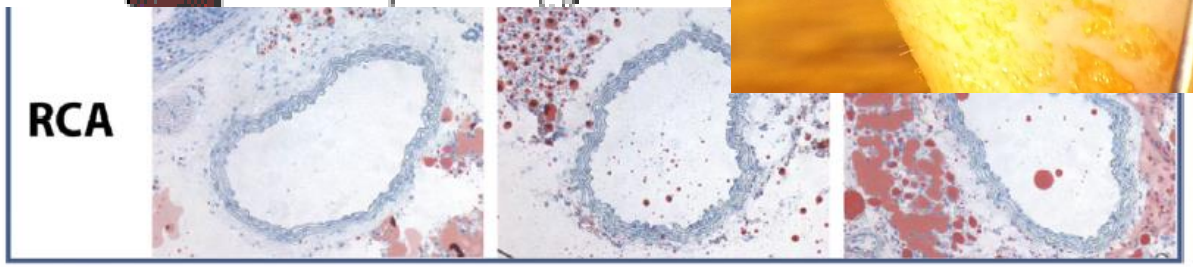


Atherosclerosis model (Subtotal occlusion)



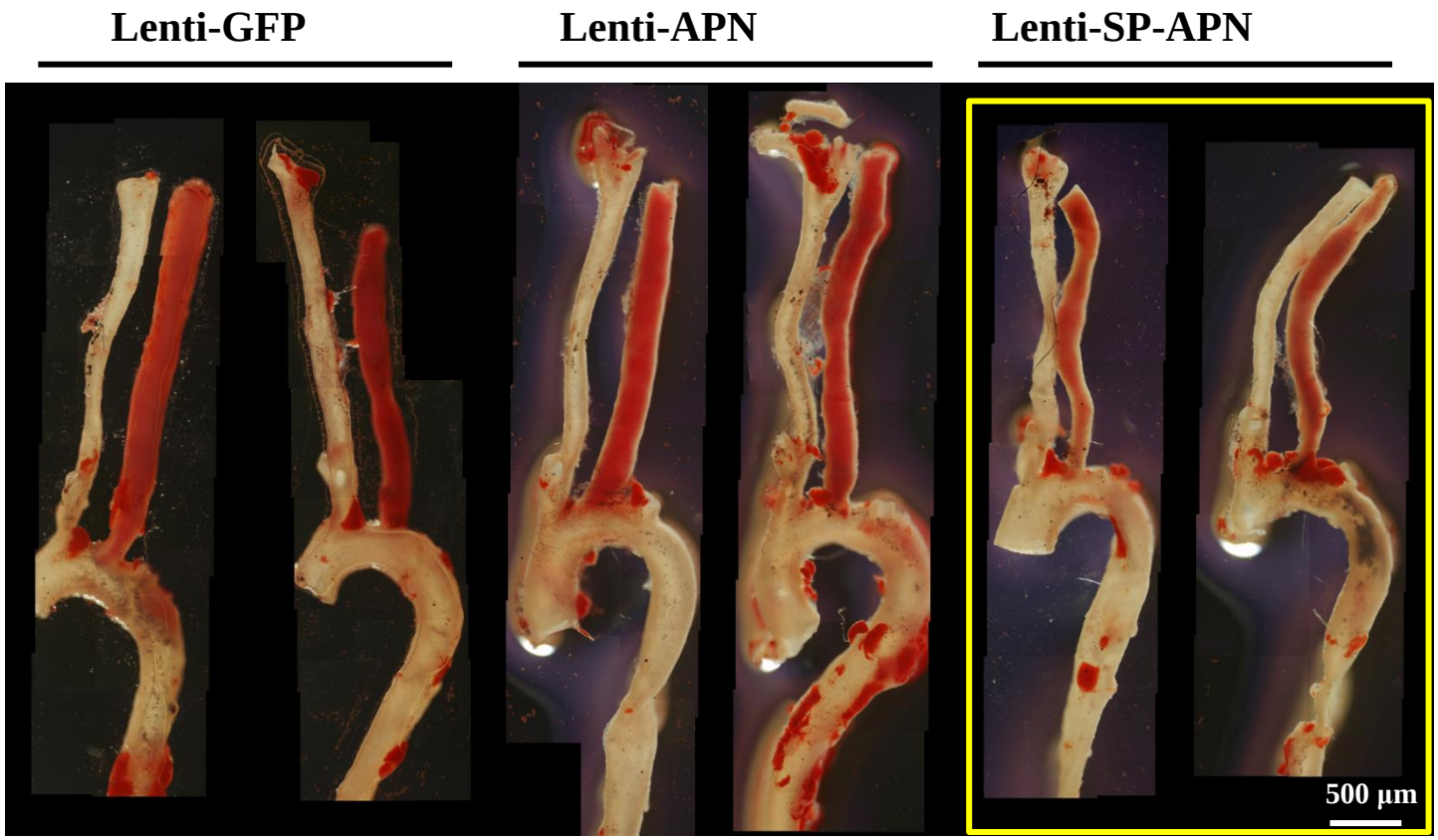






Am J Physiol Heart Circ Physiol. 2009;297:H1535-43

Lenti-SP-APN on atherosclerosis model



Conclusion

1. **Macrophage inflammation and polarization may represent novel potential therapeutic and biomarker that may be exploited in the future treatment of cardiovascular disease.**

2. **MSC-educated macrophages might provide a new therapeutic opportunity to improve cardiac outcome after acute injury.**

Thank you for your attention!

Kimchi Festival

Moodeung Mt.
Watermellon

Samhab Skates

Side Dishes

Yuk Jun

Meatball made with galbi

Law Meat

Sam gye tang

Please enjoy it!