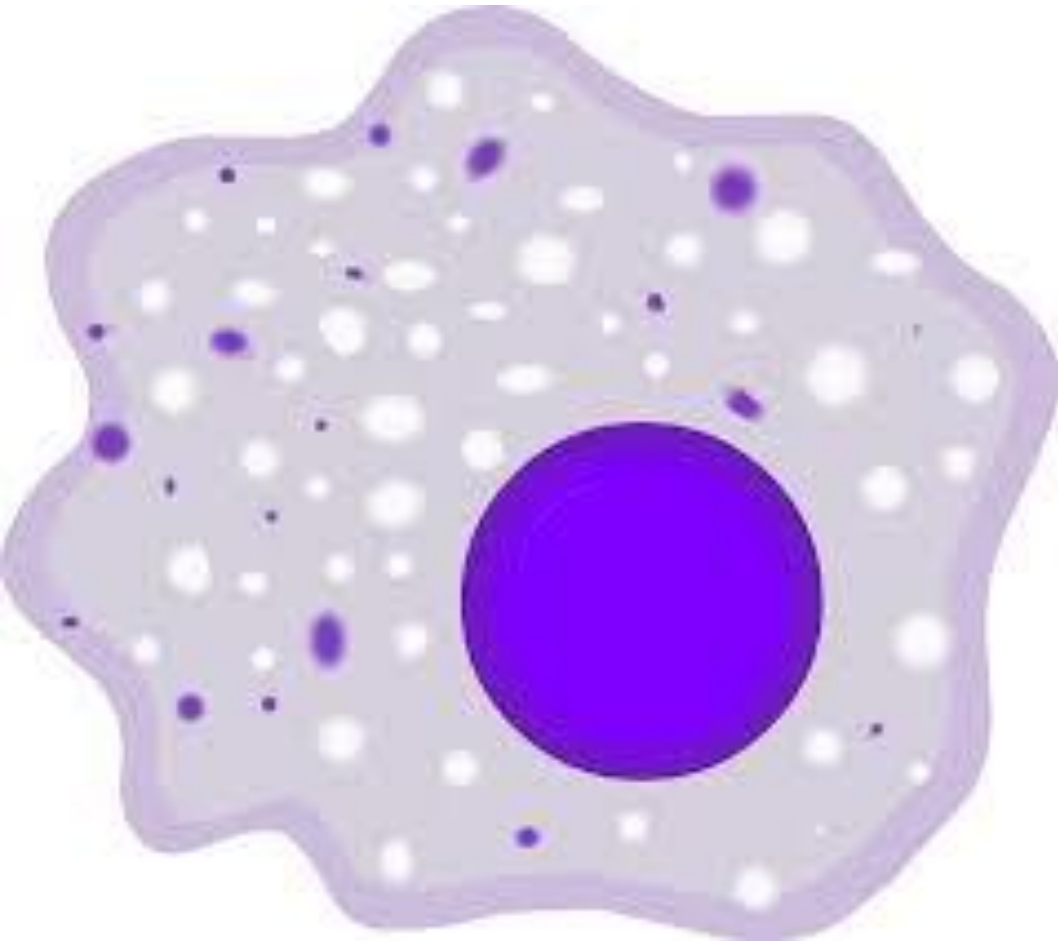
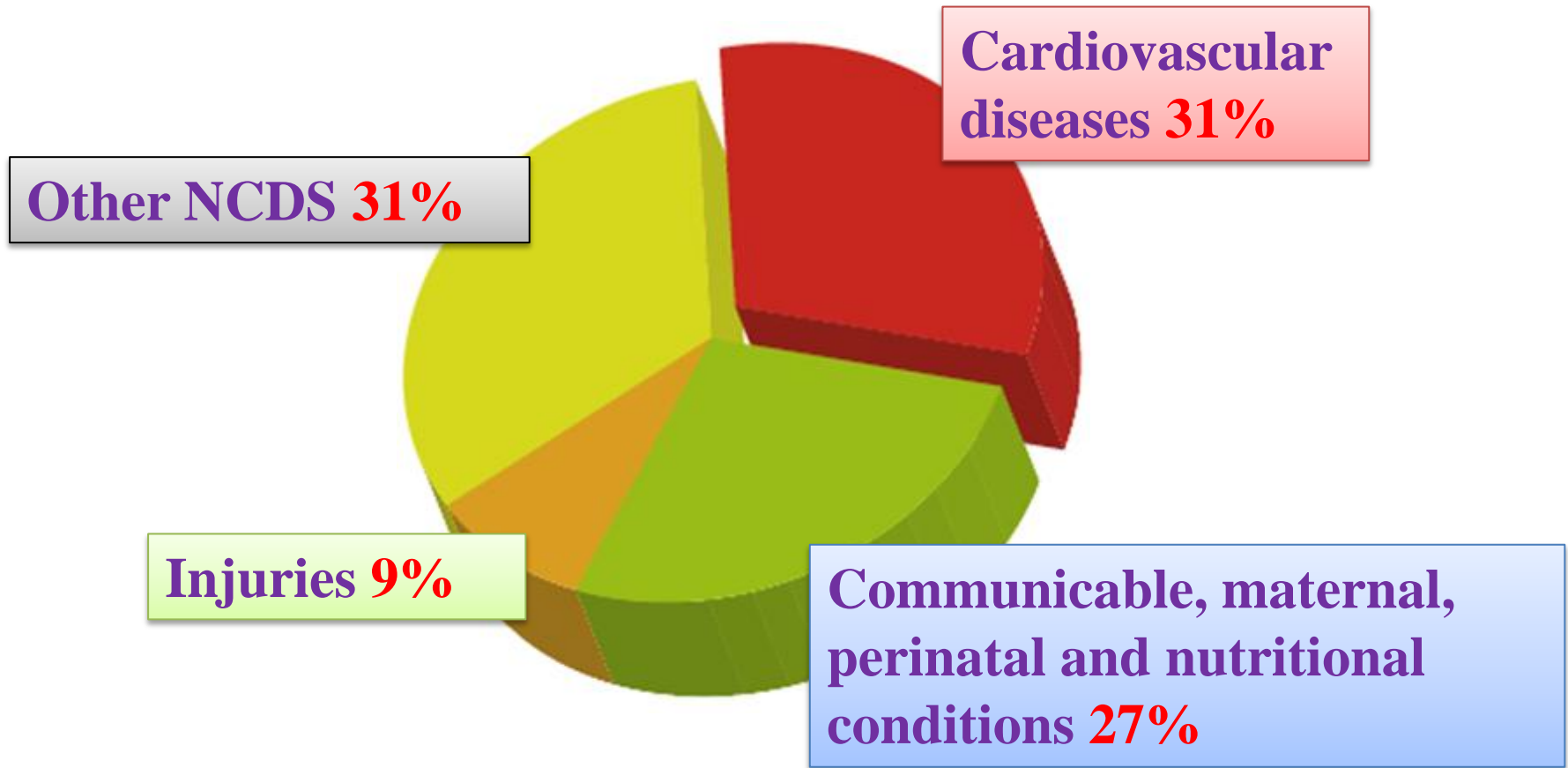


# Myeloid-Specific Deletion of SIRT1 Impairs Obesity Associated Endothelial Dysfunction and Atherosclerosis



*Ping GU, MD PhD*  
*July 11, 2016*  
*Brisbane*

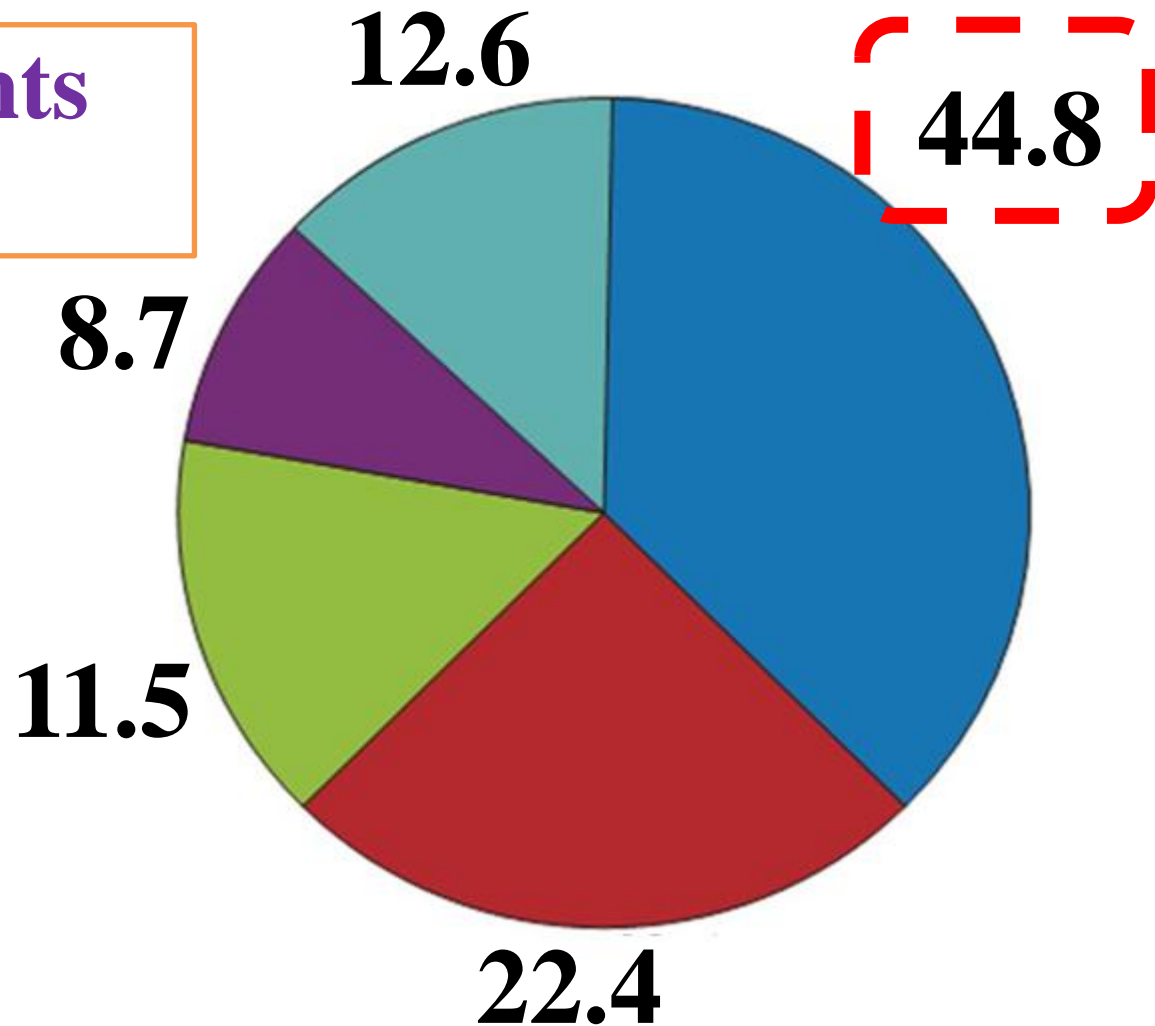
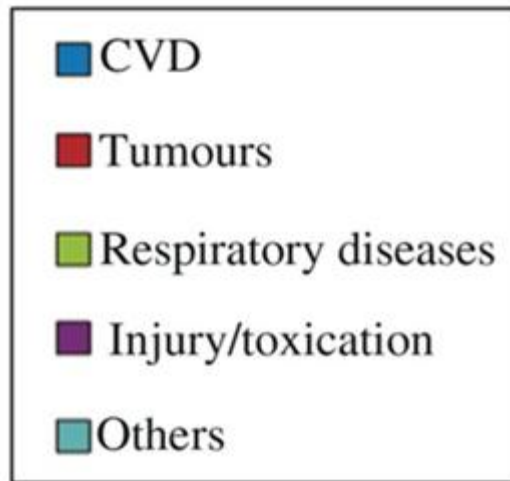
# Distribution of major causes of death



**NCDS:** Noncommunicable diseases

# Major causes of death in Chinese population(%)

230 million patients with CVD

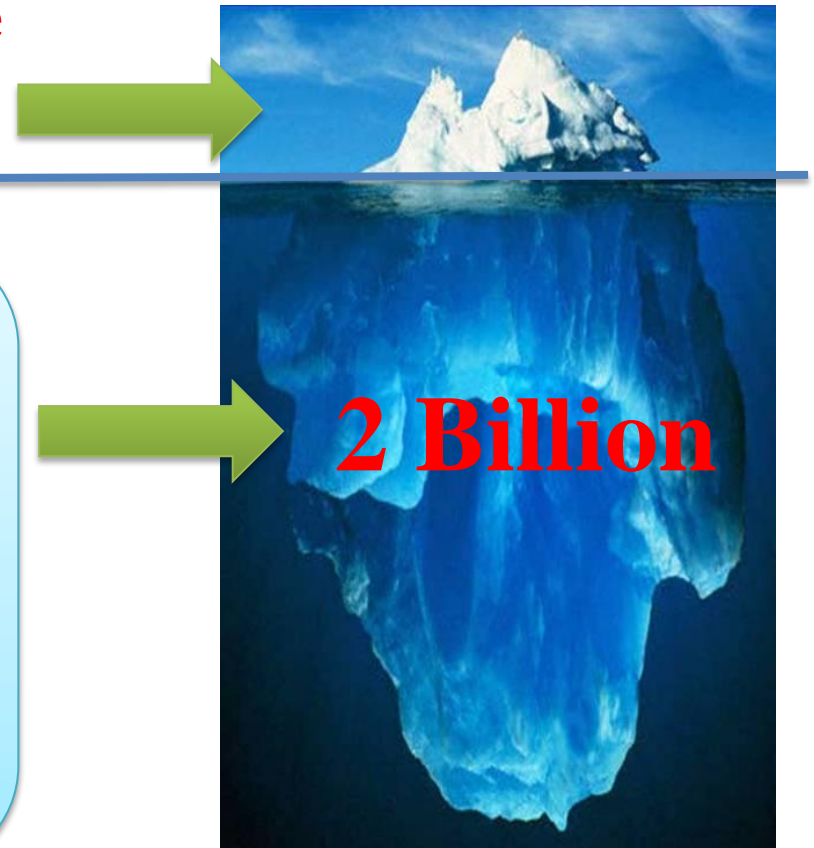


# Global Burden Hidden of Cardiovascular Diseases

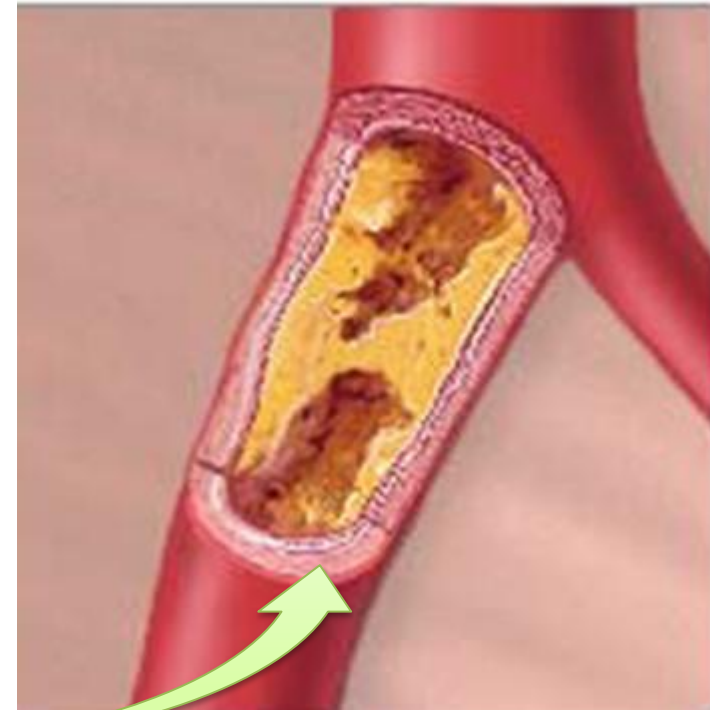
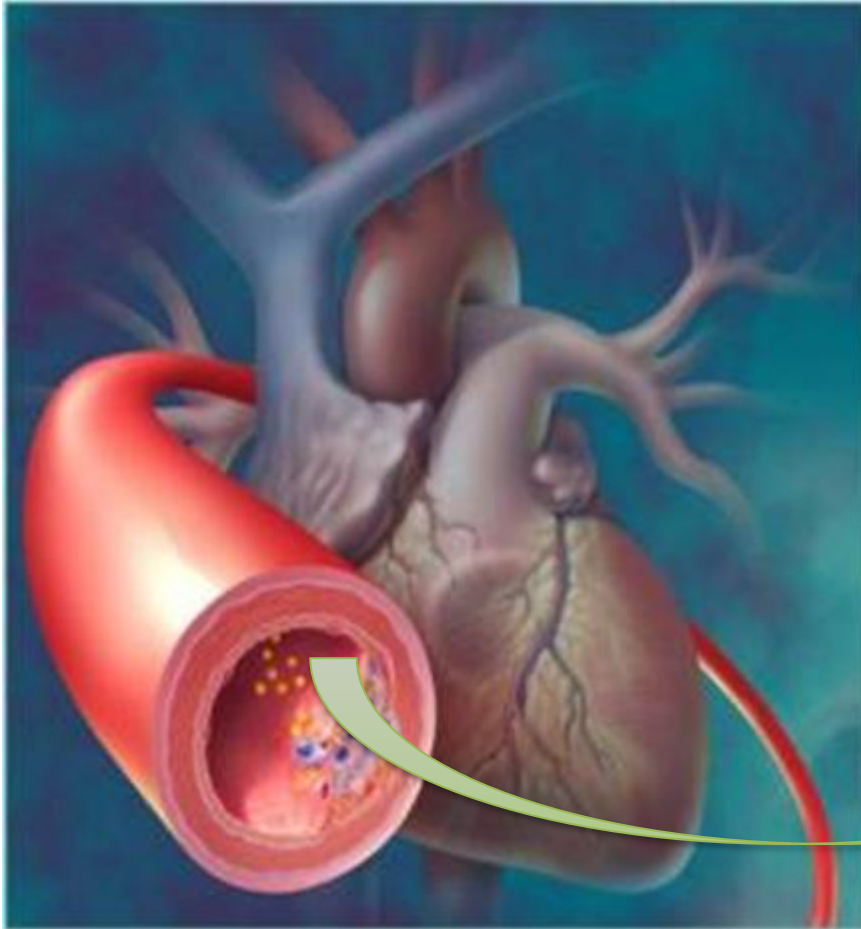
Public health burden hidden and underestimated

Heart attacks and strokes are only tip of the iceberg

- Obesity
- Physical activity
- Unhealthy diet
- Tobacco use
- Raised blood pressure
- Raised blood sugar
- Raised blood lipids

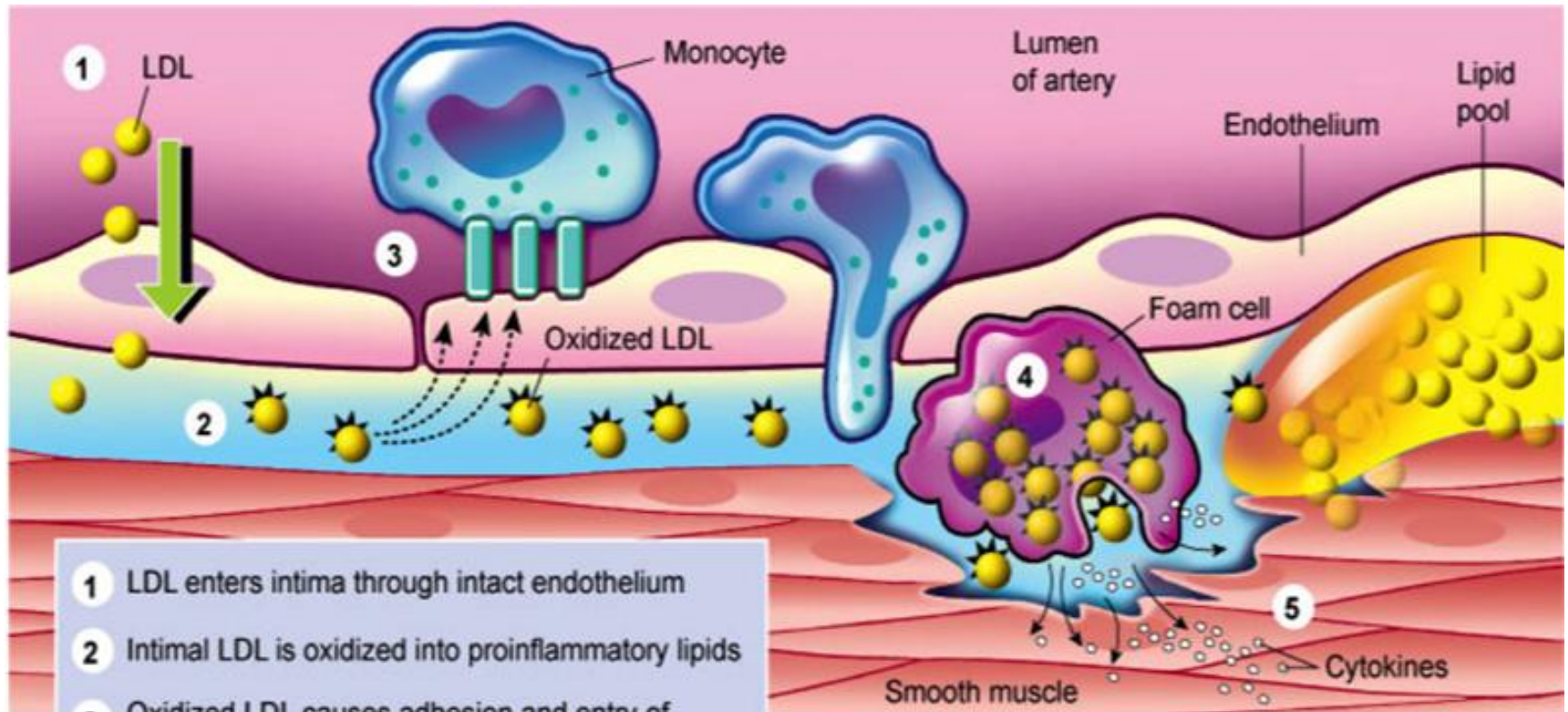


# Atherosclerosis and CVDs

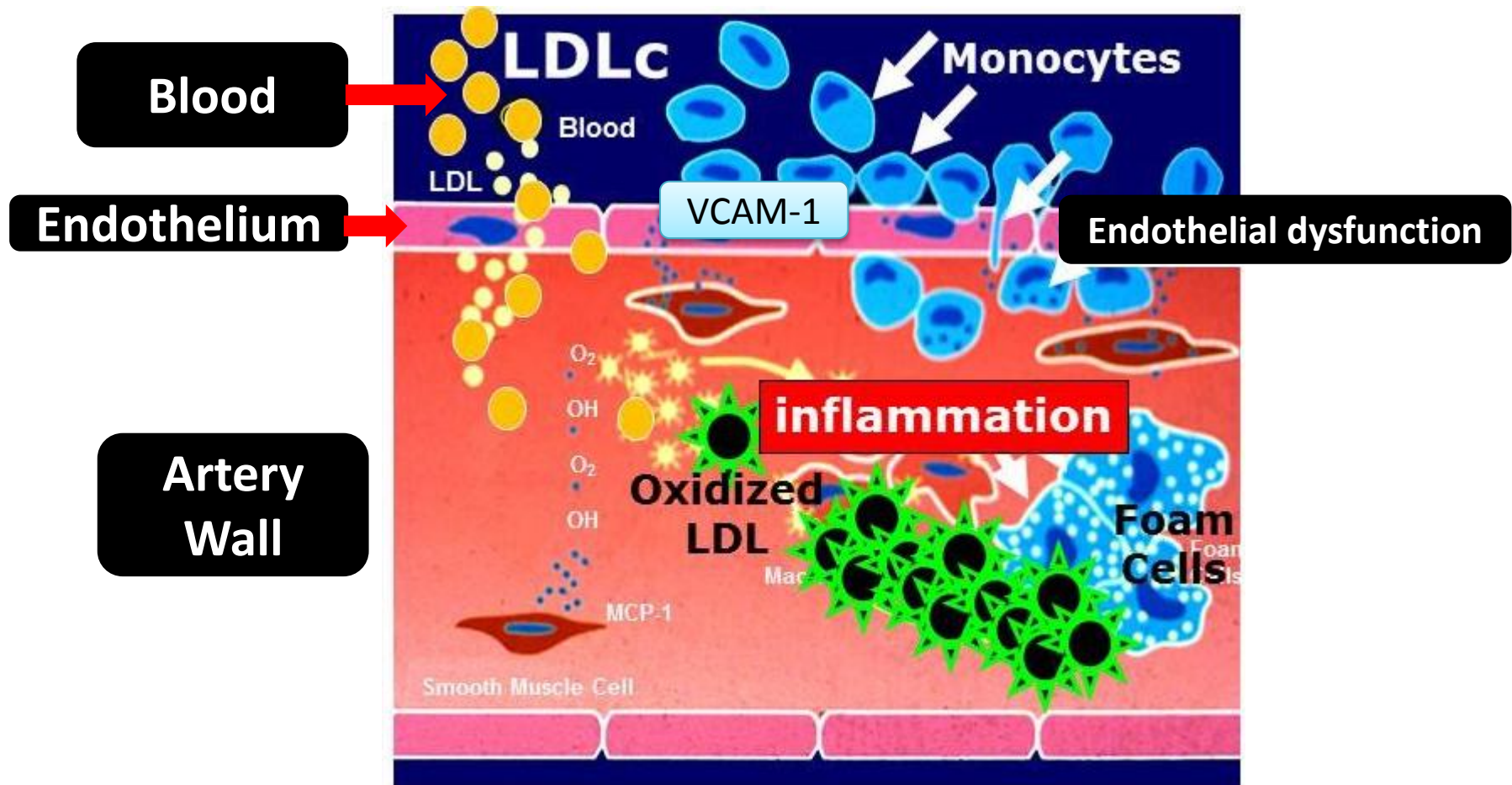


**Atherosclerosis:** the major cause of cardiovascular disease

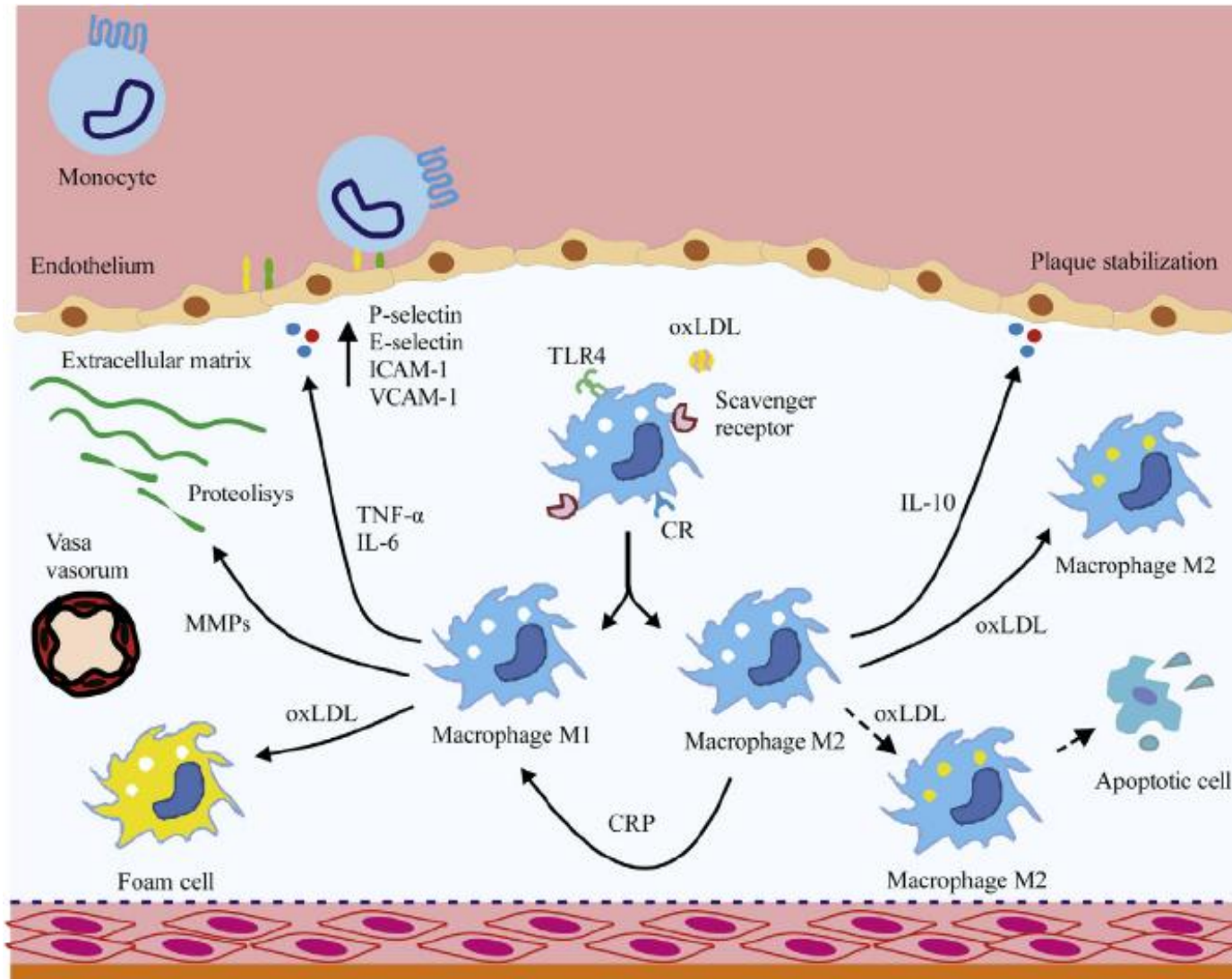
# Atherosclerosis pathophysiology



# A Healthy Endothelium is the First Defense against atherosclerosis



# Macrophages play a central role in atherogenesis

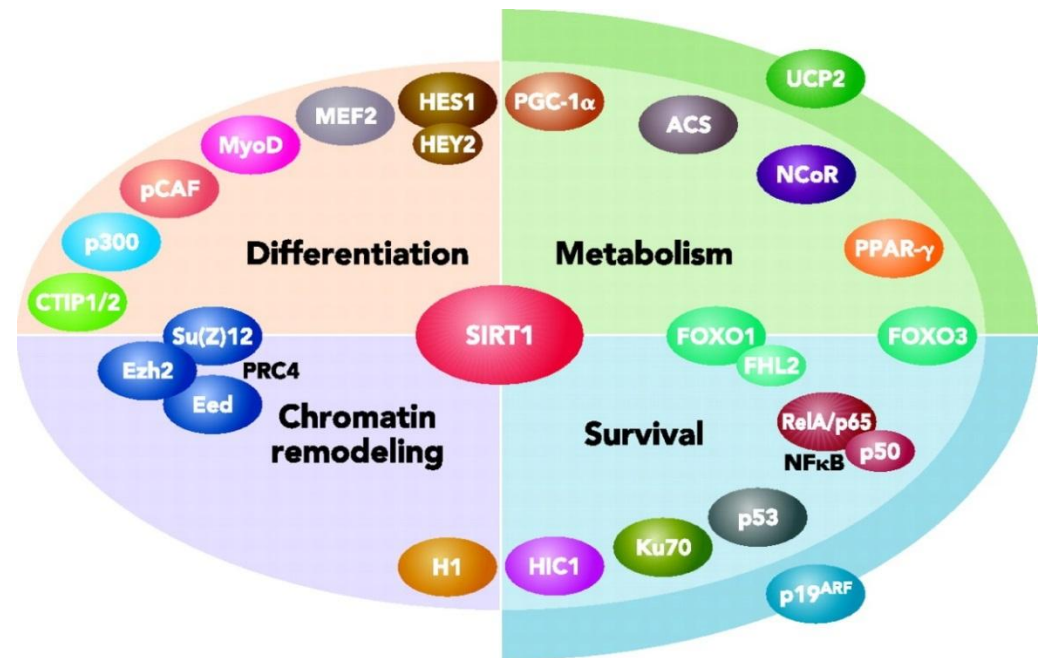
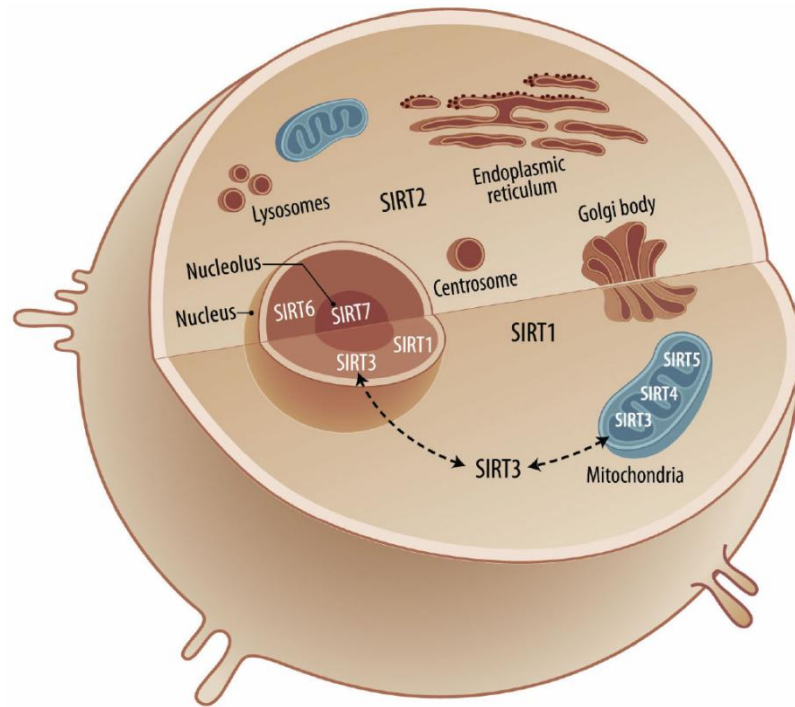




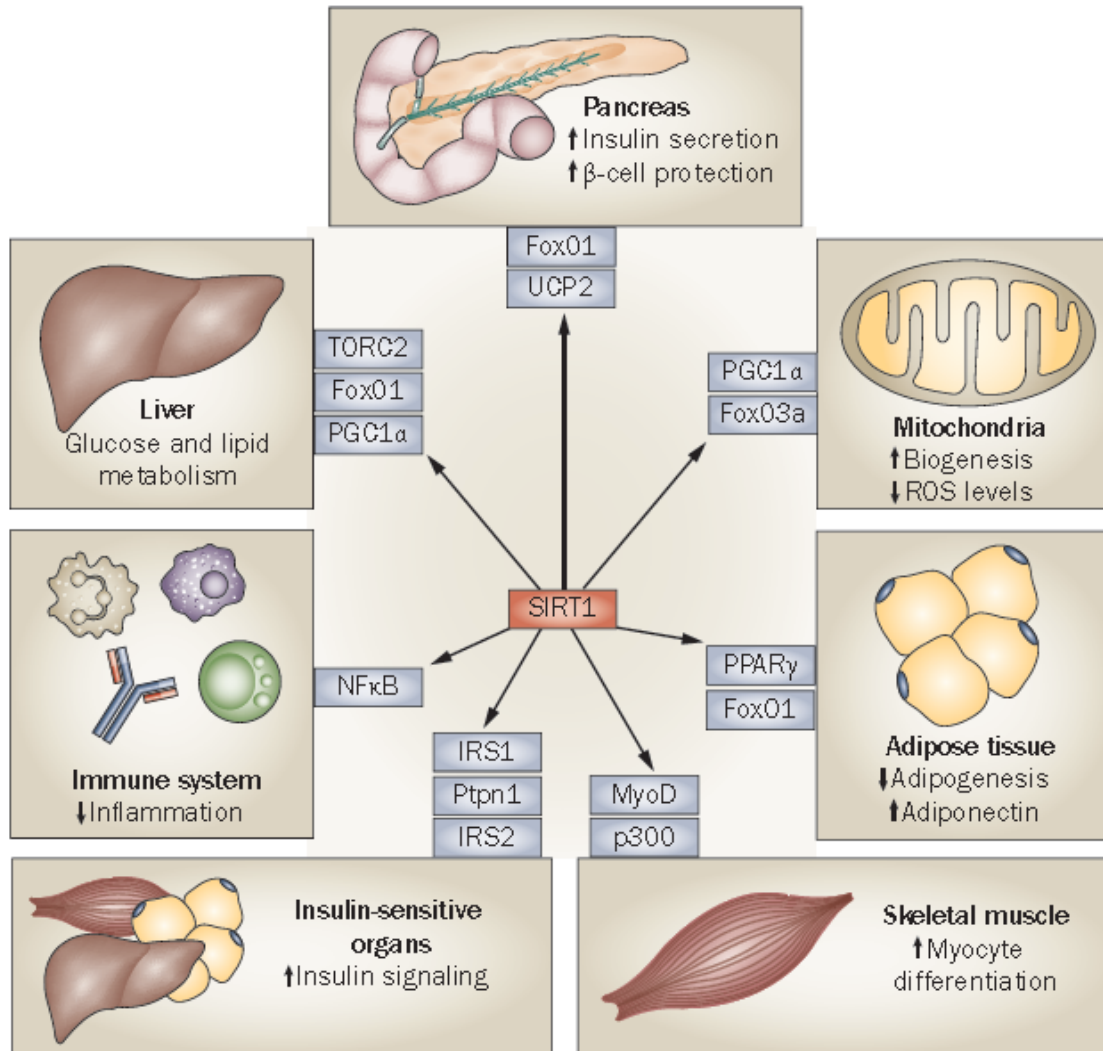
# SIRT1: A novel therapeutic target for aging associated diseases

## Sirtuin Protein Family

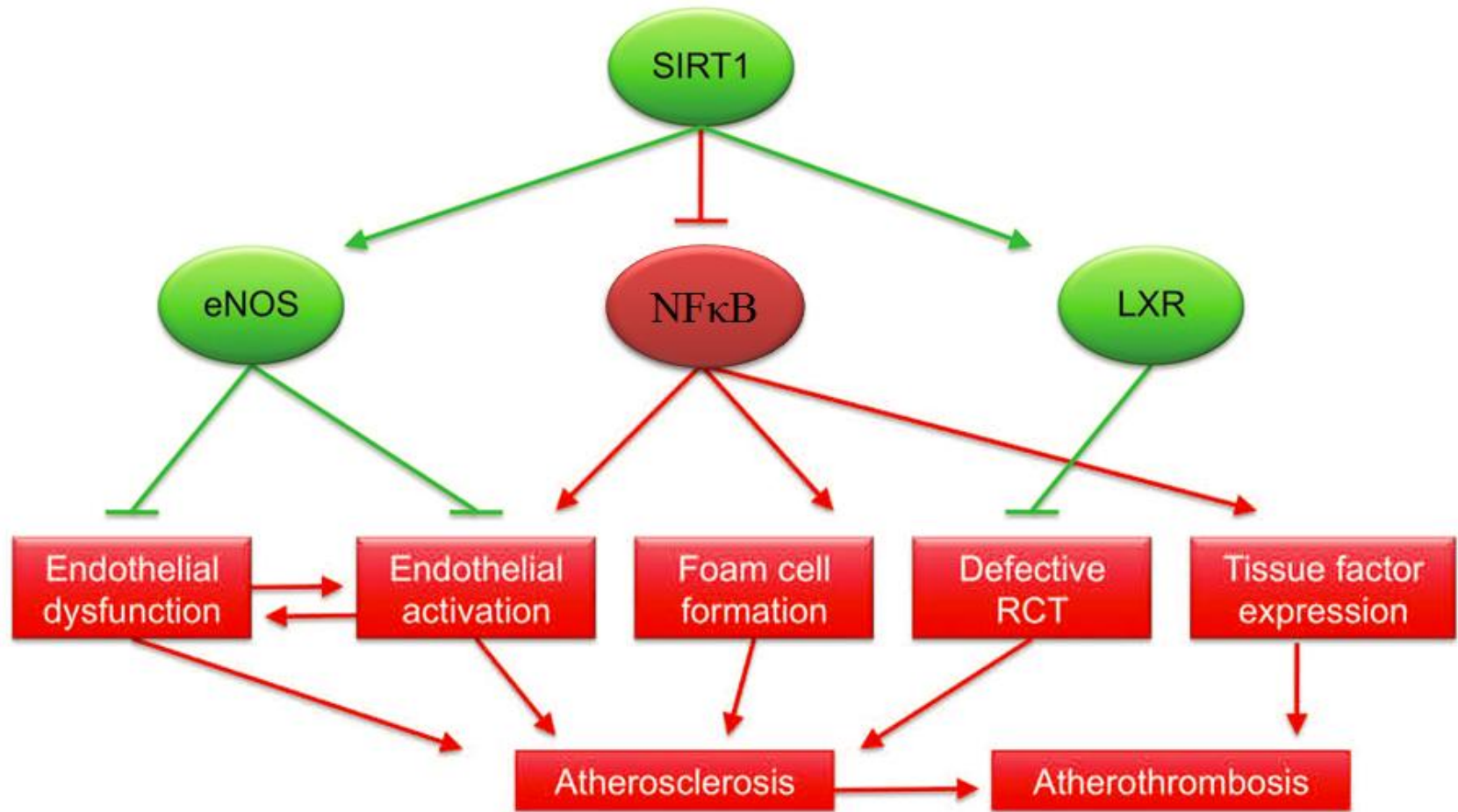
## Effect of SIRT1



# SIRT1 controls metabolism by distinct mechanisms in different tissues

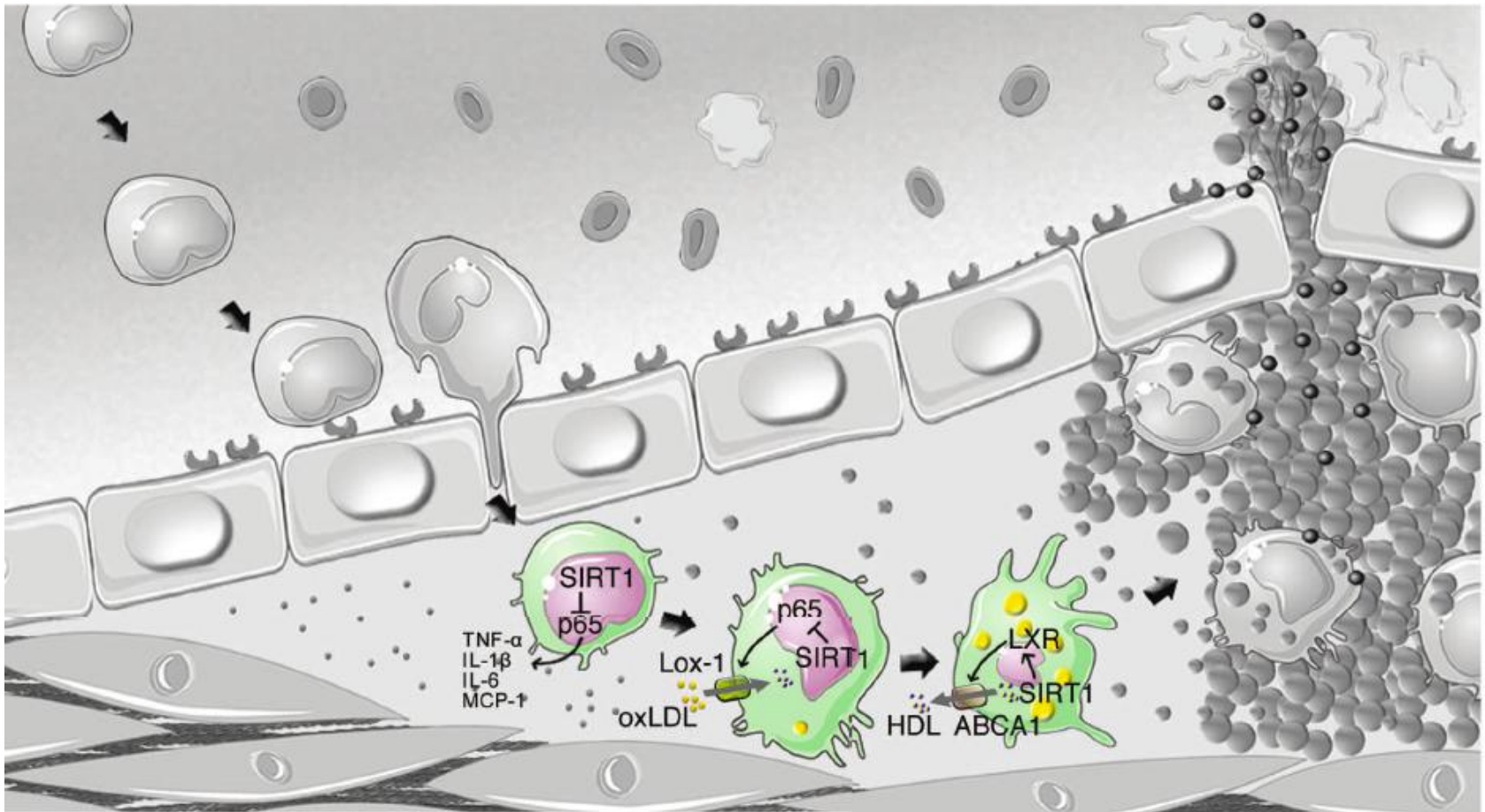


# Beneficial effects of SIRT1 on atherosclerosis and thrombosis



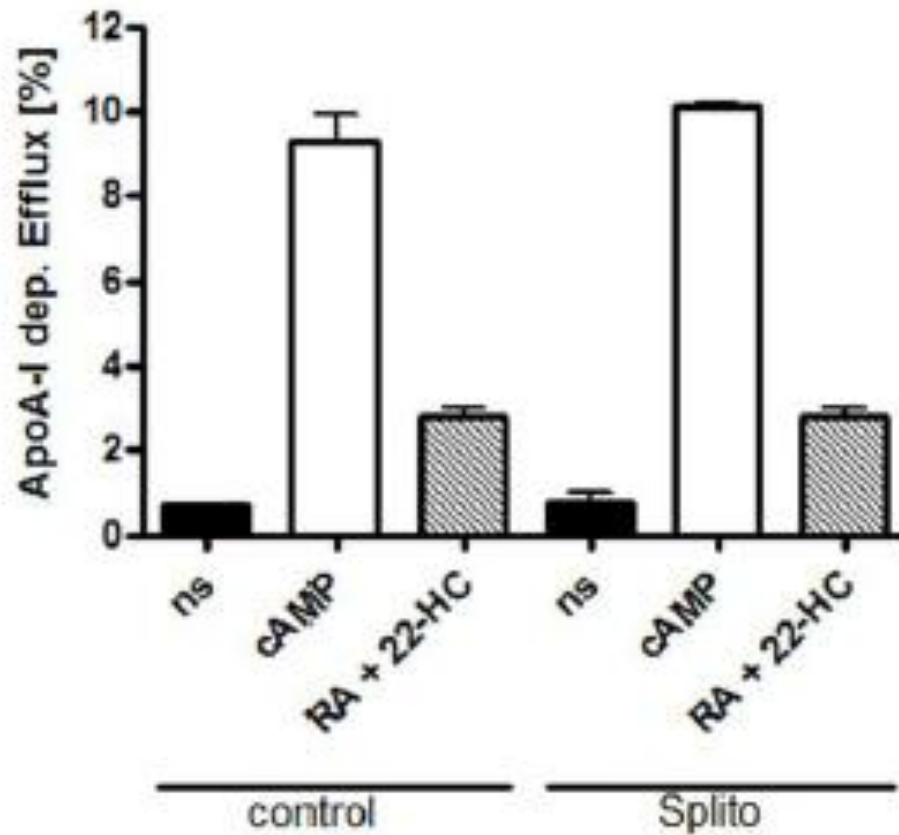
# SIRT1 in Macrophage

## Cholesterol Uptake and Foam Cell Formation

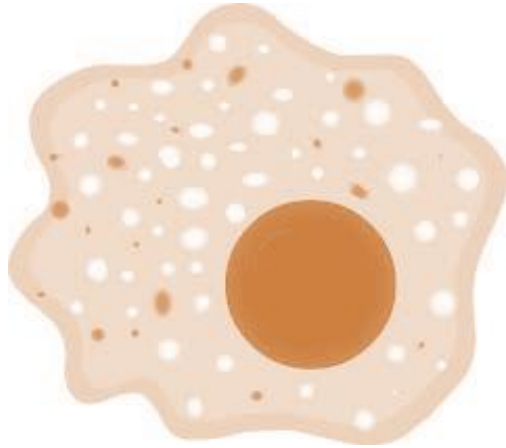


# SIRT1 does not affect cholesterol efflux in macrophages

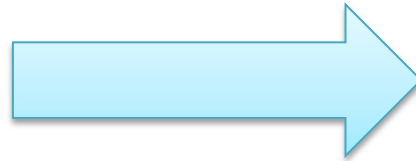
---



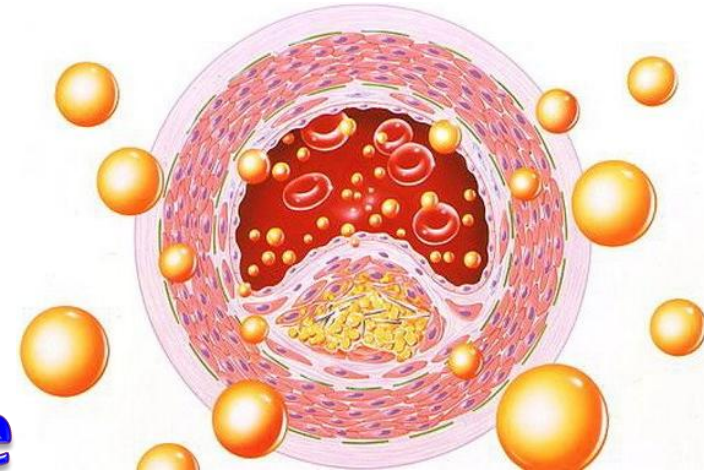
# Macrophage



## SIRT1



# Atherosclerosis

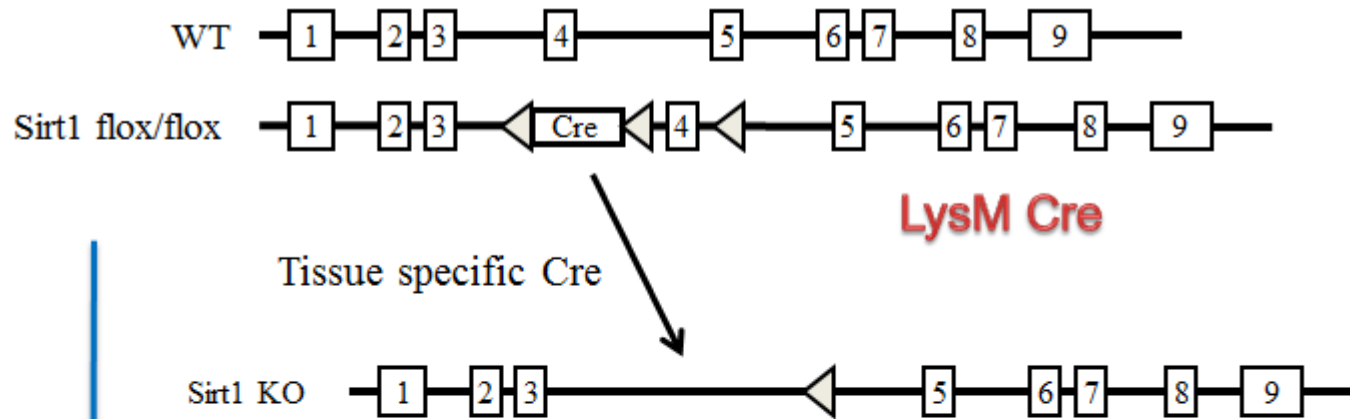


## Other possible Mechanism?



Via modulating endothelial function??  
Via modulating macrophage polarization???

# Generation of macrophage specific Sirt1 KO mice



WT MKO

**Q1. whether deletion of SIRT1 in  
macrophage affects endothelial  
function ?**

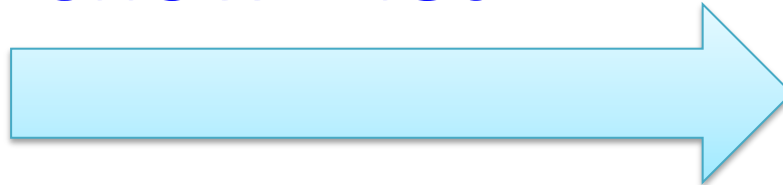


# Methods

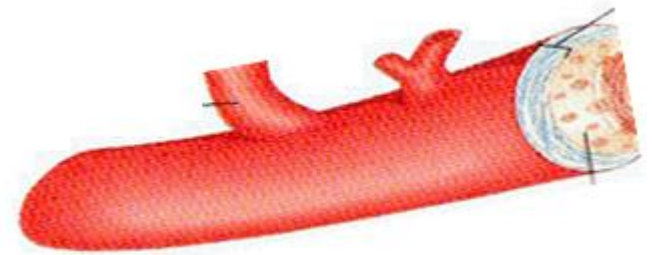


**MKO**

**High Fat /Standard  
Chow Diet**



**16 weeks**



**Aortic Artery**

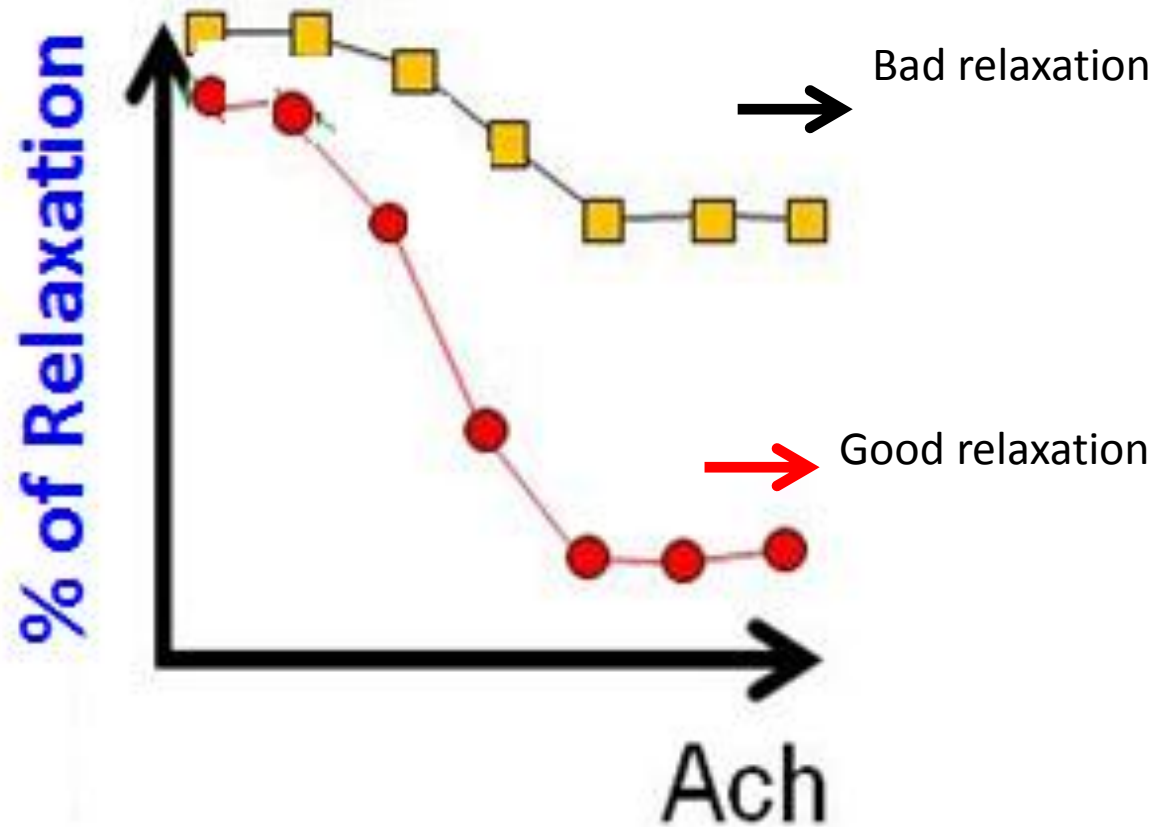


**WT**

# Wire myograph

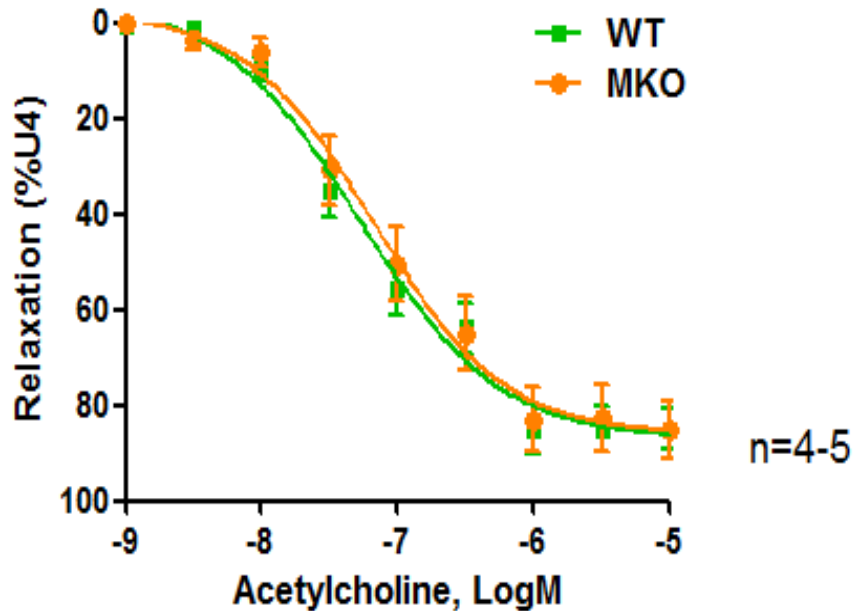


Wire myograph

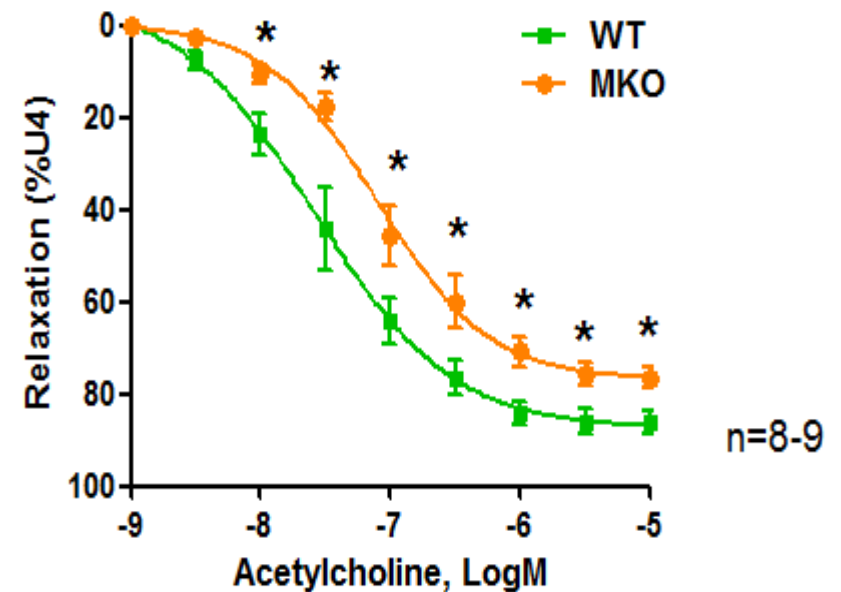


Compared with aorta from wild type mice, the relaxation of aorta from knock out mice was significantly reduced in obesity.

Lean

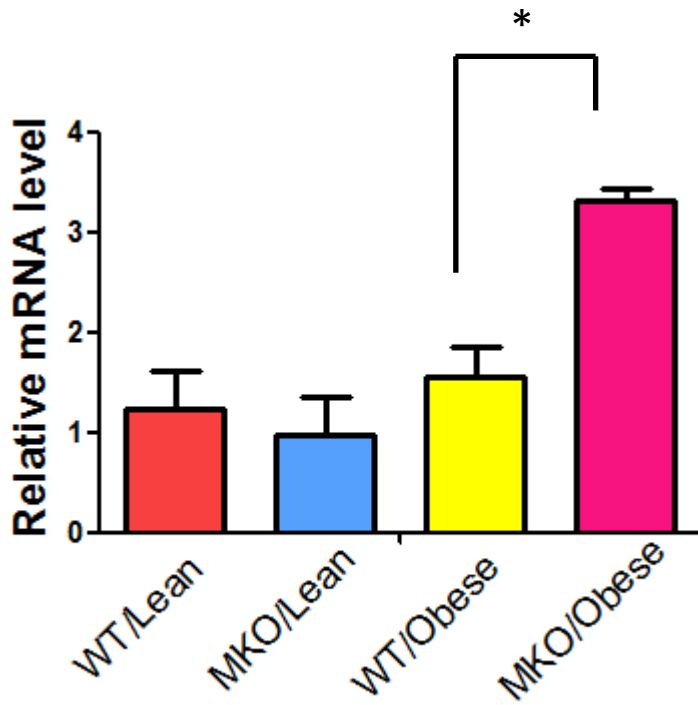


Obesity

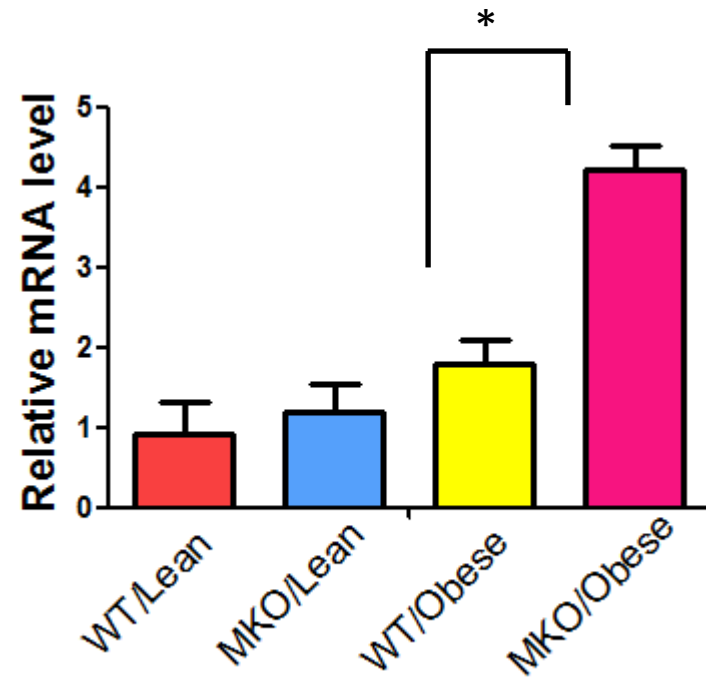


Compared with aorta from wild type mice, The mRNA levels of E-Selectin and ICAM were increased from knock out mice.

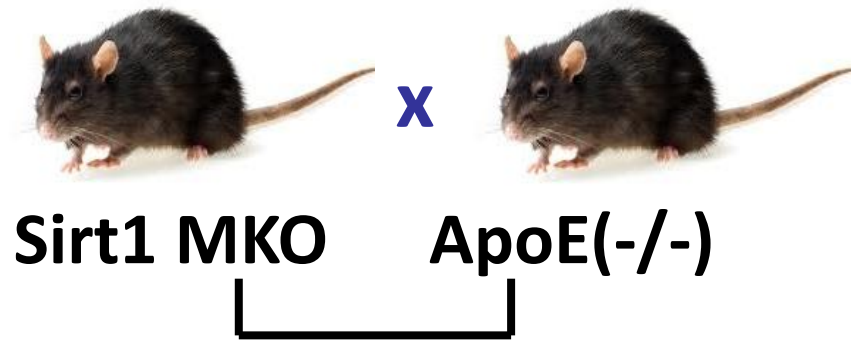
### E-selectin



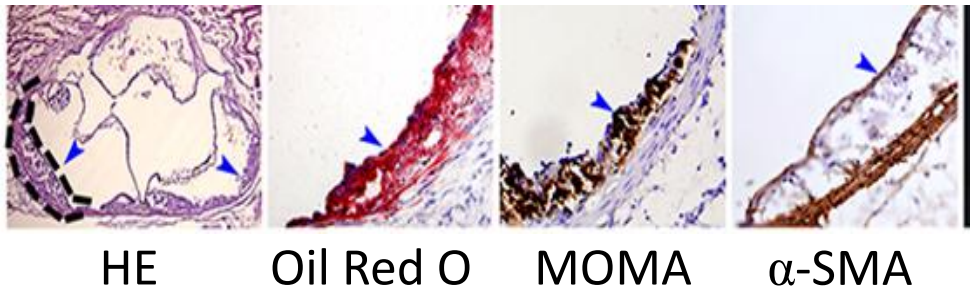
### ICAM-1



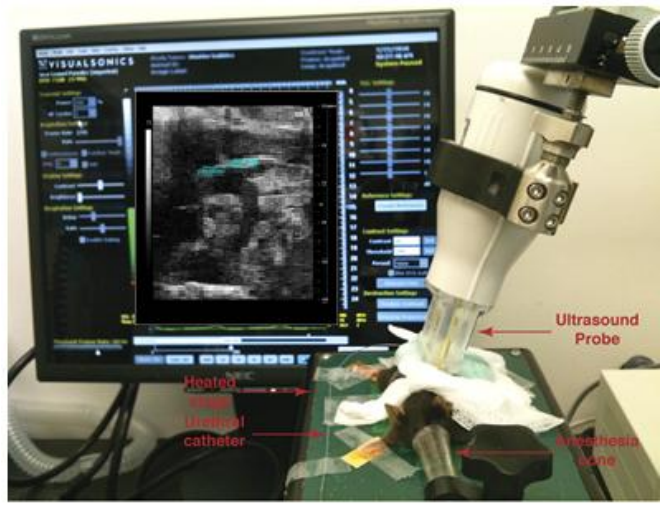
**Q2. whether deletion of SIRT1 in macrophage affects atherosclerosis?**



In Vitro

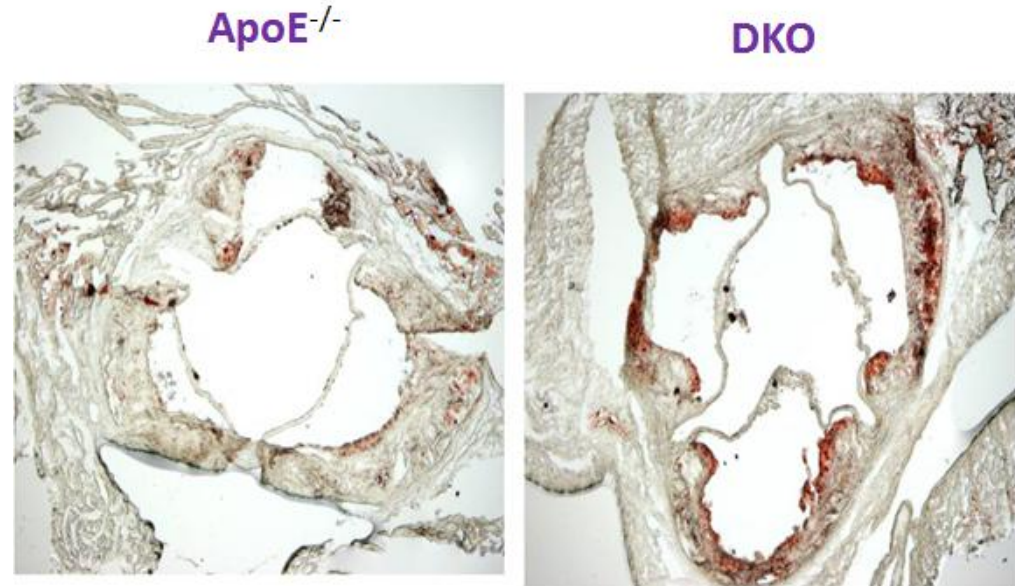
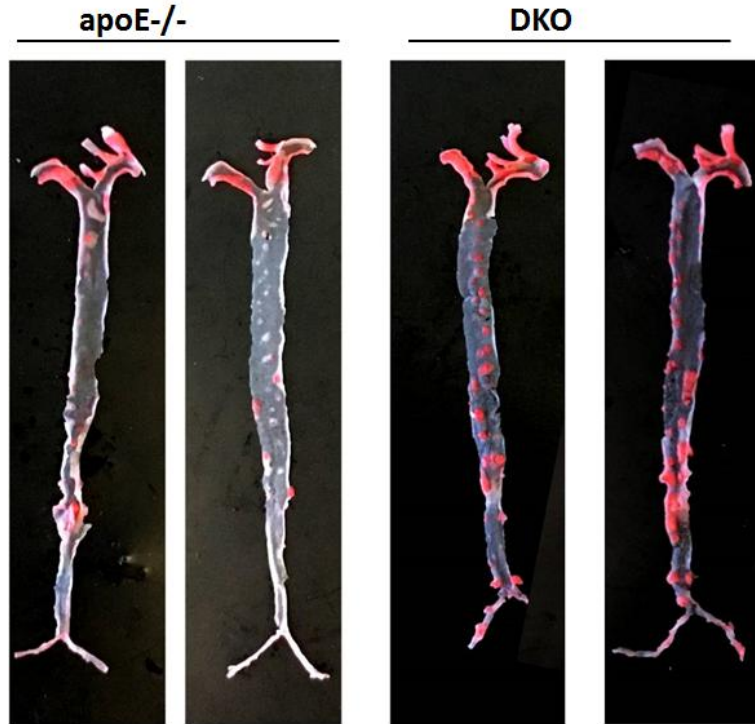


In Vivo



Ultrasound

# Deletion of SIRT1 in macrophage are more susceptible for high fat high cholesterol induced atherogenesis in apoE deficient mice



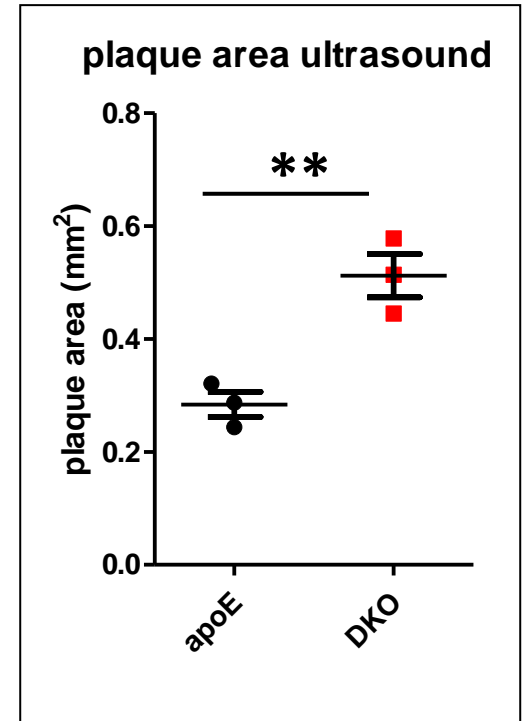
Oil Red O

# DKO mice showed more severe plaque by ultrasound imaging in aortic arch region

ApoE<sup>-/-</sup>



DKO



# Ultrasound

\*\*p<0.01, N=3.



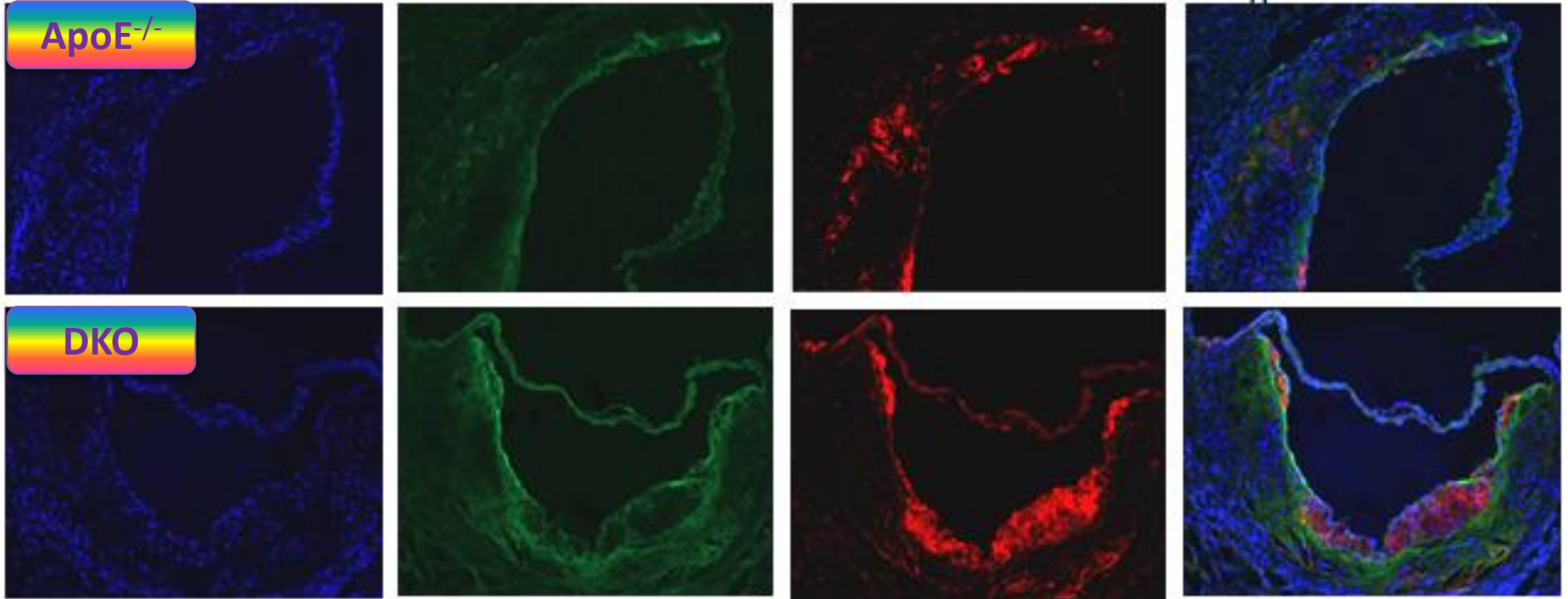
**Deletion of SIRT1 in macrophage showed stronger signals for MOMA-2 and  $\alpha$ -SMA**

DAPI

$\alpha$ -SMA

MOMA-2

merge



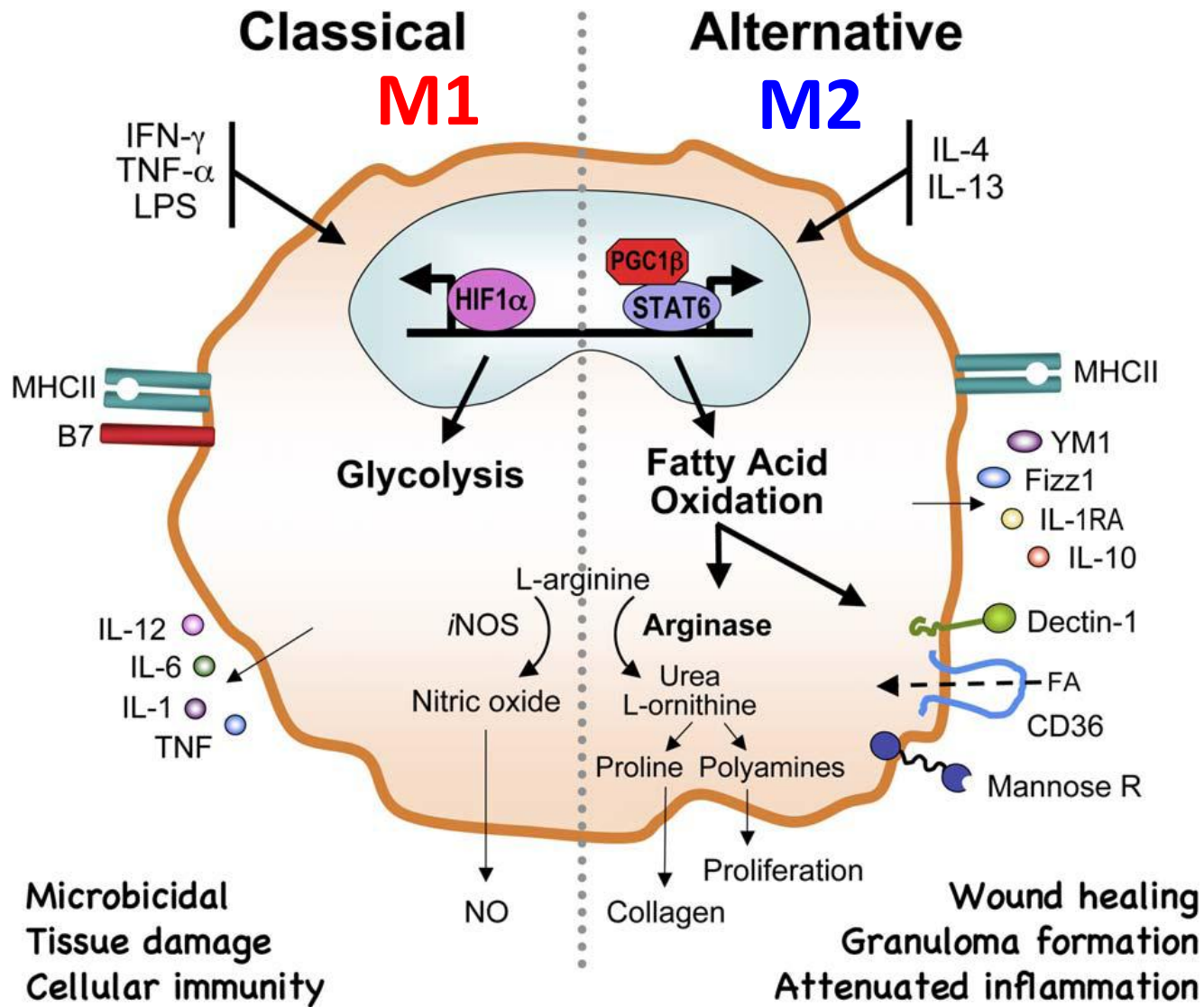
Immunofluorescence staining

# Summary I

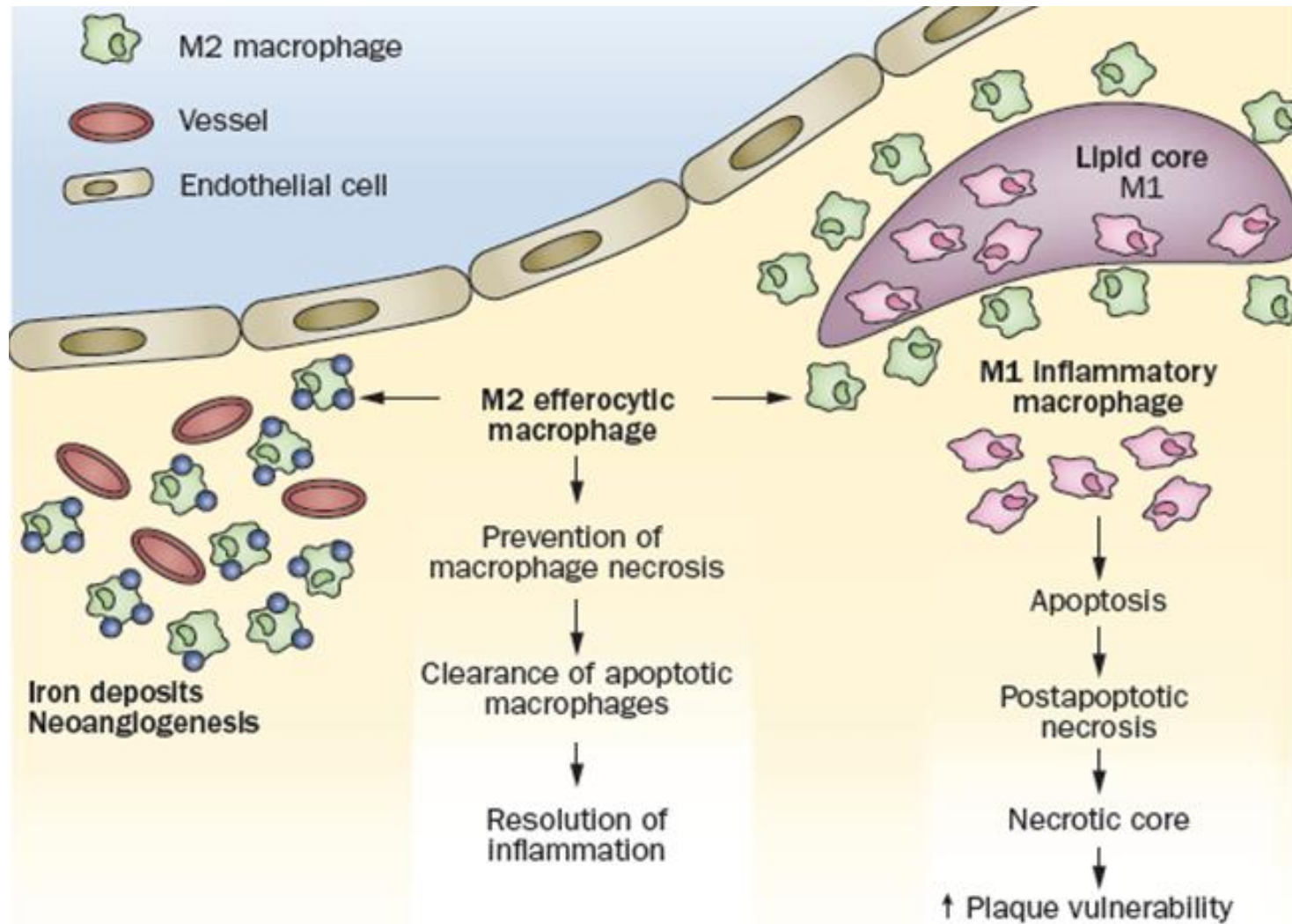
According to our experiments, deletion of SIRT1 in macrophage induced endothelial dysfunction and atherogenesis.

**Q3. How SIRT1 in macrophage affects endothelial function and atherosclerosis?**

# M1 and M2 Macrophage

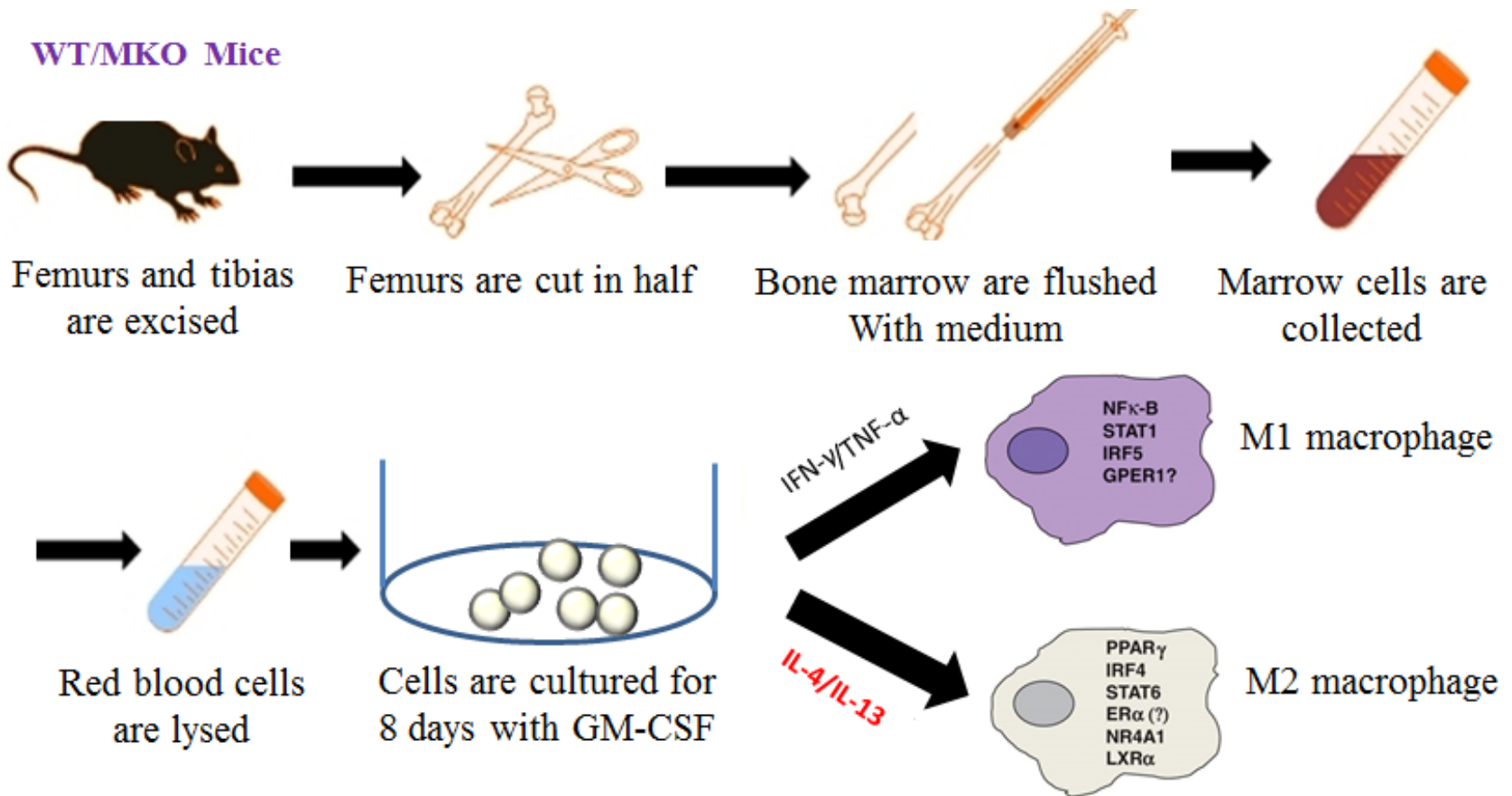


# Potential role of M2 macrophages in atherosclerotic plaques



**Q4. whether SIRT1 Influences the  
macrophage M1–M2 Polarization  
Balance ?**

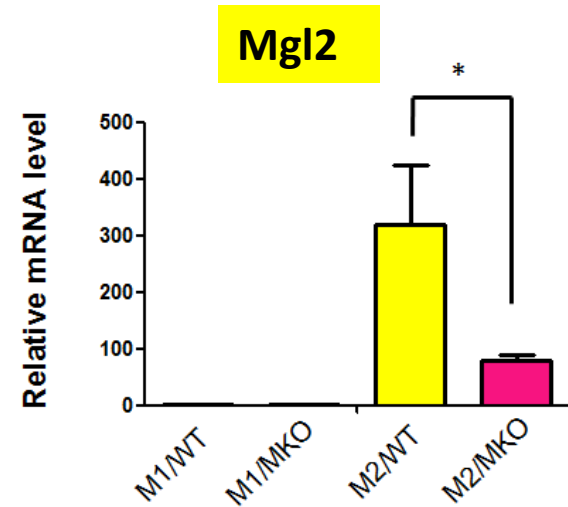
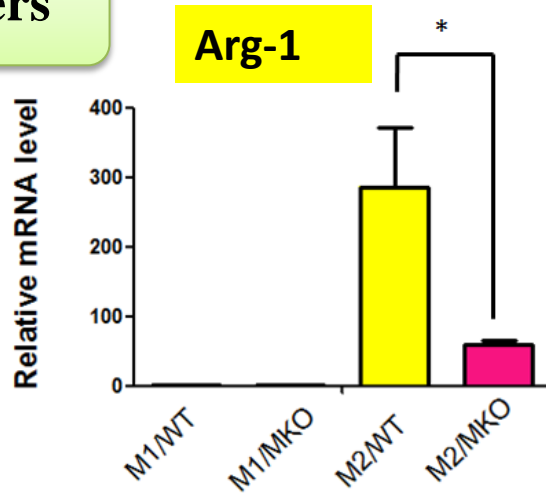
# Methods



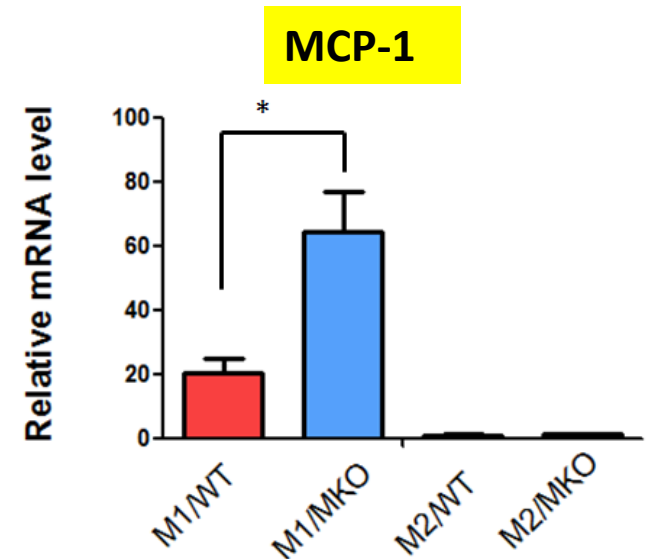
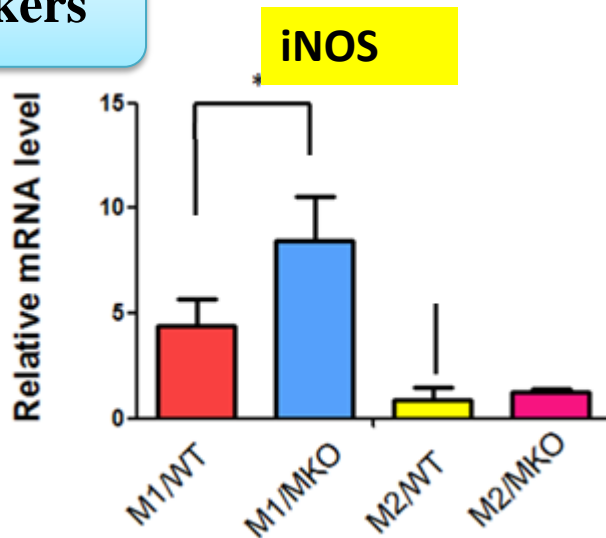
**BMM cultures and  
Differentiation**

# Deletion of SIRT1 in macrophage impaired macrophage polarization

## M2 markers



## M1 markers



**Q5. Whether SIRT1 affects endothelial function by regulation of macrophage polarization?**



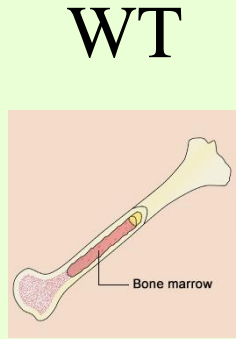
# Methods

Porcine Aortic  
Endothelial Cells  
(PAECs)

Bone Marrow

BMMs

M2 Macrophage



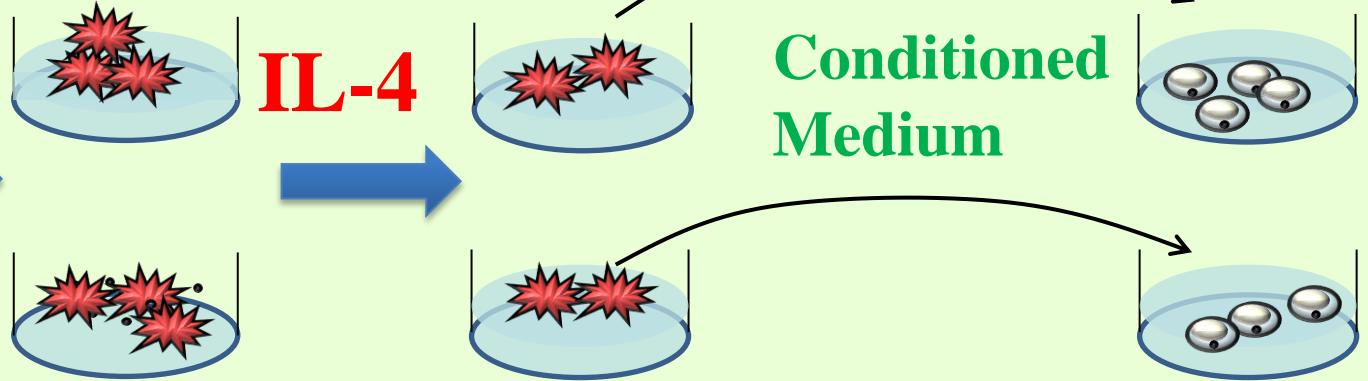
IL-4

Conditioned  
Medium

MKO

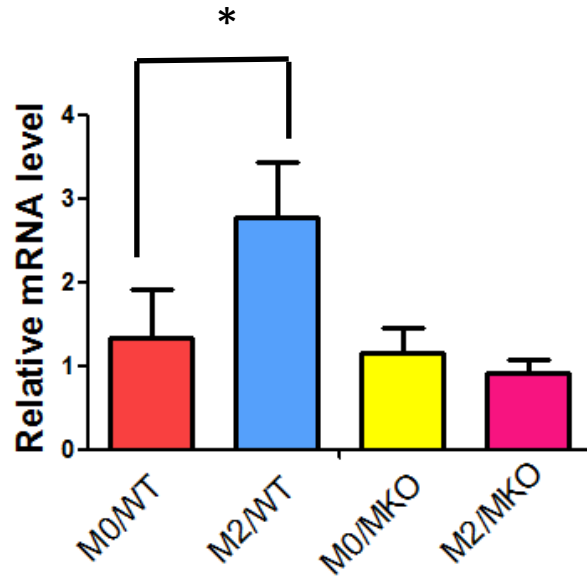
Donor

Recipient

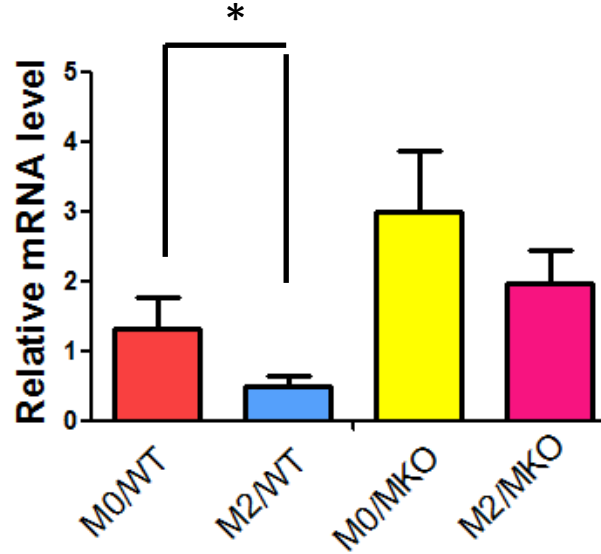


# M2 macrophage improved endothelial function

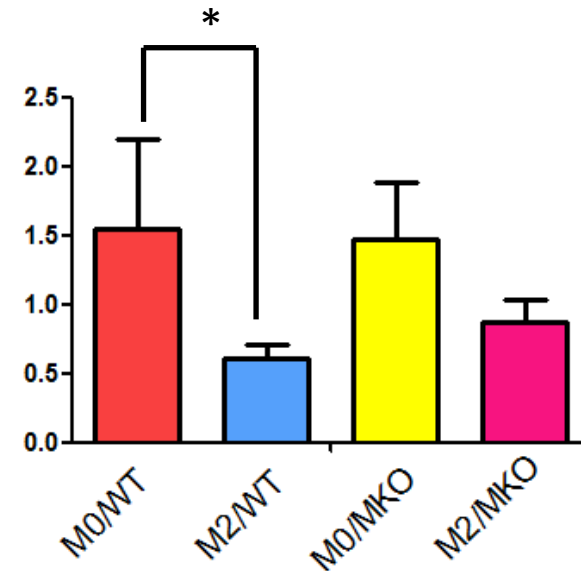
eNOS



E-selectin



ICAM-1



# Summary II

- **SIRT1 plays a pivotal role in controlling macrophage polarization.**
- **SIRT1 in macrophage protects endothelial function by regulation balance of M1 and M2 macrophage.**

## Future Research

**How SIRT1 modulates the macrophage polarization?**

# Acknowledgement

## University of Hong Kong

**Prof. Aimin XU**

**Hannah HUI, PhD**

**Zhe HUANG, PhD**

**Jin LI, PhD**

**Kelsey ZHONG, PhD**

## Jin Ling Hospital

**Prof. Jiaqing SHAO**

**Bin LU, MD, PhD**

**Jian MA**

**Cuihua YANG**

*Thank  
you*

