2015. 4. 춘계심장학회

Macrophage Polarization and Functional Phenotypes in Cardiovascular Disease

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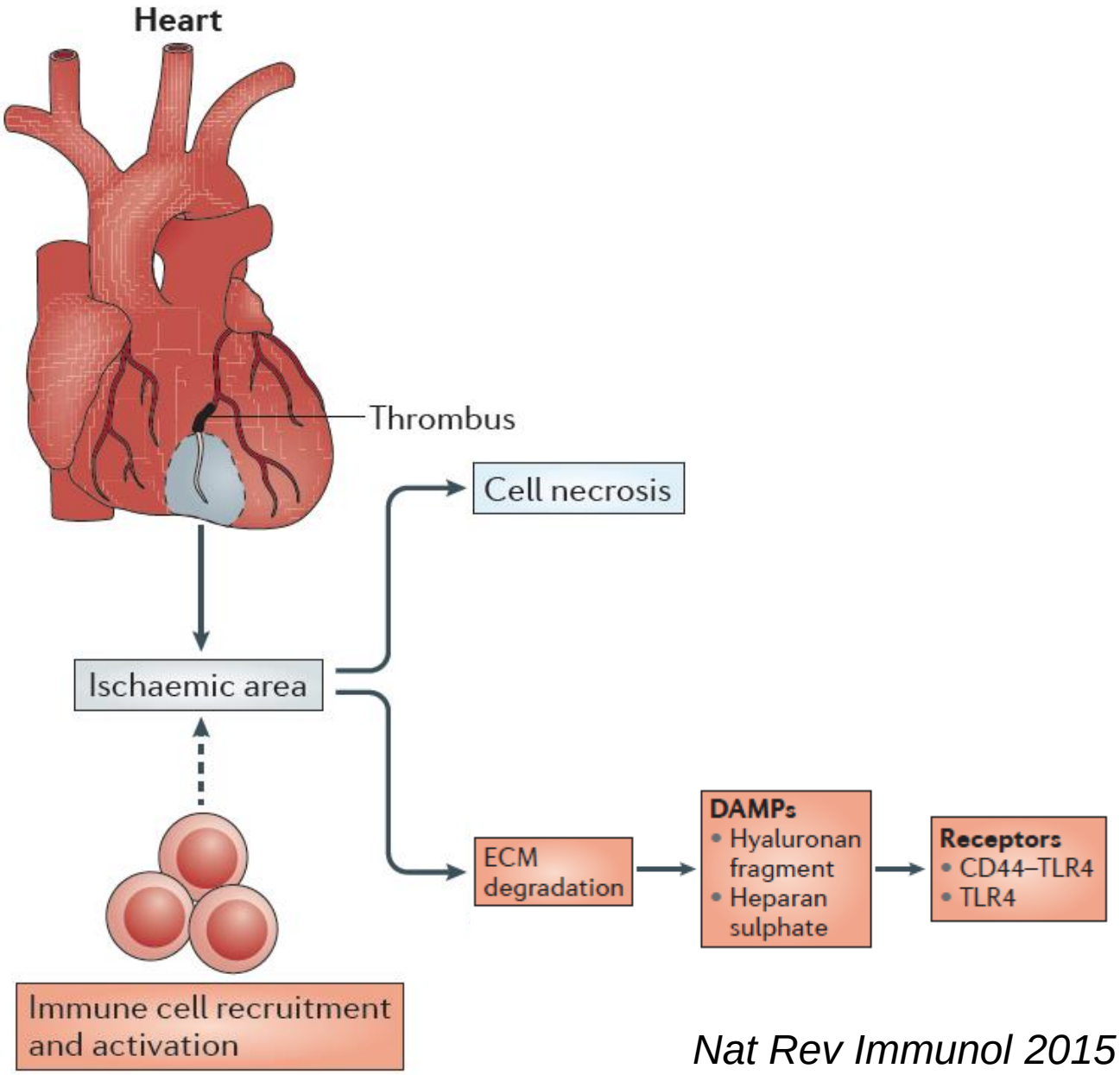
심혈관센터 순환기내과

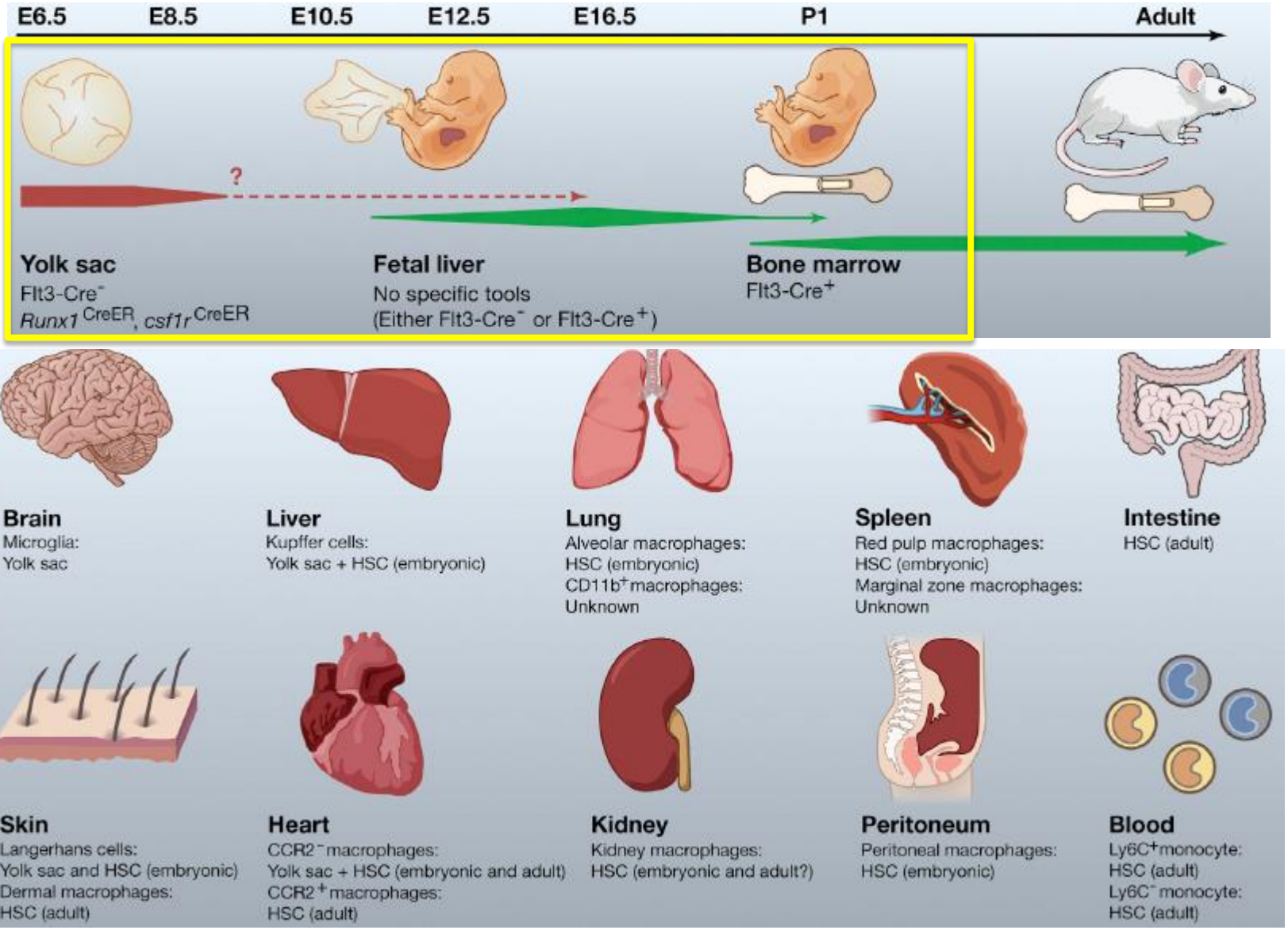
안영근

Cardiac injury and sensing damaged tissue

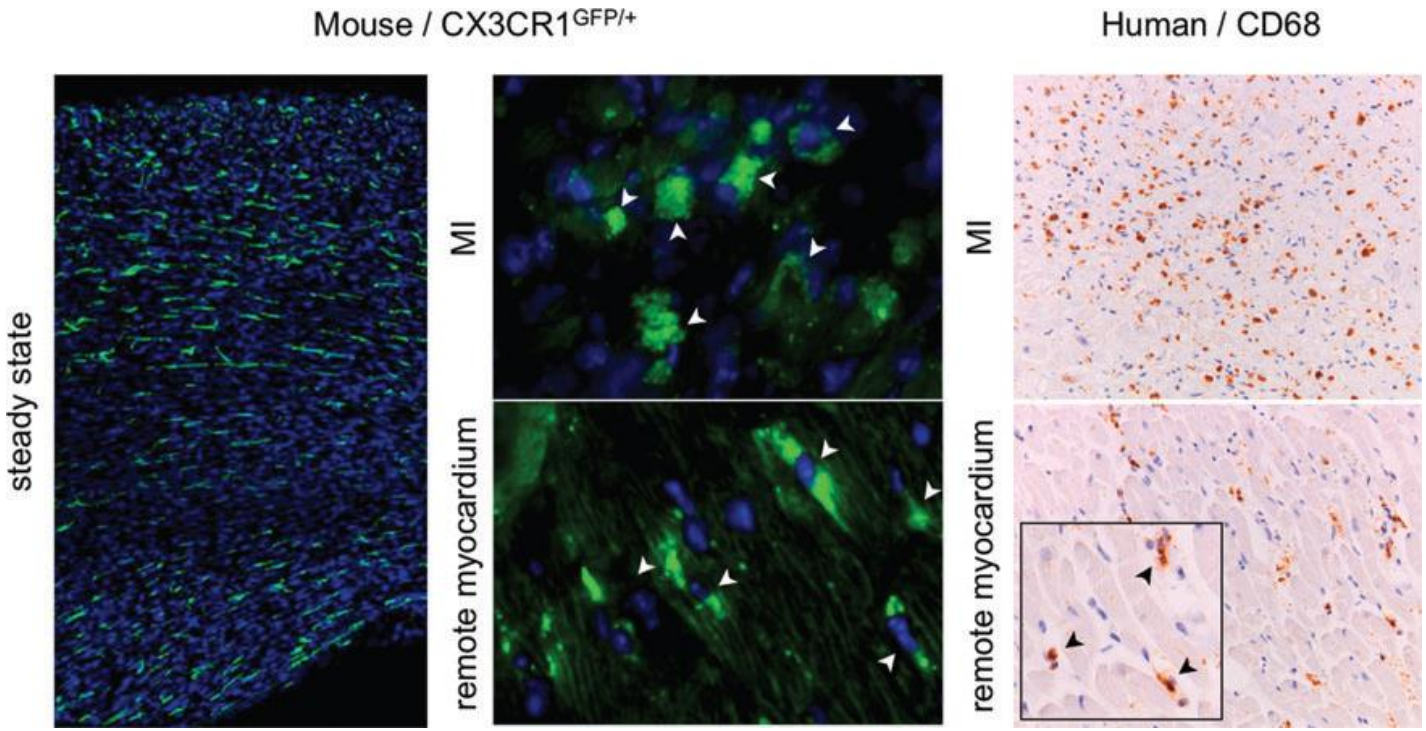


Nat Rev Immunol 2015

Macrophage Lineages, Ontogeny, and Contribution to Resident Tissue Macrophages

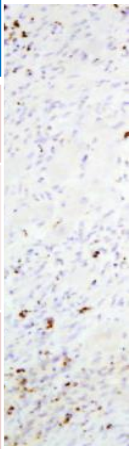


Immunity. 2014;41:21-35



Non

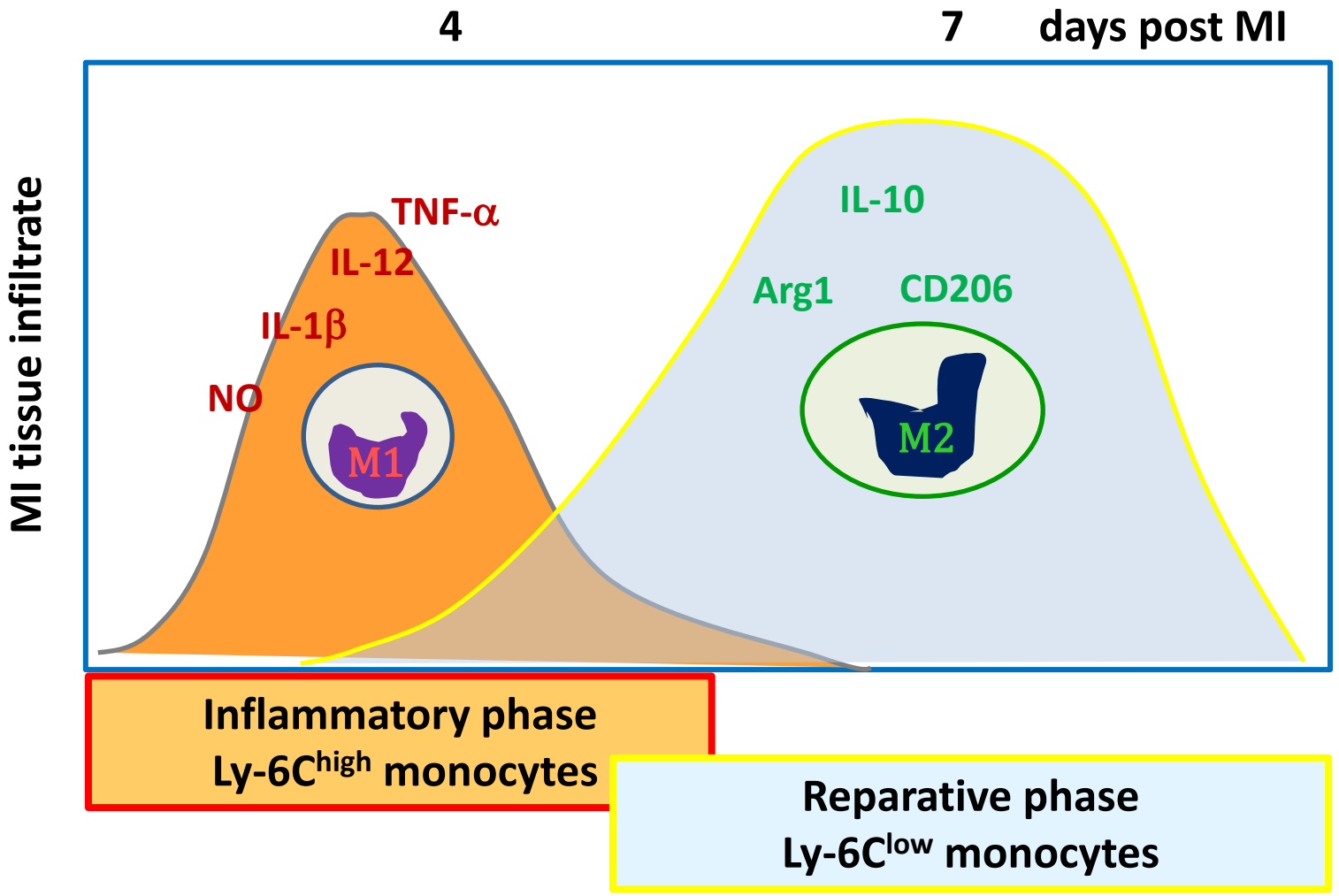
Role of post-MI	
Phagocytosis	Remove necrotic myocytes and apoptotic neutrophils
Chemotaxis	Recruit additional macrophages to injury site to amplify response
Secretion	Regulate scar formation by secreting growth factors, angiogenic factors, and MMPs
Angiogenesis	Restore blood flow



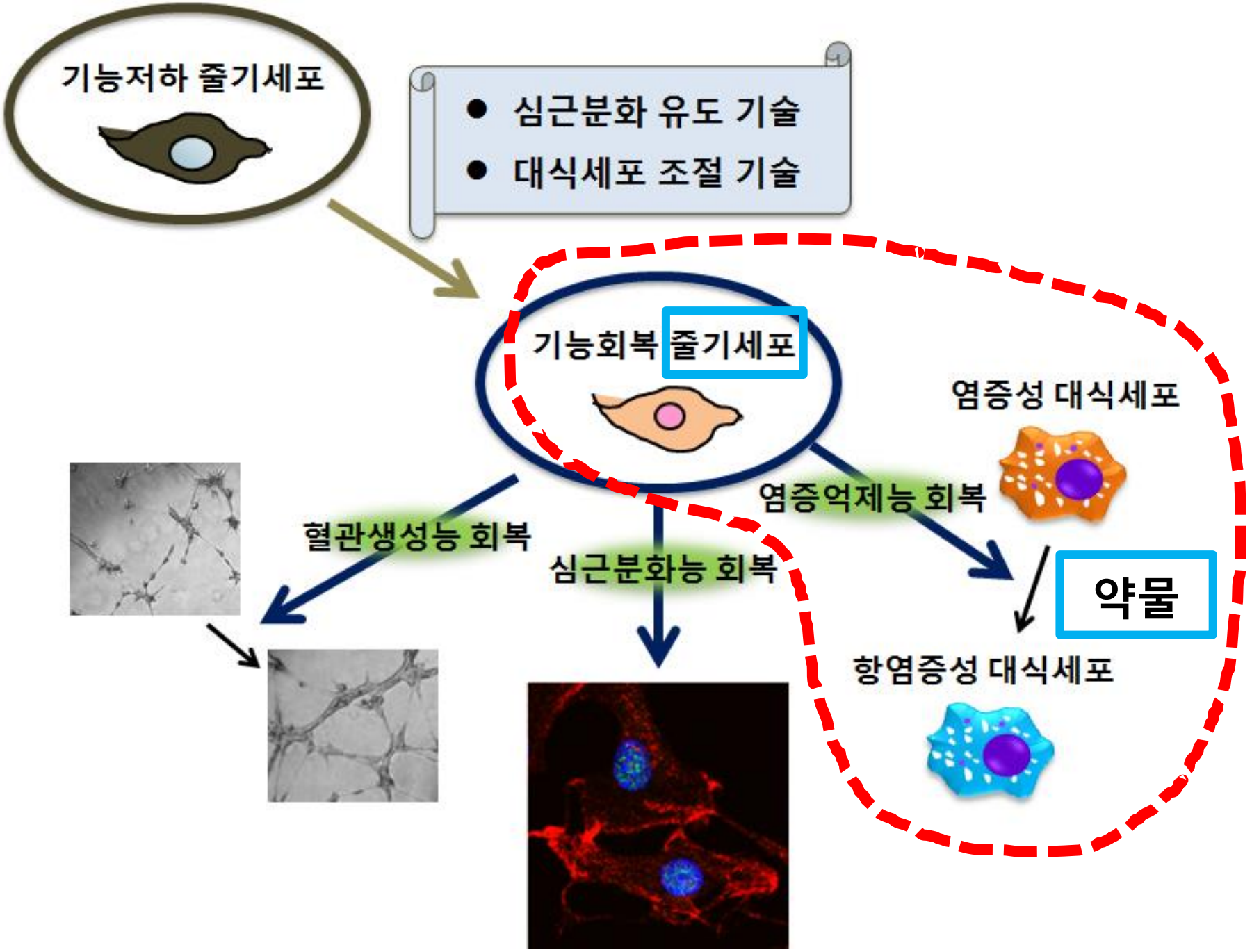
23.

Int J Cardiol. 2008;130;147–158.

Cardiovasc Res. 2014;102:240-8.



Arter Thromb Vasc Biol. 2009;29:1419–1423.
Circulation. 2010;121:2437-2445.
Circ Res. 2014;114:1611-22.


기능저하 줄기세포
심근분화 유도 기술
대식세포 조절 기술
기능회복 줄기세포
염증성 대식세포
염증억제능 회복
혈관생성능 회복
심근분화능 회복
약물
항염증성 대식세포

1. Regulation of Macrophage Polarization in Infarcted Myocardium by Stem cells

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

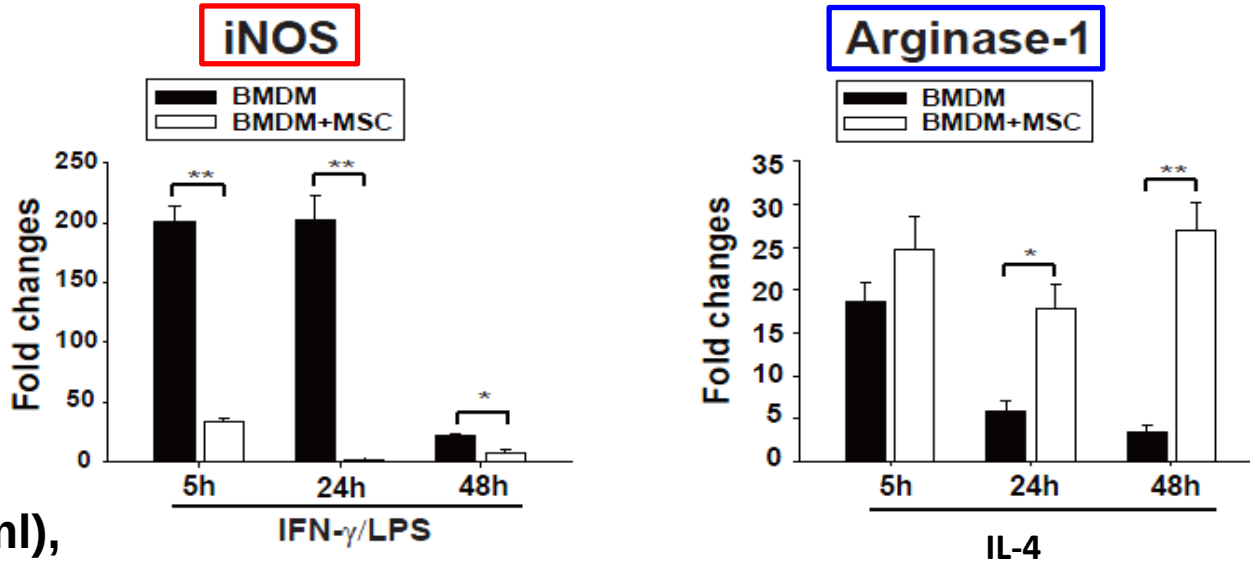
www.nature.com/emm

ORIGINAL ARTICLE

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

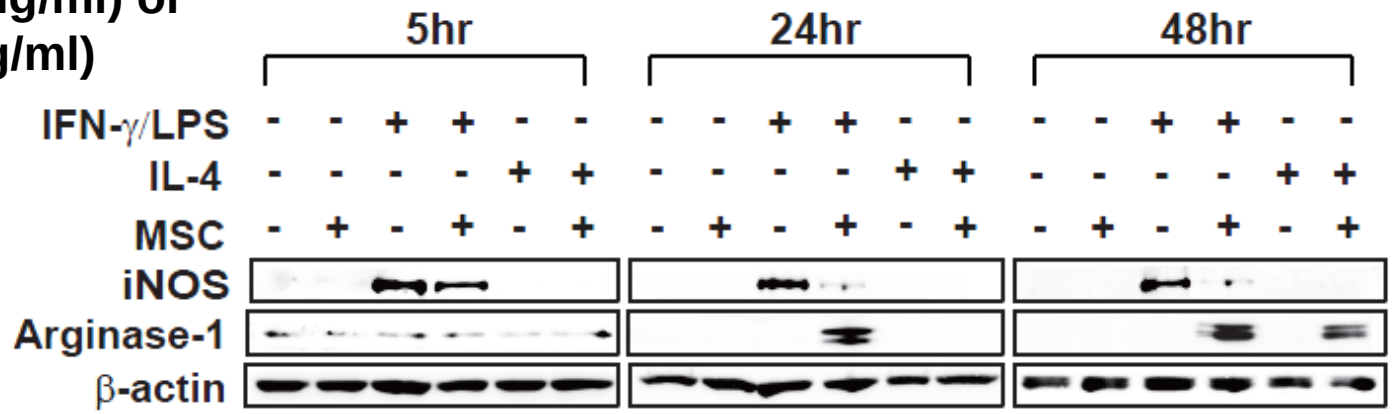
Dong-Im Cho[1], Mi Ra Kim[1], Hye-yun Jeong[1], Hae Chang Jeong[2], Myung Ho Jeong[2,3], Sung Ho Yoon[4], Yong Sook Kim[1,3] and Youngkeun Ahn[2,3]

MSCs regulated iNOS and Arg1 reciprocally in activated BMDMs



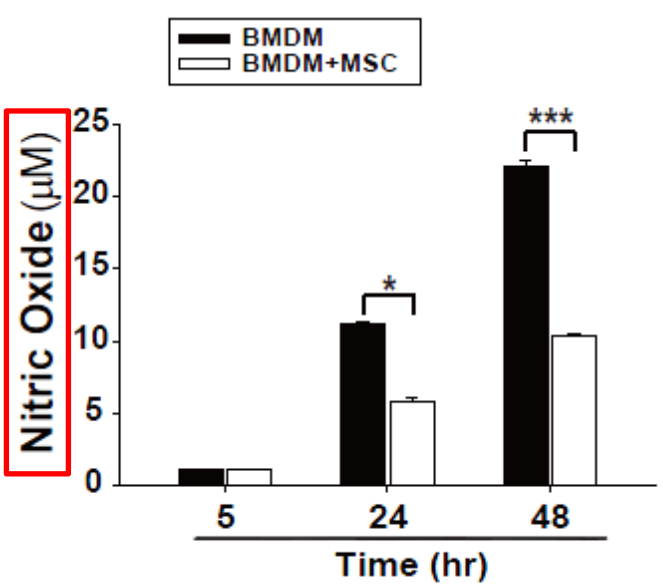
LPS (100 ng/ml), IFN-γ (30 ng/ml) or IL-4 (20 ng/ml)

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

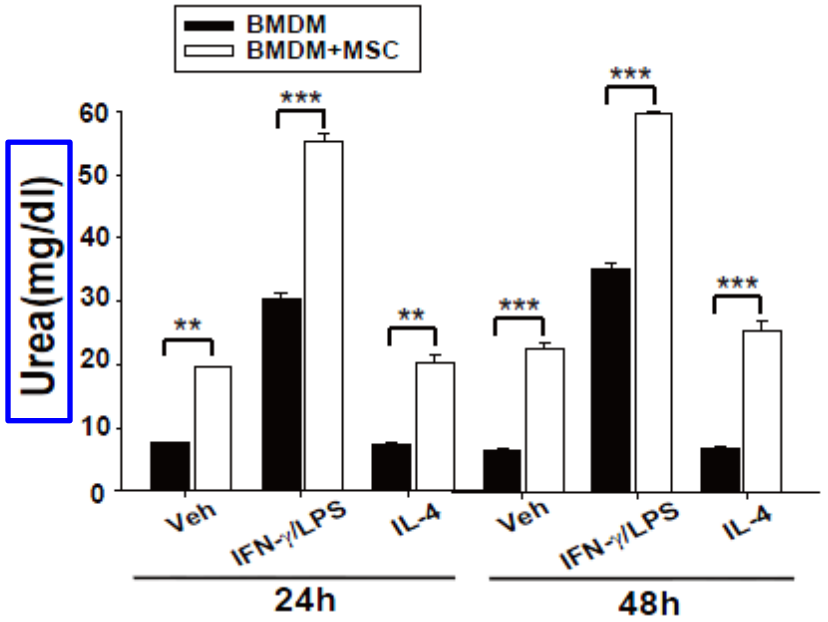


The iNOS decreased, however, the arginase-1 increased in BMDMs co-cultured with MSCs.

The enzymatic activities of iNOS and arginase-1



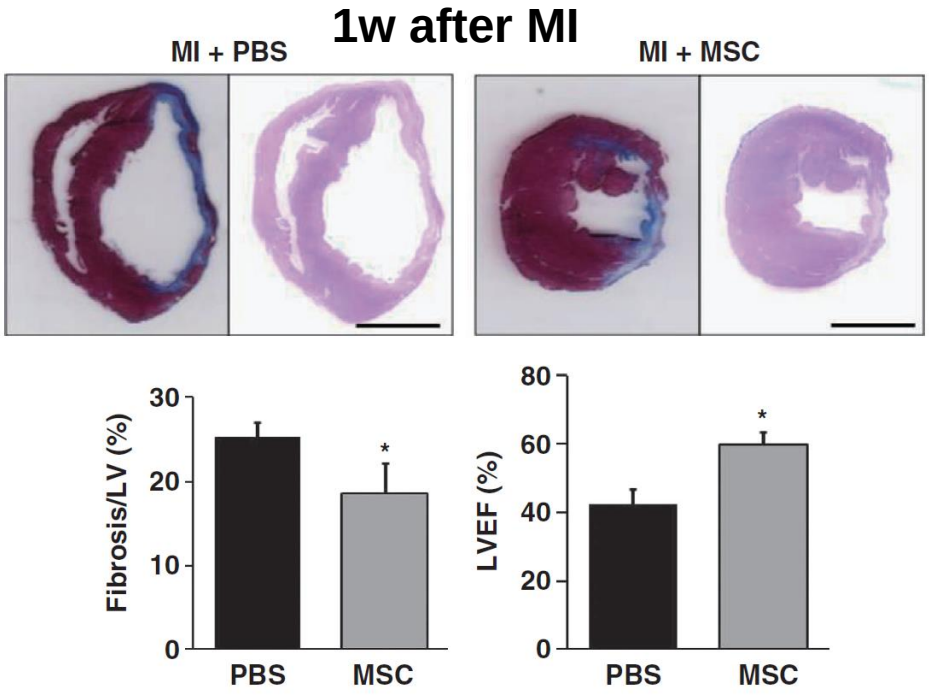
IFN-γ/LPS

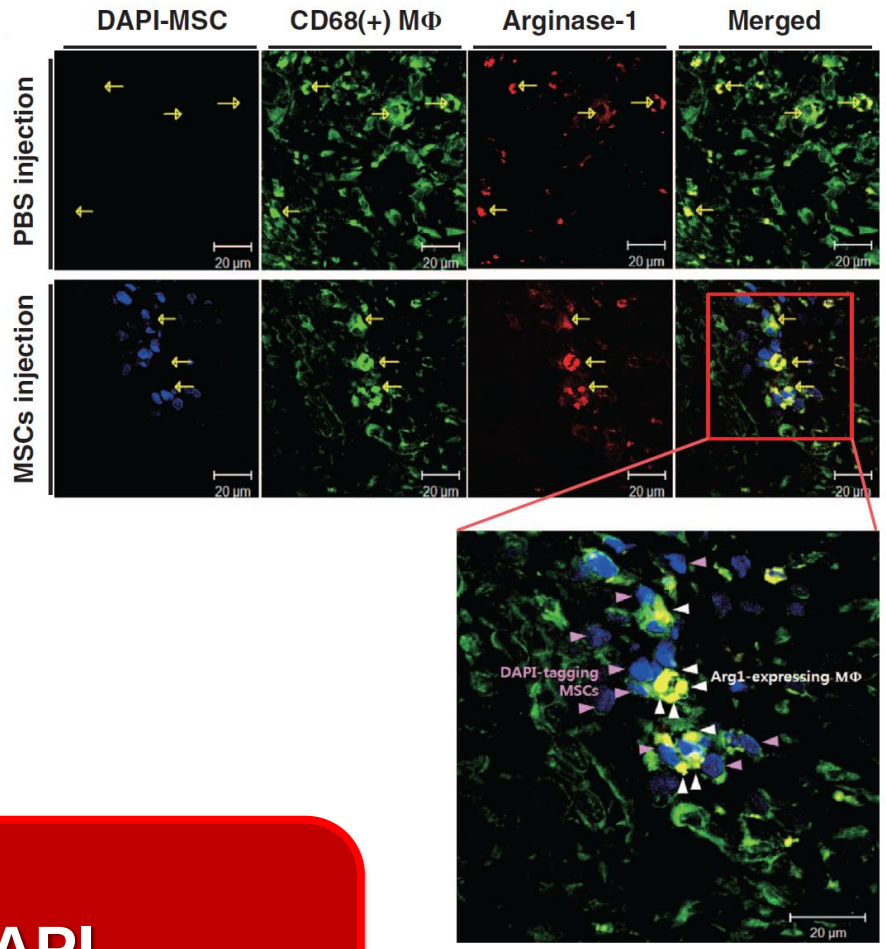


MSCs regulated iNOS and arginase-1 reciprocally in activated BMDMs.

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

The identification of arginase-1-expressing macrophages in infarct myocardium

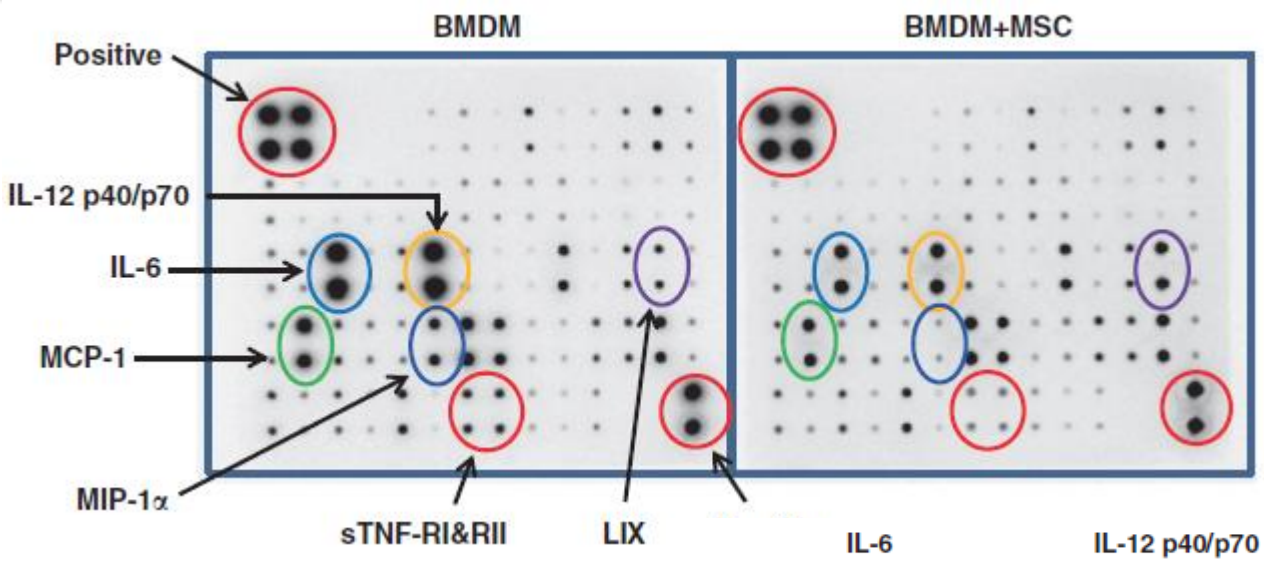


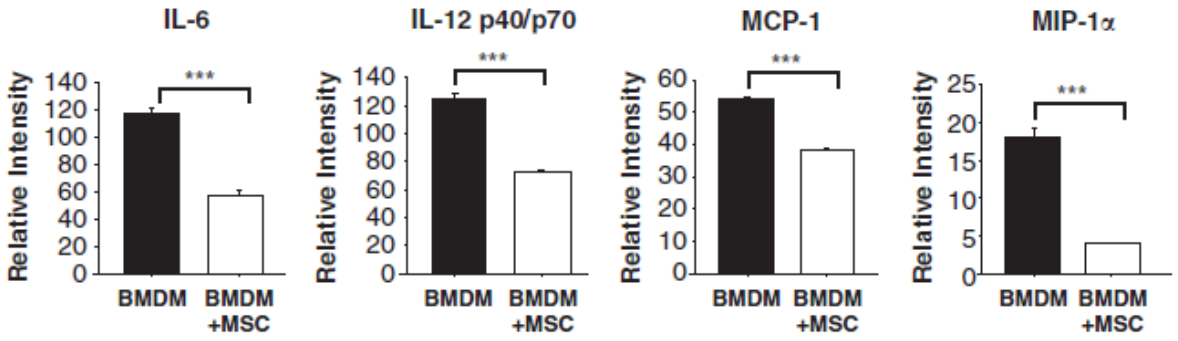


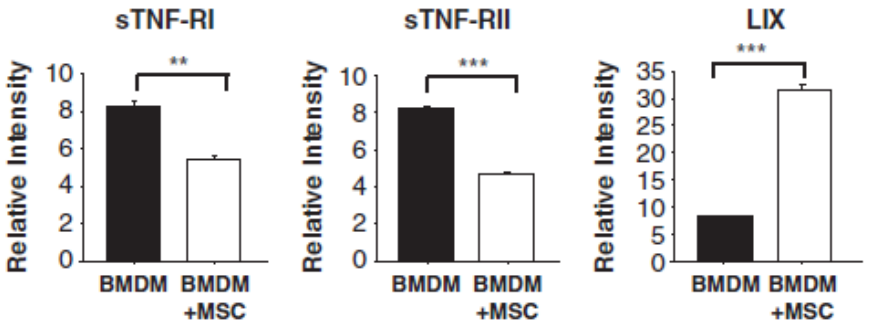
Arg1-expressing CD68 (+) macrophages (yellow) near DAPI-labeled MSCs (blue) were observed in the infarct zone.

*$p<0.05$

Inflammation-related cytokine secretions from BMDMs analyzed by protein array



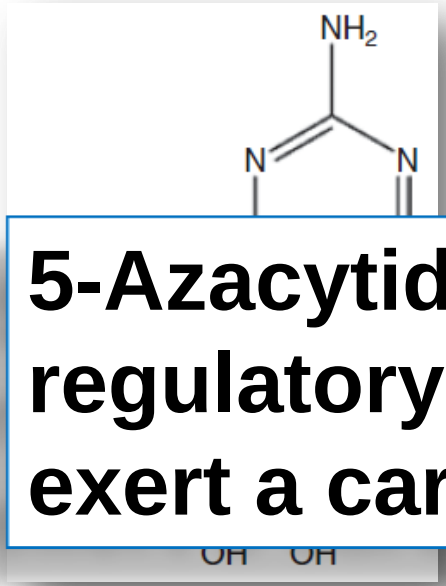




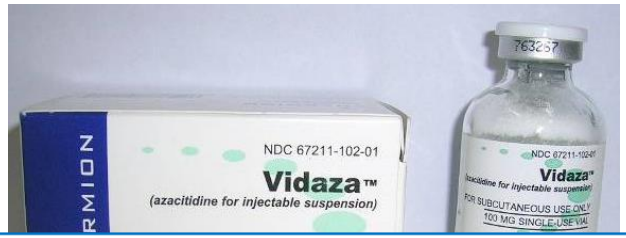
BMDMs were cultured for 24h with IFN-γ/LPS

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

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

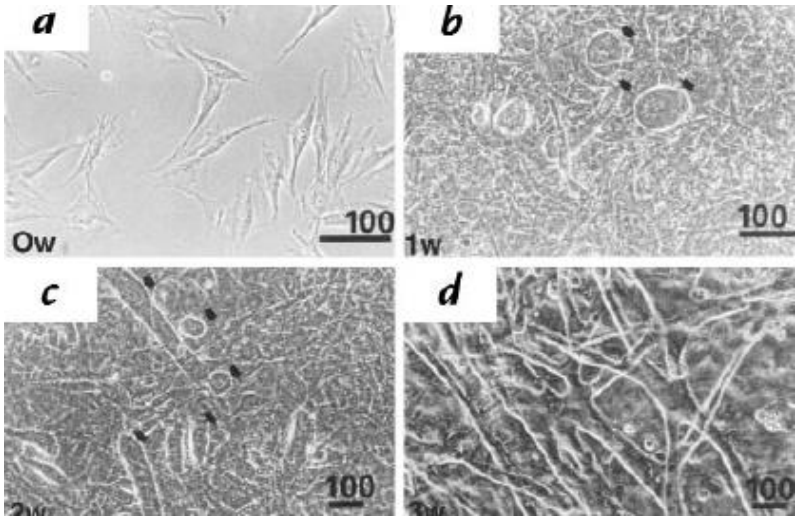


Azacitidine
(5-azacytidine)



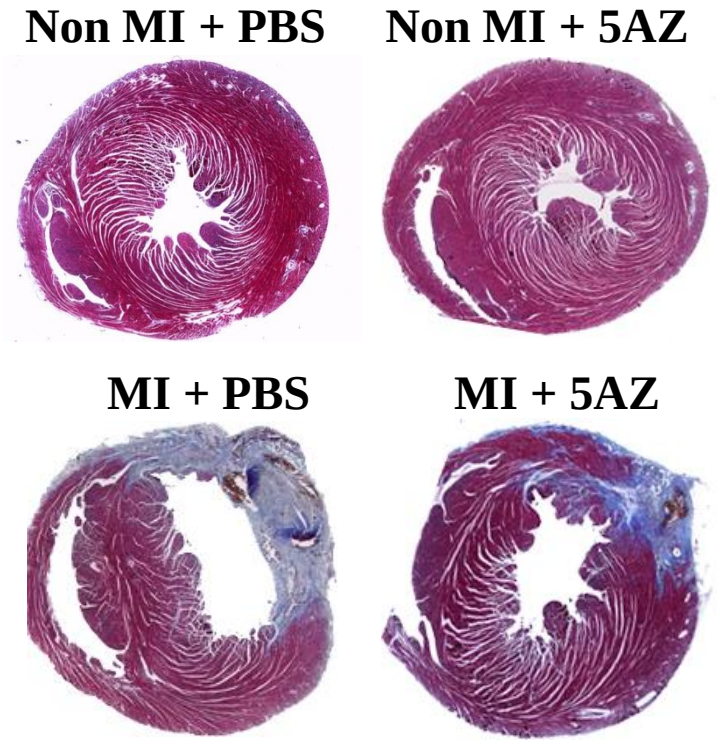
5-Azacytidine modulates interferon regulatory factor 1 in macrophages to exert a cardioprotective effect

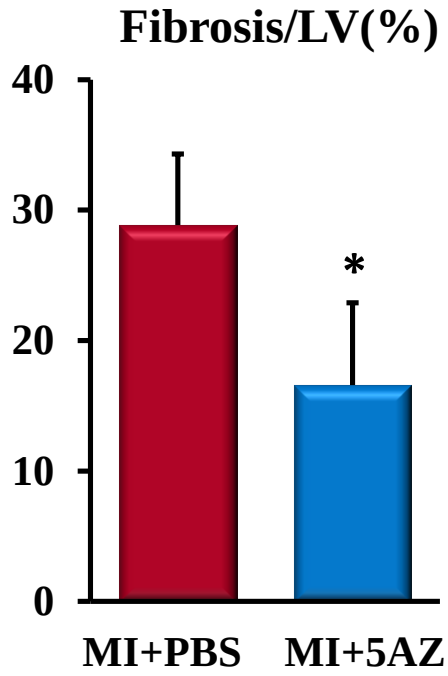
Hiroaki Kodama,[1] Jing Pan,[1] Motoaki Sano,[1] Toshiyuki Takahashi,[1] Shingo Hori,[1]
Hitoshi Abe,[2] Jun-ichi Hata,[2] Akihiro Umezawa,[2] and Satoshi Ogawa[1]



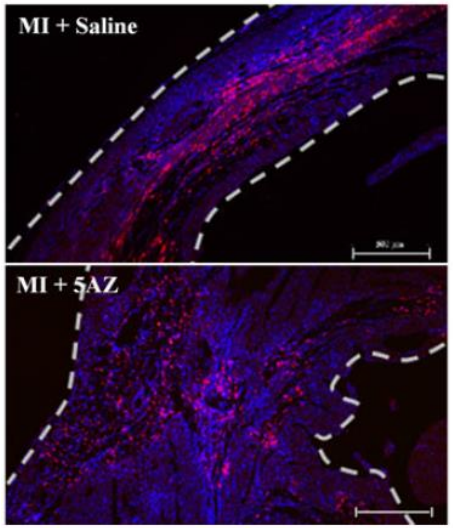
J Clin Invest. 1999;103:697-705

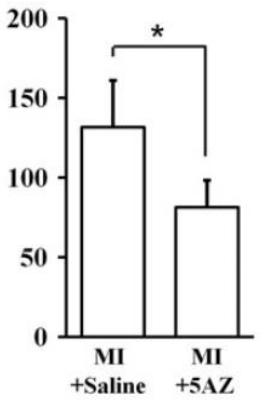
Reduced Cardiac Fibrosis by 5AZ Treatment; MI Model

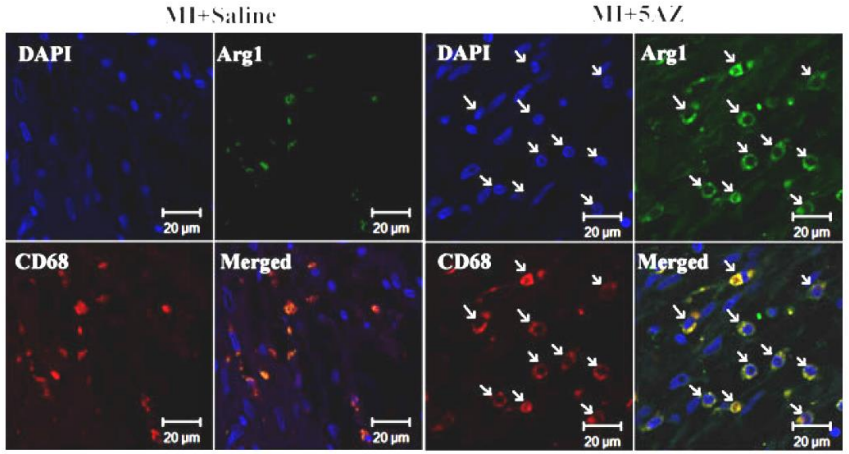




SD rats (weighing 200-230 g)
Tx after 1d of MI, 5AZ (2.5 mg/kg) every other d via ip for 2w



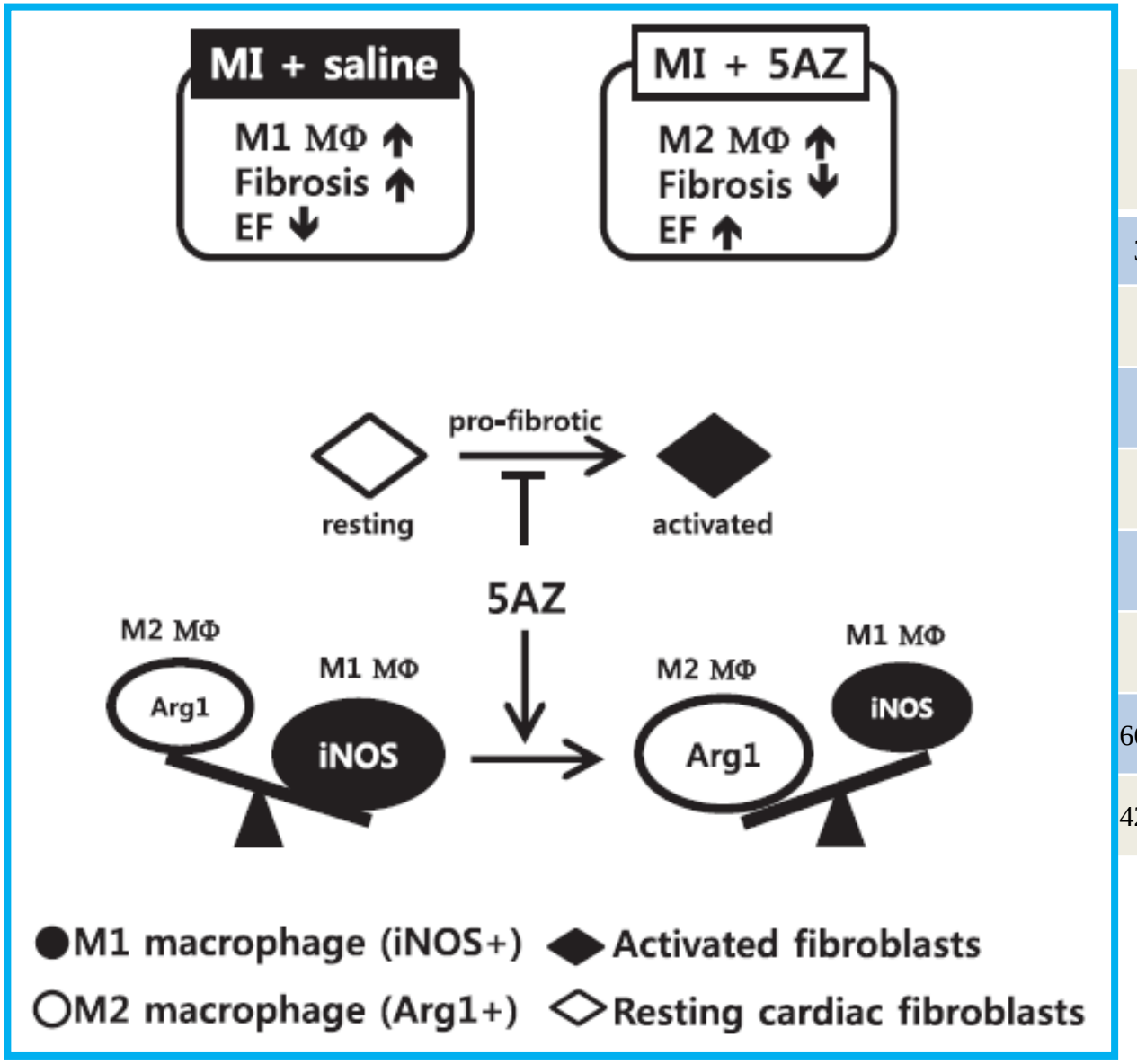




*p<0.05

JCMM. 2014;18:1018-1027

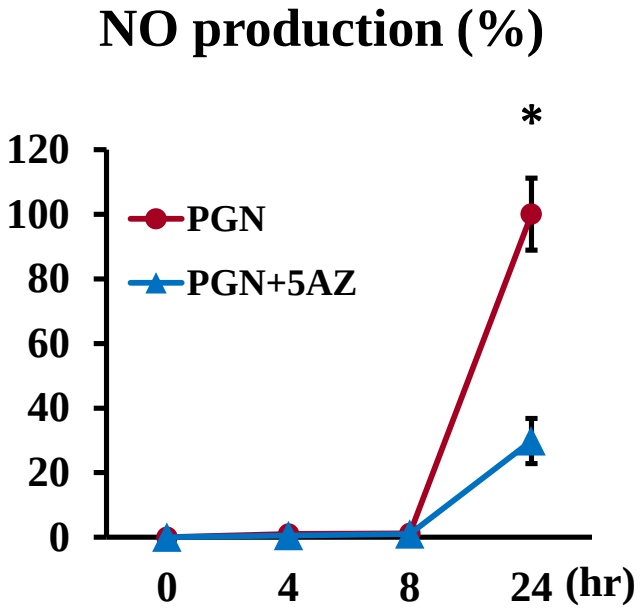
Preserved Cardiac Function by 5AZ Treatment; MI Model

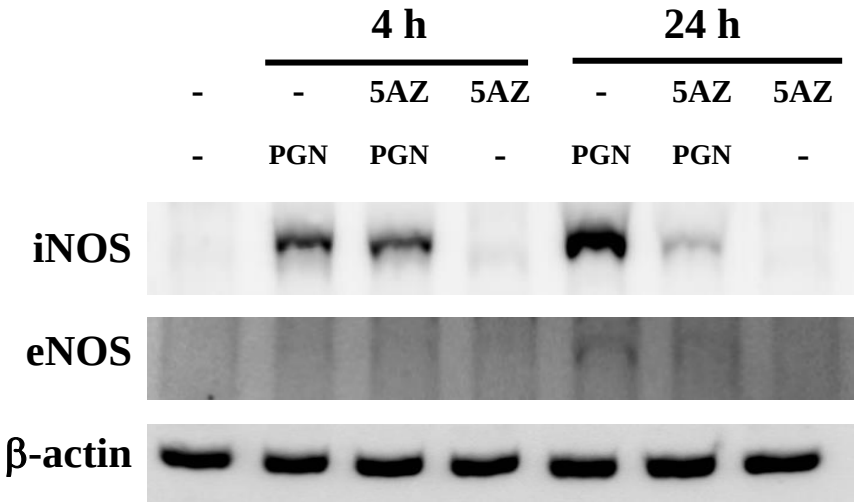


MI (n = 6)	MI+5AZ (n = 6)
316.40 ± 24.21	**314.04 ± 6. 89**
10.10 ± 0.23	**7.35 ± 0.91***
8.12 ± 1.77	**5.35 ± 0.77***
42.52 ± 2.58	**59.00 ± 8.03***
18.38 ± 1.10	**27.57 ± 5.14***
12.83 ± 1.85	**5.38 ± 0.94***
6610.36 ± 282.37	**8299.76 ± 411.56***
4219.50 ± 163.98	**4661.37 ± 210.73***

*$p<0.05$

Inhibition of NO Generation and iNOS by 5AZ Treatment



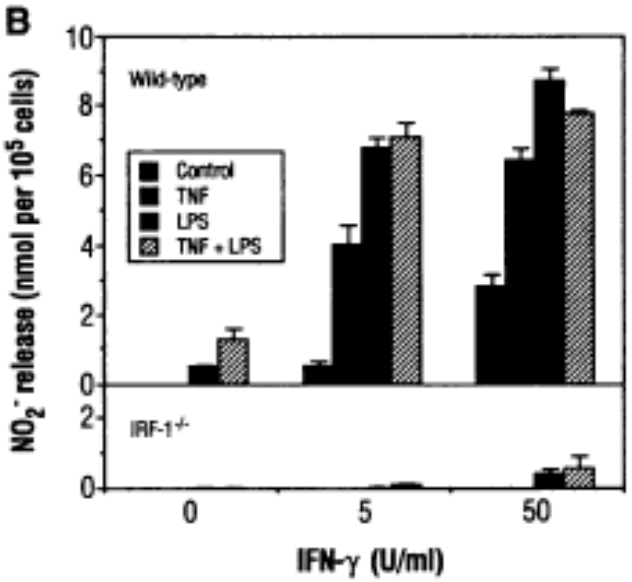


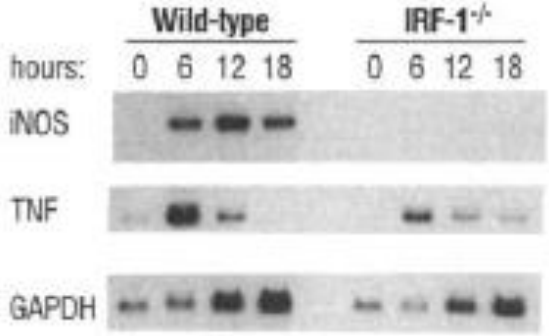
RAW264.7 murine monocyte/macrophage cell line
PGN (10 μg/ml)
5AZ (10 μM)

**p<0.05*

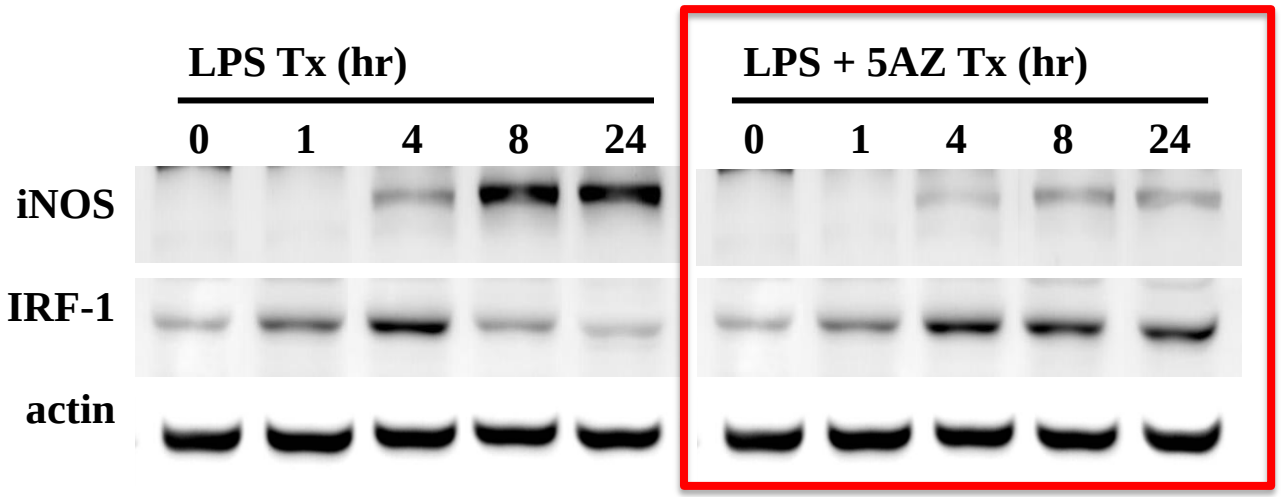
Requirement for Transcription Factor IRF-1 in NO Synthase Induction in Macrophages

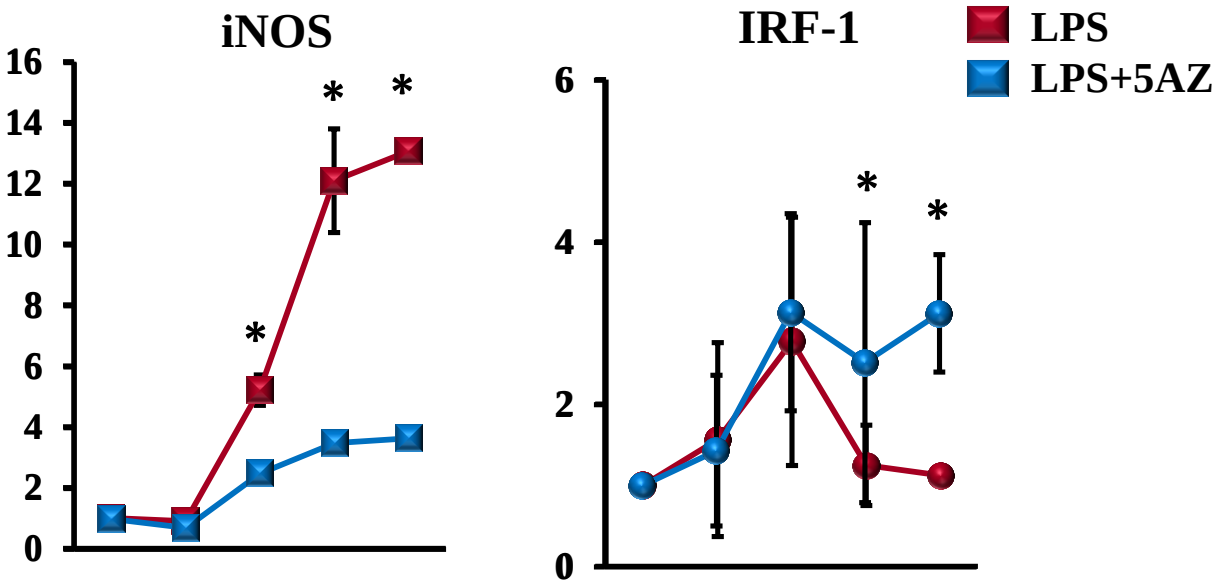
R. Kamijo,* H. Harada, T. Matsuyama, M. Bosland, J. Gerecitano, D. Shapiro, J. Le, S. I. Koh, T. Kimura, S. J. Green, T. W. Mak, T. Taniguchi, J. Vilček†





Altered Protein Levels of iNOS and IRF-1 by 5AZ



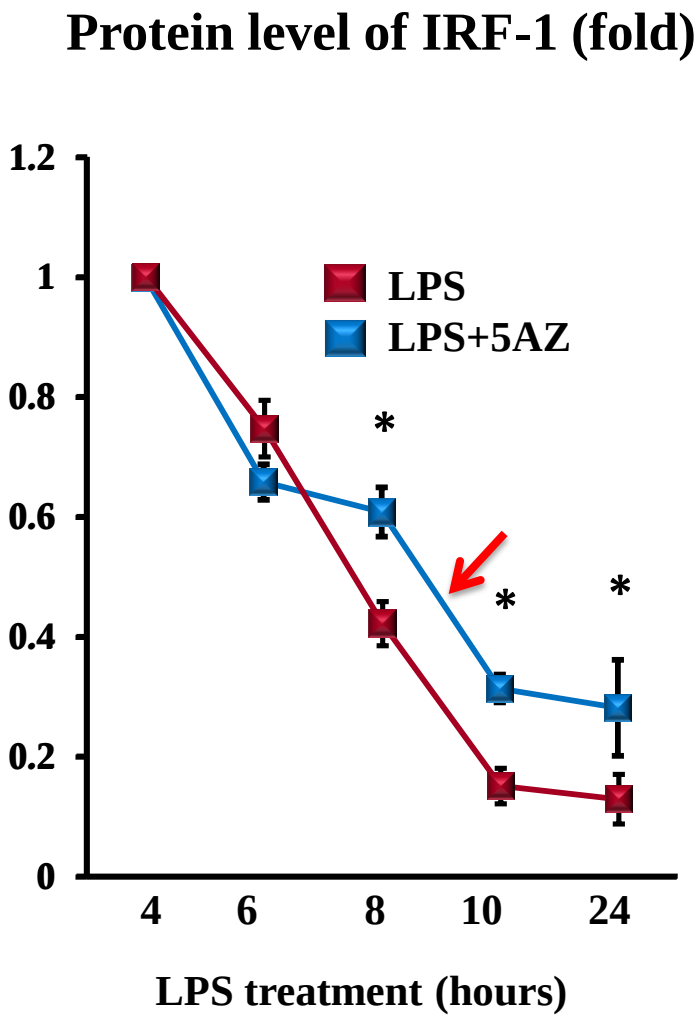


LPS: 100 ng/mL
5AZ: 10 μM

**p<0.05*

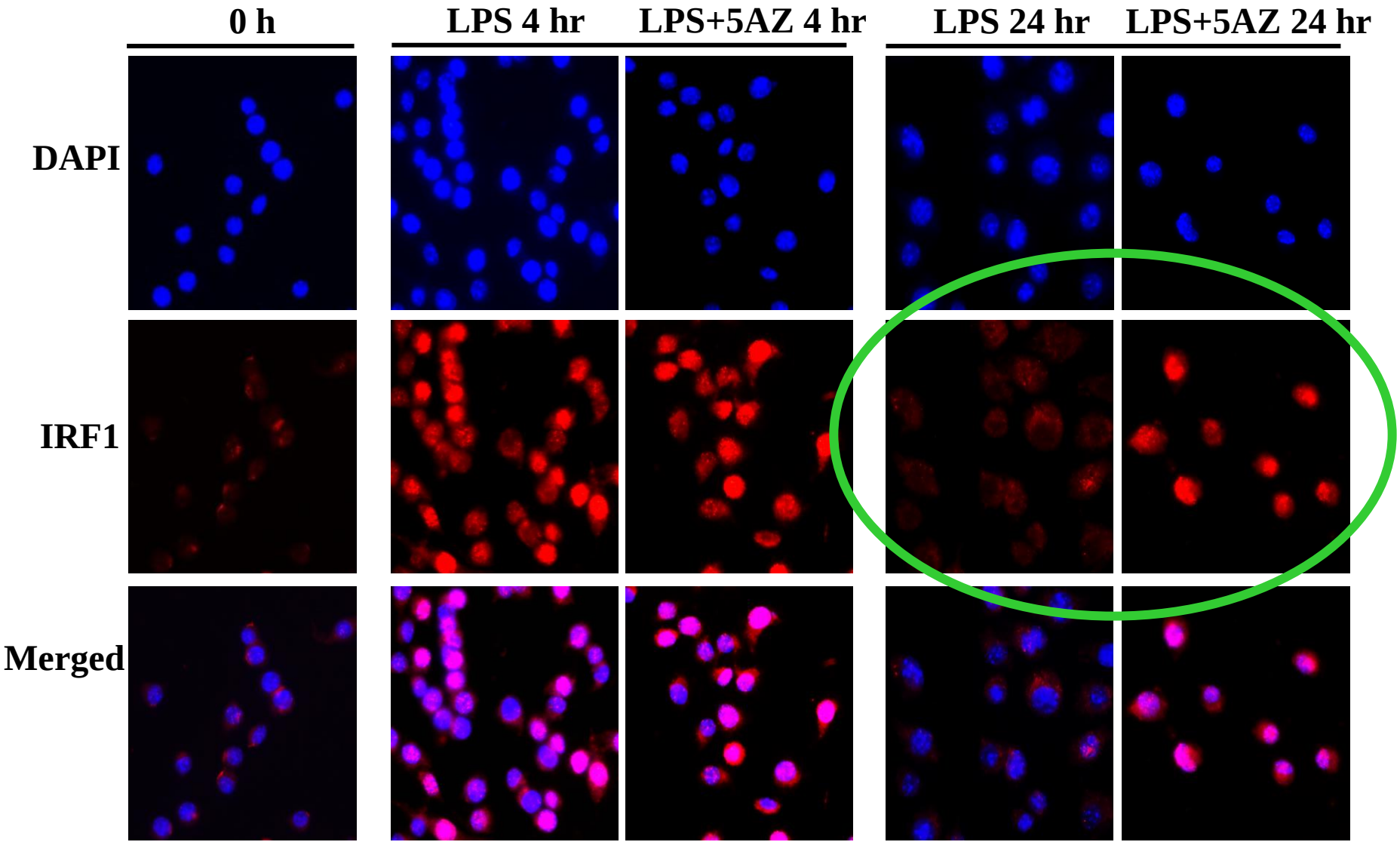
Sci Rep, minor revision

5AZ increases the stability of IRF1 protein

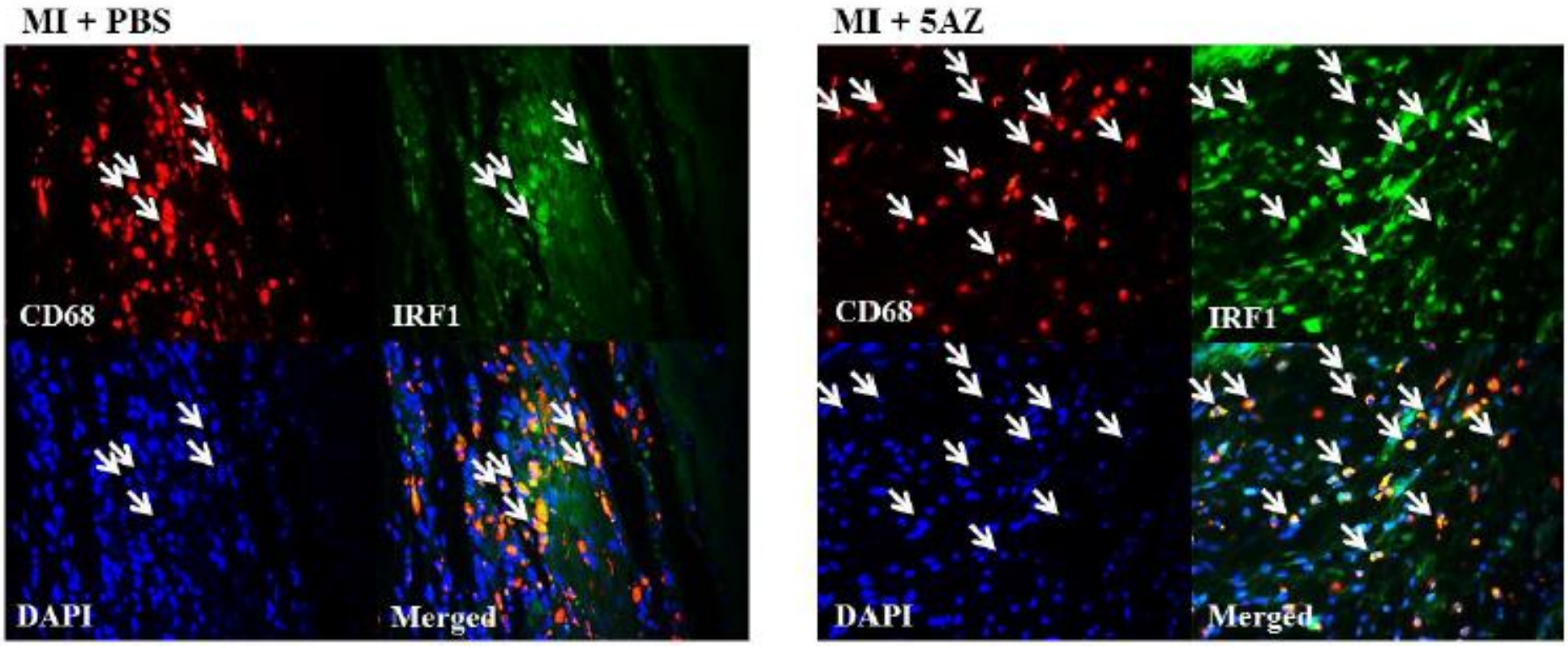


*p<0.05

Localization of IRF-1 in RAW264.7 Cells



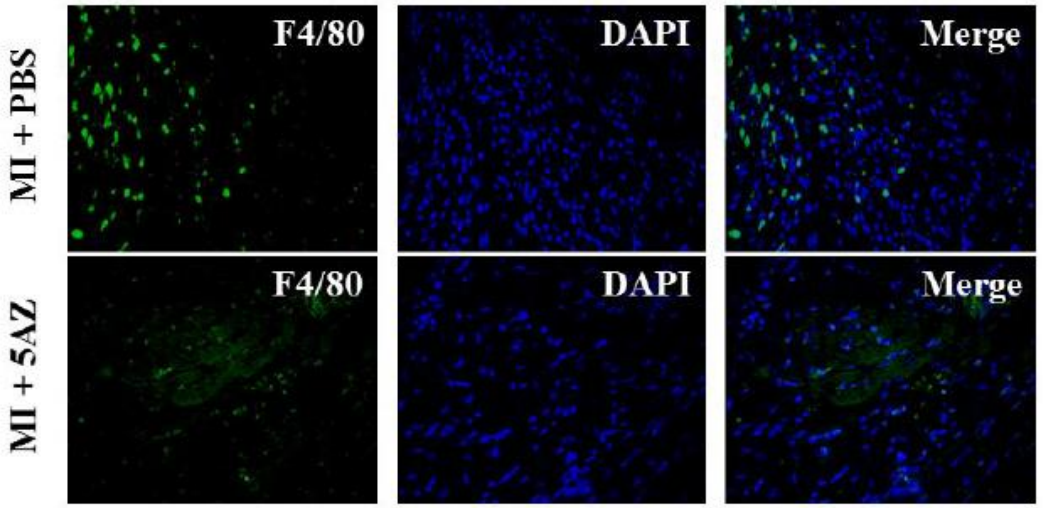
IRF1-expressing macrophages in infarct myocardium

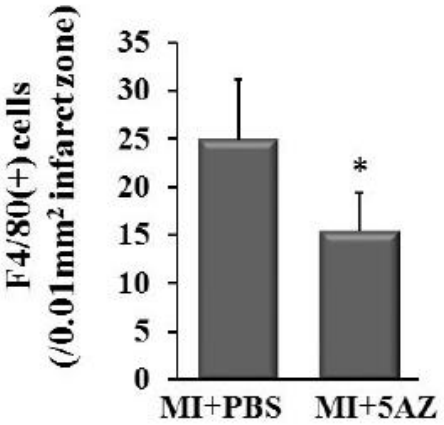


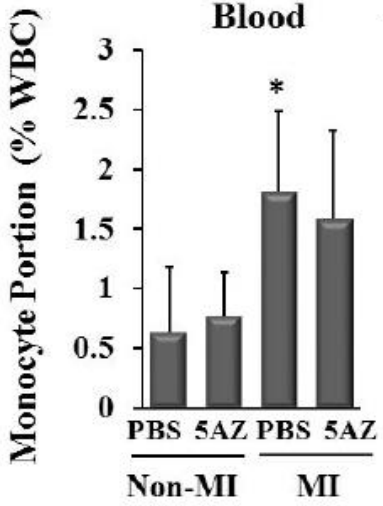
SD rats (weighing 200-230 g)
After 1d of MI, 5AZ (2.5 mg/kg of BW) every other d via ip for 2w

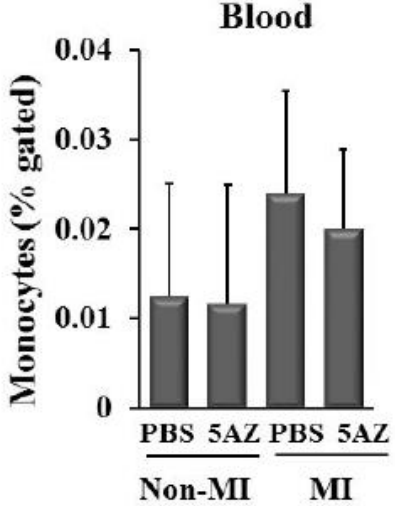
Population of Macrophages

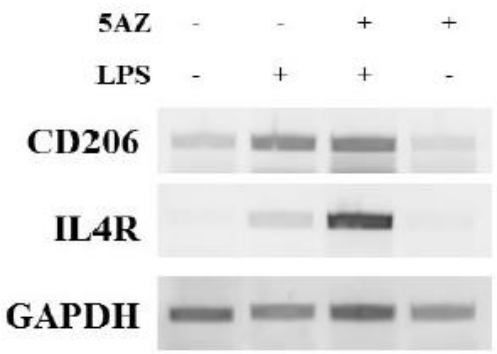
BALB/c mice After 1d of MI, 5AZ (5 mg/kg of bw) every other d via ip for 2w

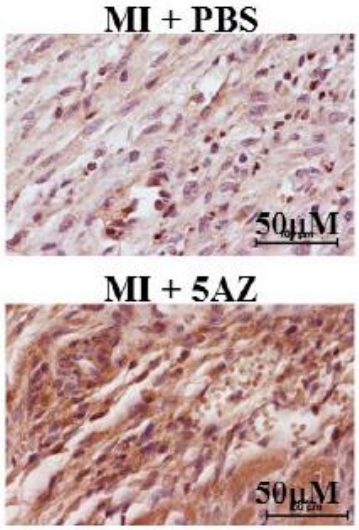




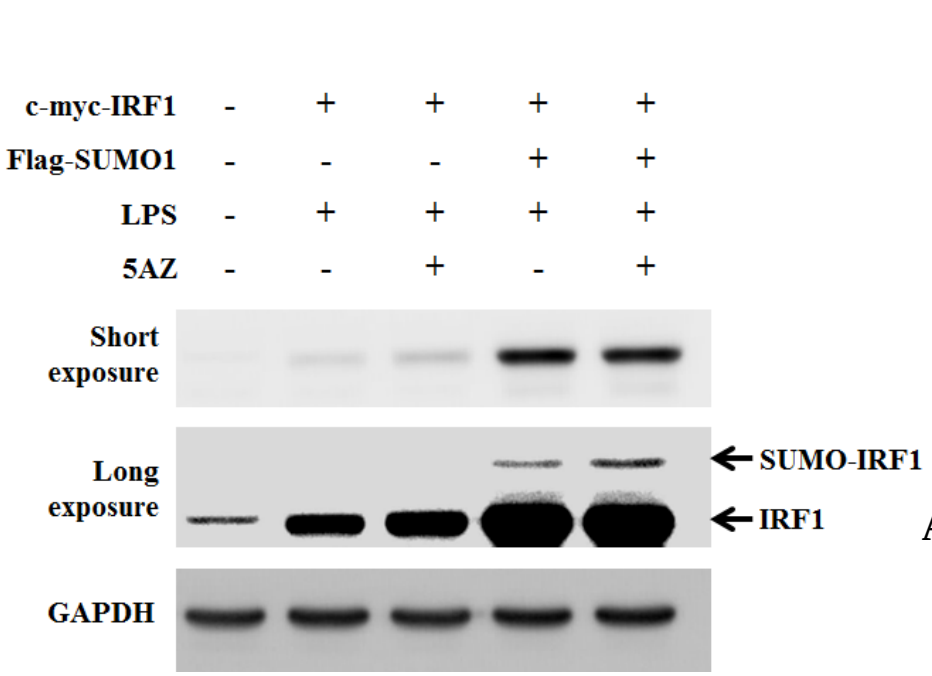


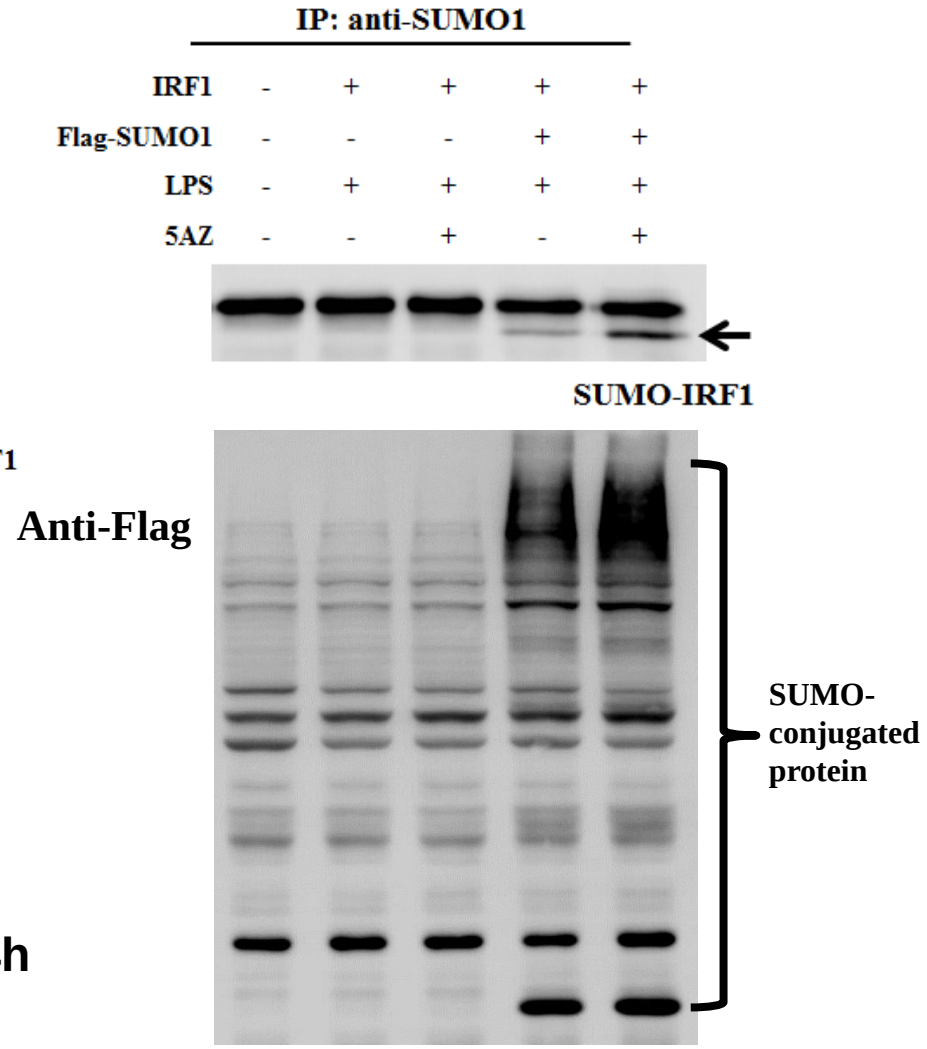






Sumoylation of IRF1 by 5AZ

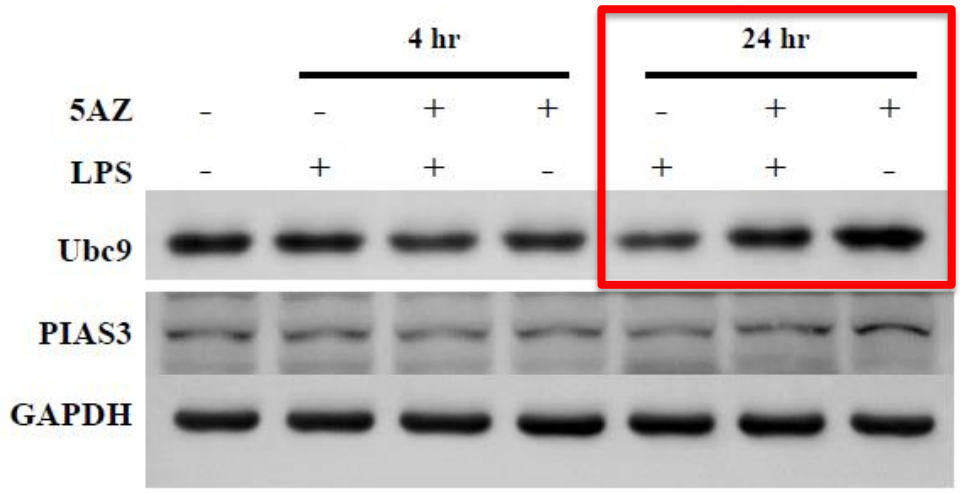


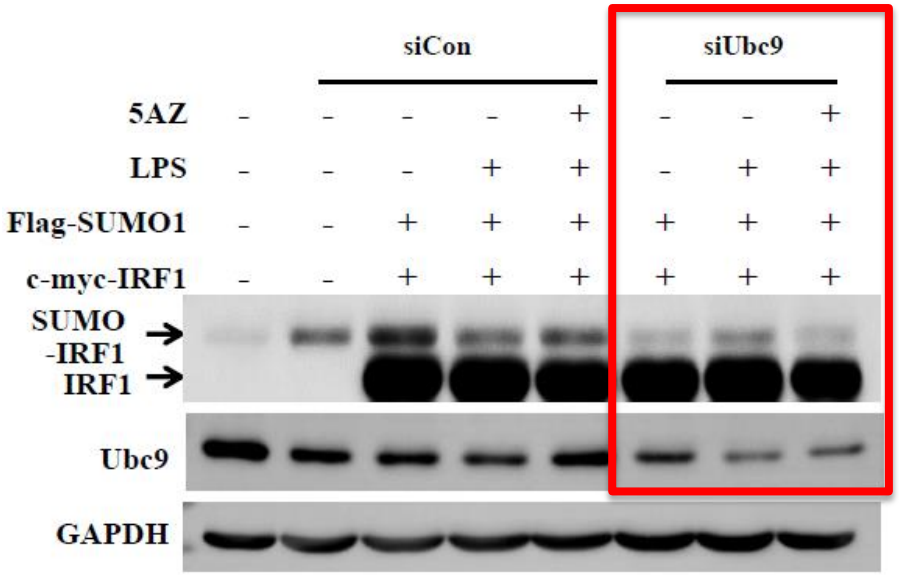


c-myc-IRF1 and flag-SUMO-1 transfected to NIH3T3 cells for 24 h
LPS with or without 5AZ for another 24h

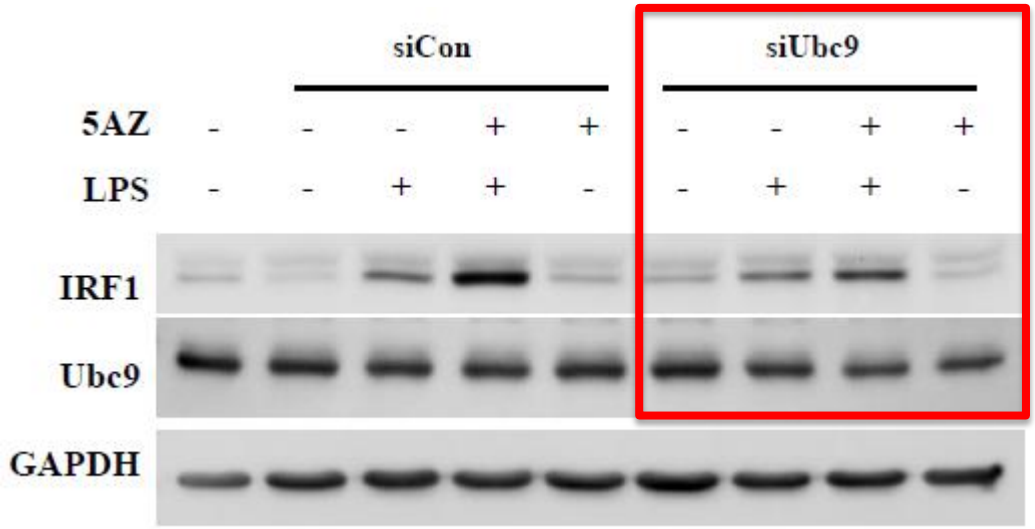
Small **U**biquitin-like **Mo**difier (**SUMO)**

Ubc9 and PIAS3 are SUMO-1 conjugating enzymes essential for sumoylation of IRF1



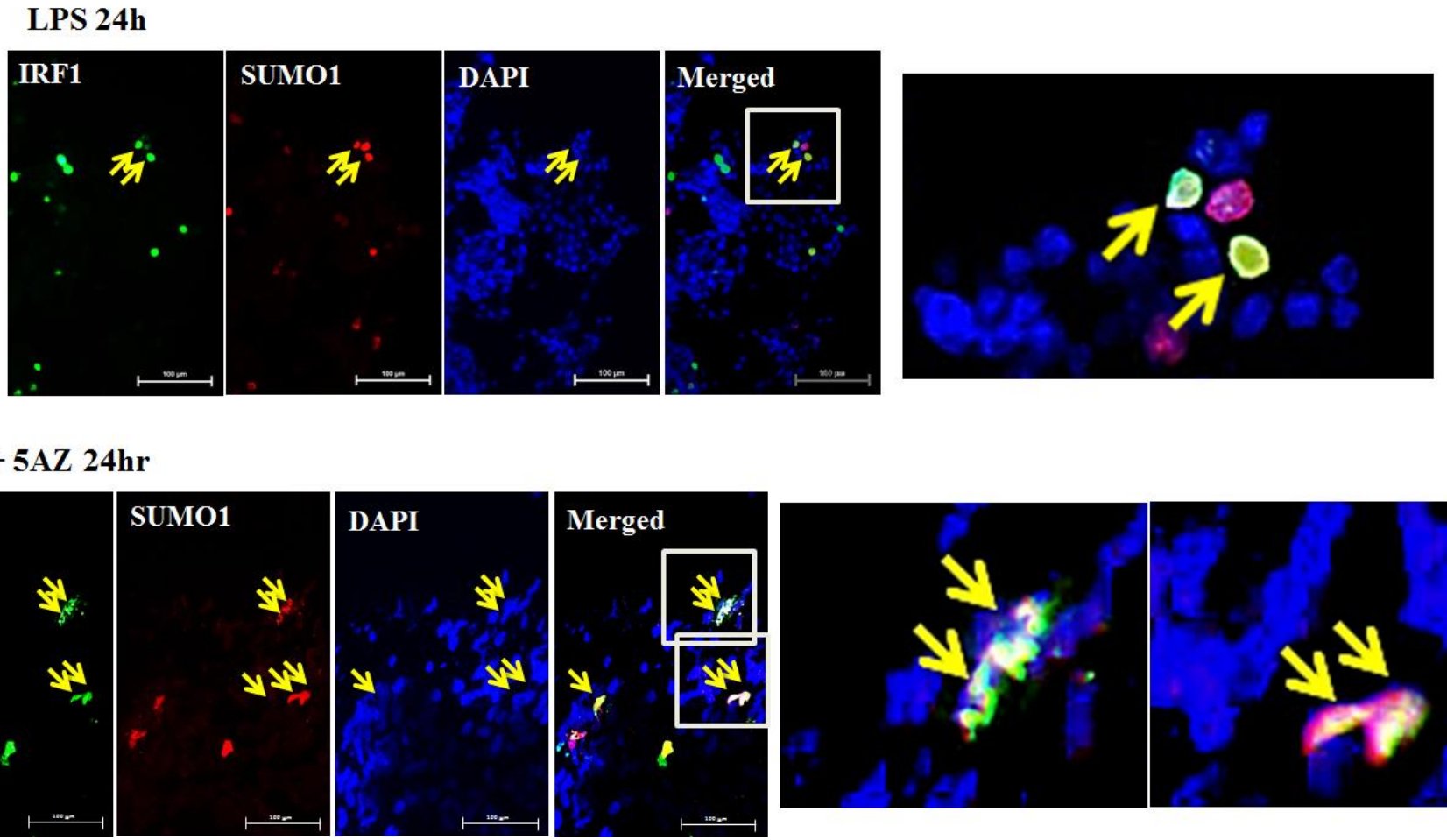


HeLa cells



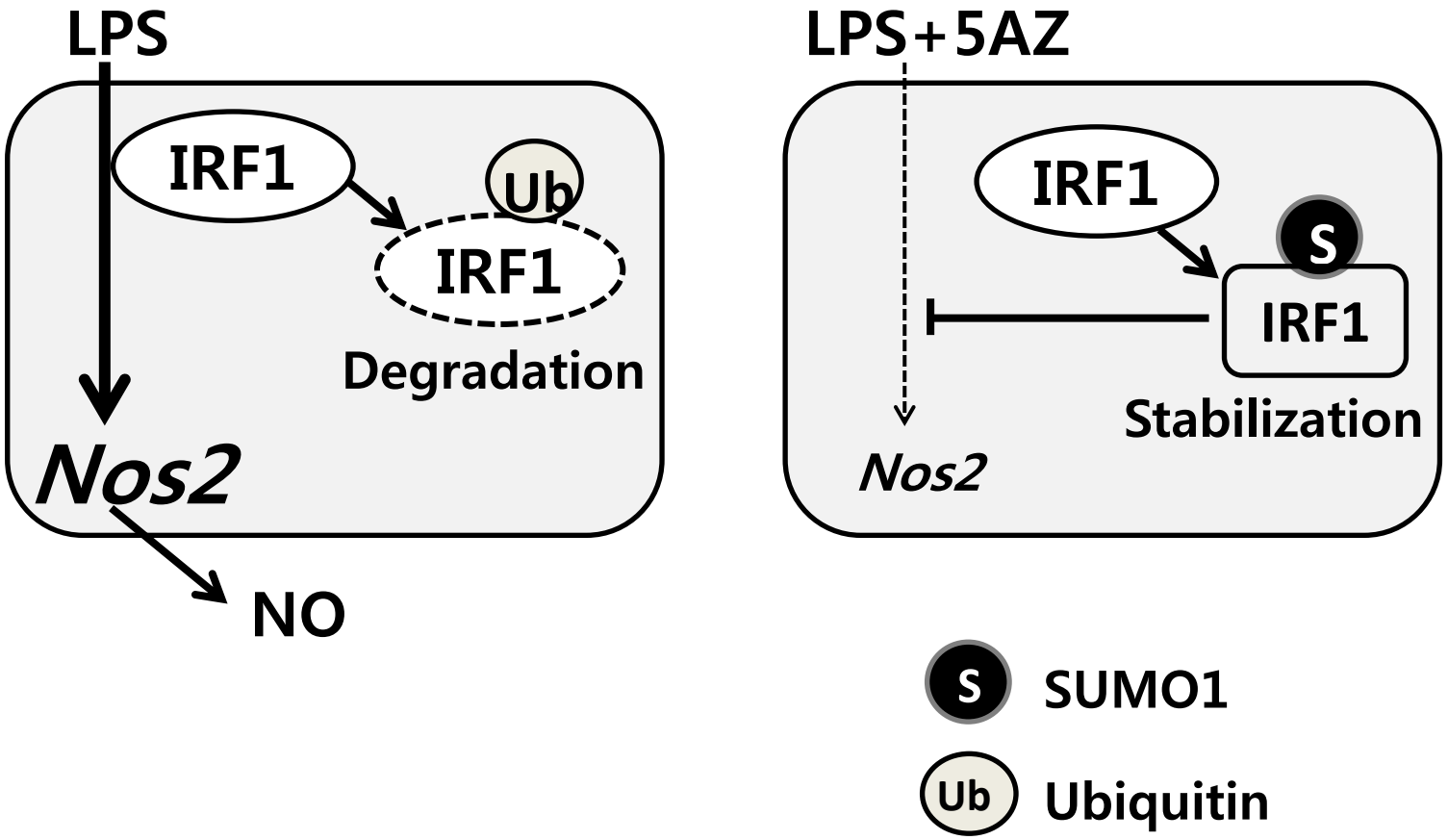
RAW264.7 cells

5AZ potentiates sumoylation of IRF1

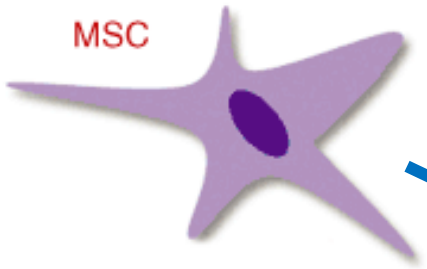


c-myc-IRF1 and flag-SUMO-1 transfected
into 293T cells
LPS or LPS+5AZ for 24 h

Proposed model of IRF1 sumoylation in LPS-stimulated macrophages



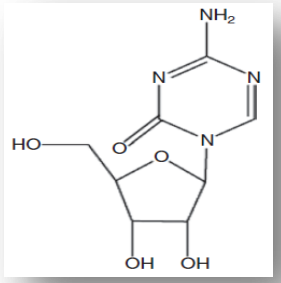
Modulation of Macrophage Polarization



M2 Resolving

M1 Inflammatory

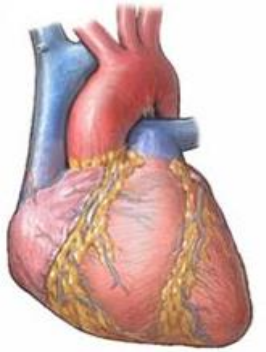
Proinflammatory cytokine



(5-AZ)

Injury

Myocardial infarcts



Improved infarct healing

결론

1. **Macrophage plasticity and polarized activation provides a basis for macrophage-centered diagnostic and therapeutic strategies.**

2. **Modulation of macrophage polarization has emerged as a critical control point of inflammation in cardiovascular diseases.**

OPEN

Gene Therapy (2014) **21**, 353–362

www.nature.com/gt

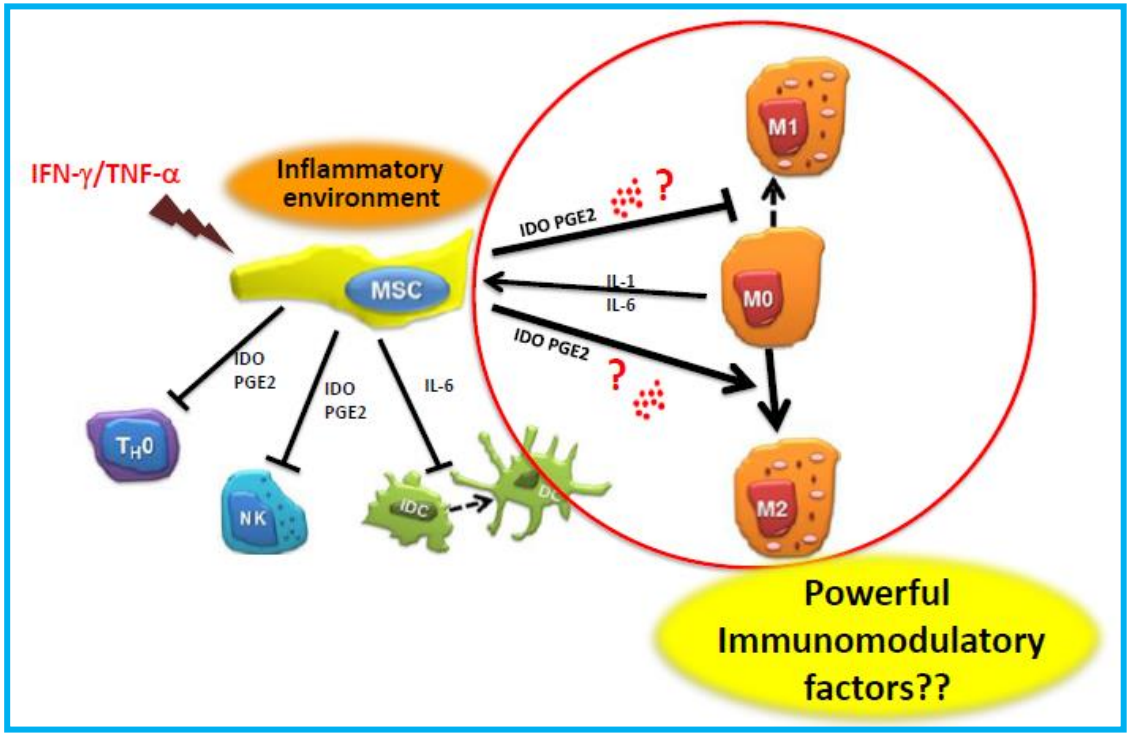
More Powerful Macrophage-specific Promotor

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]

Fizz-1 knock-out mice MI model




감사합니다.