

# **Macrophage microRNA-155 and Atherosclerosis**

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Assistant Professor

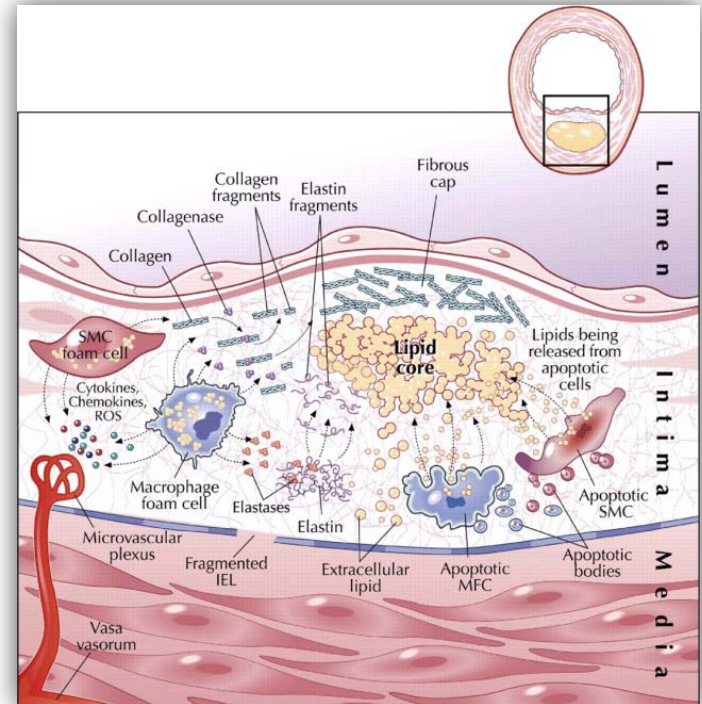
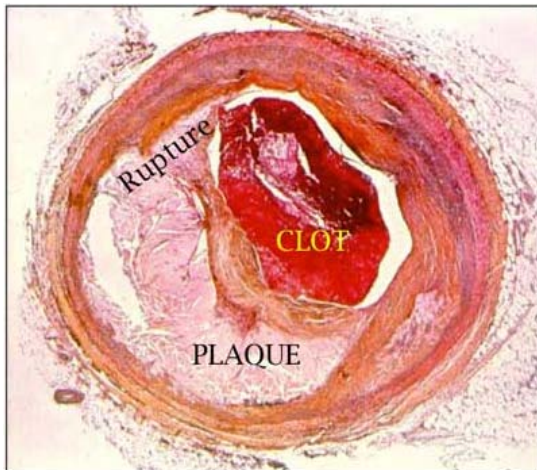
USC, Cell Biology and Anatomy

**2009 IDeA Regional Meeting**

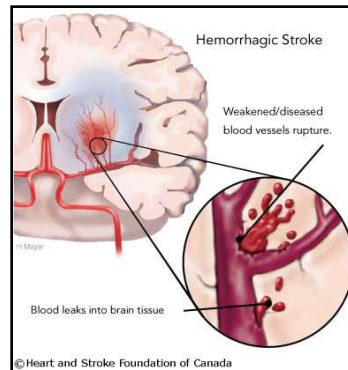
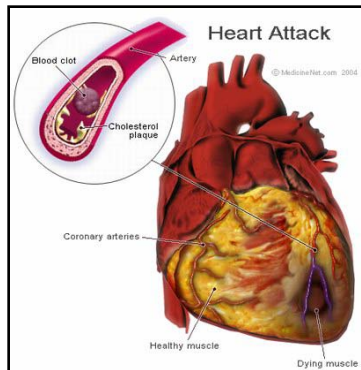
**Charleston, Nov. 10**

# Atherosclerosis

A chronic inflammation in arterial wall



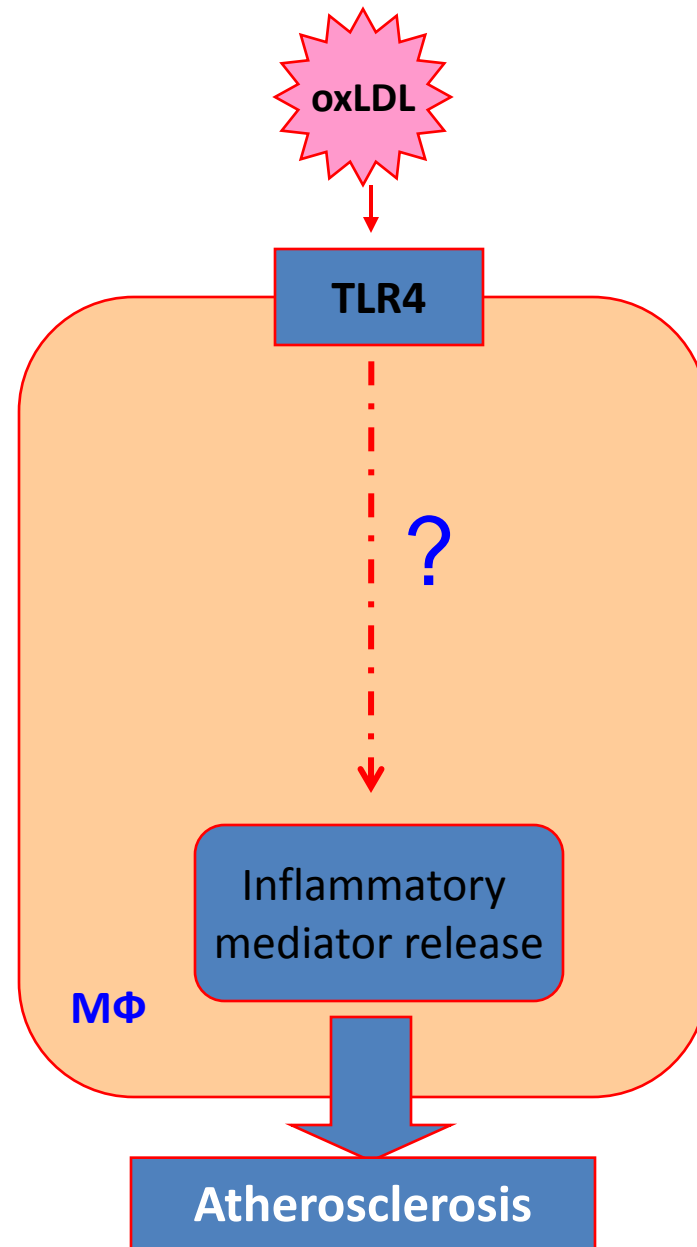
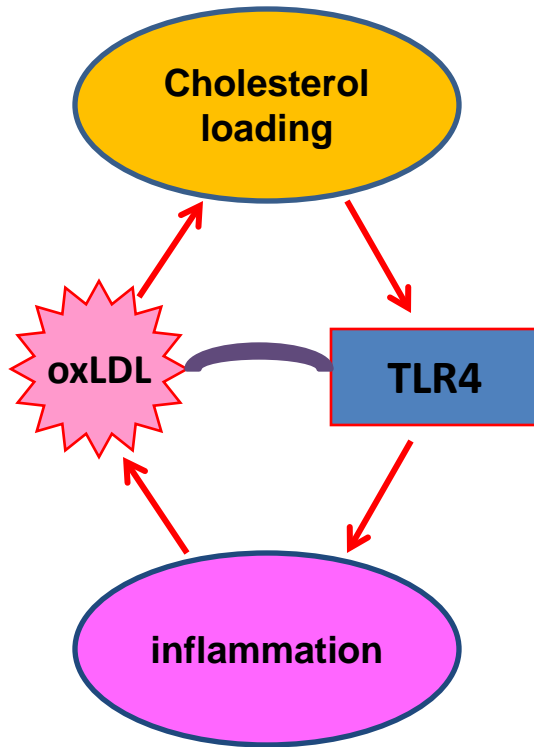
Libby, P. et al. J Am Coll Cardiol  
2006;48:A33-A46



## Cholesterol Inflammation

“Partners in crime”

# MΦ cholesterol homeostasis and inflammation, the role in atherogenesis



# Anti-inflammation therapy and atherosclerosis

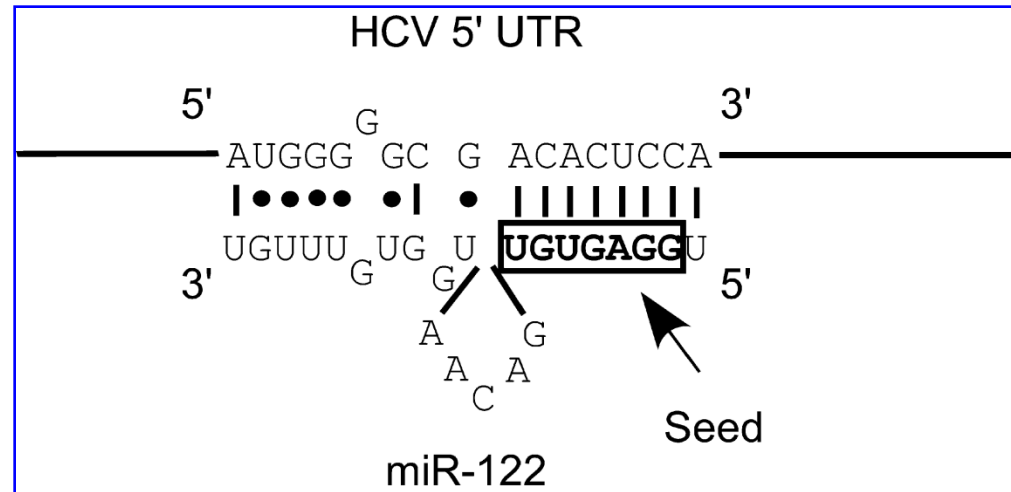
- **Inhibitors of cyclooxygenase 2 (COX-2): Vioxx – increase heart attack and stroke** (*Topol, New England Journal of Medicine 2004*)
- **TNF $\alpha$  blockade -- destabilizes plaques?** (*Aggarwai, Autoimmun Rev 2005*)
- **Inhibition of lipoxygenase pathway – contradictory** (*Bäck, Current Pharmaceutical Design 2009*)
- **Vaccination against atherosclerosis?** (*Hansson, Semin Immunopathol, 2009*)
- **Boosting Treg population → ↑inherent atheroprotective immunity?** (*Mallat, J Lipid Res. 2009*)

**Mechanistic link between inflammation and atherosclerosis?**

**How to modulate inflammation to achieve beneficial outcome?**

# microRNAs: A new class of gene regulators

- Endogenous, small noncoding RNAs
- A fast expanding family
  - Human > 600 miRs
  - Mouse > 500 miRs
- To date estimate: >1/3 genes are regulated by miR
- Mature miR: 20-23 nts; imperfect/perfect match with target mRNAs  
→ mRNA degradation/translational repression



*Joplin et al (2005), Science 309:1577*

# miR155: A possible player in atherogenesis?

- Bic gene is a non-coding RNA.

*Tam W et al. (2001) Gene*

- Bic encodes microRNA-155, which is up-regulated in human B cell lymphoma

*Eis P et al. (2005) PNAS*

- Uniquely expressed in activated cells of immune system (T, B, MΦ). Is required for cytokine release from T and B cells.

*Thai T et al. (2007) Science*

*Rodriguez A et al. (2007) Science*

- Up-regulated in macrophages by Toll-like receptor (TLR) ligands.

*O'Connell RM et al. (2007) PNAS*

- miR-155 inhibition sensitizes CD4<sup>+</sup> Th cells for Treg mediated suppression

*Heiko, Plos ONE, 2009*

- Targets:

Fibroblasts: Angiotension II type I receptor (ATIR) (*Martin, JBC 2006*)

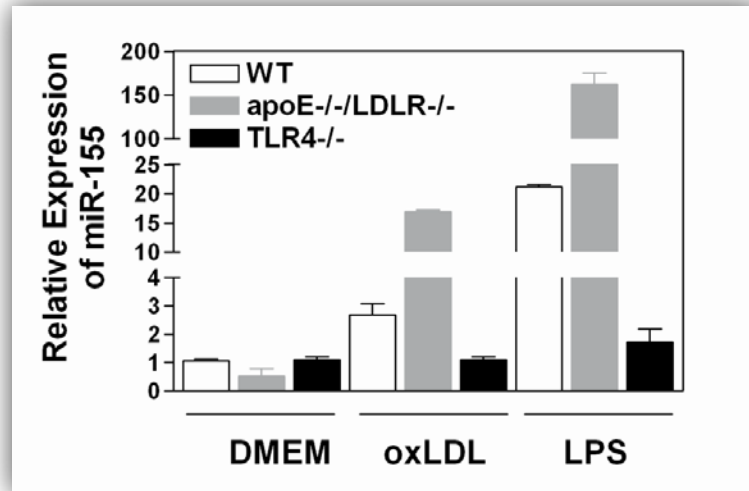
B cells: Pu.1 (*Vigorito, Immunity, 2007*); activation-induced cytidine deaminase (AID) (*Teng, Immunity, 2008*)

Dendritic cells: TAB2 (An adaptor in TLR/IL1 signaling) (*Ceppei, PNAS 2009*)

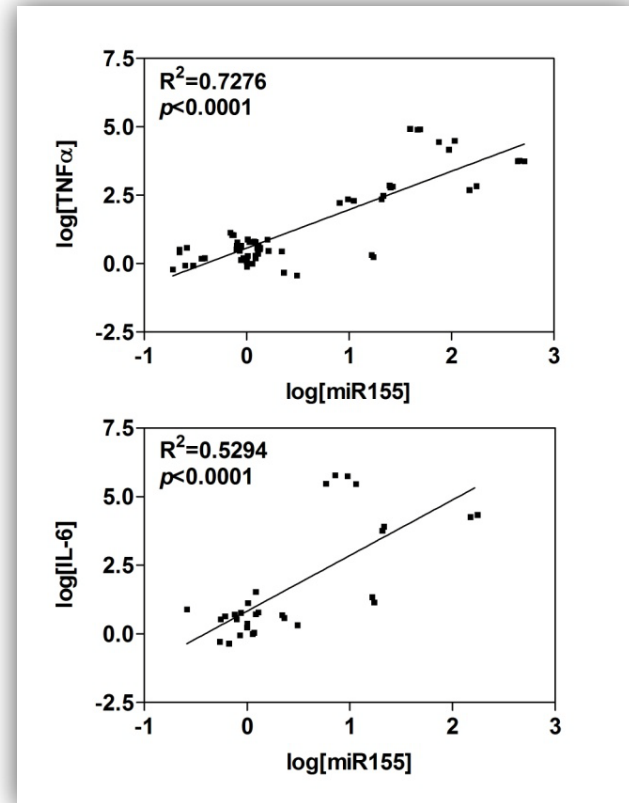
Hematopoietic cells: Inositol phosphatase SHIP1 (*O'Connell, PNAS 2009*)

Macrophages: Suppressor of cytokine signaling 1 (SOCS-1) (*Androulidaki, Immunity, 2009*)

# miR155 is up-regulated in macrophages via TLR-4 during inflammatory responses

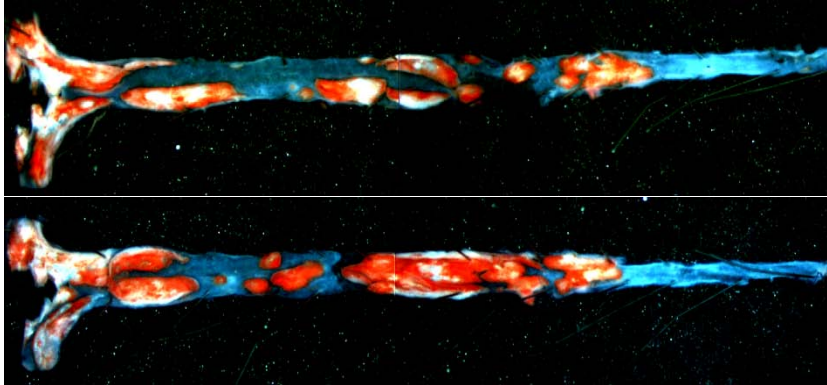


1. Oxidized LDL up-regulates miR155 expression in MΦs via TLR4.
2. Cholesterol-loaded MΦs express miR155 at higher level than control MΦs when stimulated.

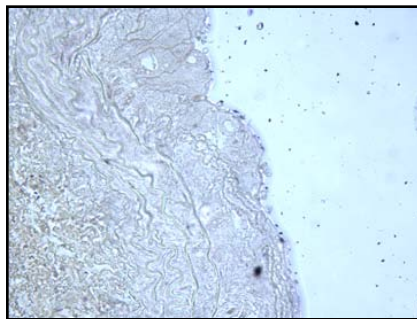
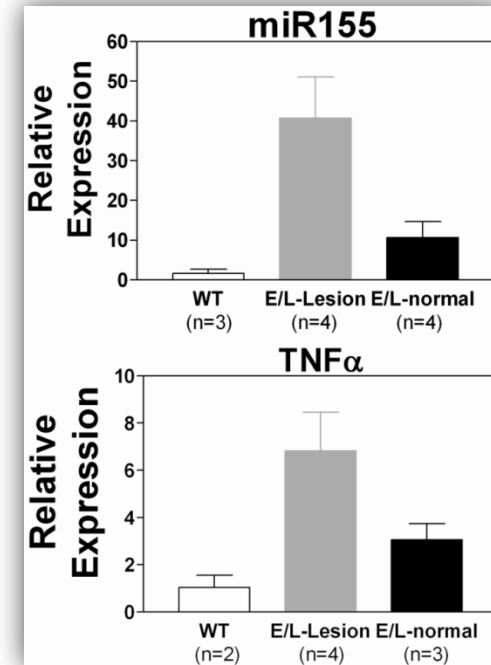


In macrophages, miR155 expression correlates with inflammatory cytokine expression.

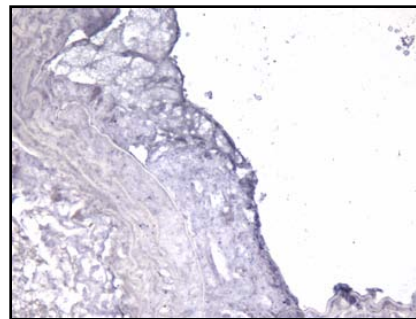
# miR155 is up-regulated in mouse atherosclerotic lesions



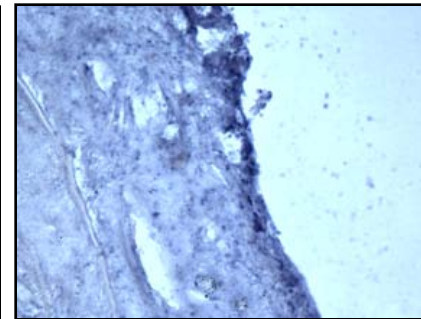
↑ En face aorta oil-red O staining (*apoE<sup>-/-</sup>/LDLR<sup>-/-</sup>*)  
miR155 and TNF $\alpha$  expression in lesions →



Scrambled probe 400X



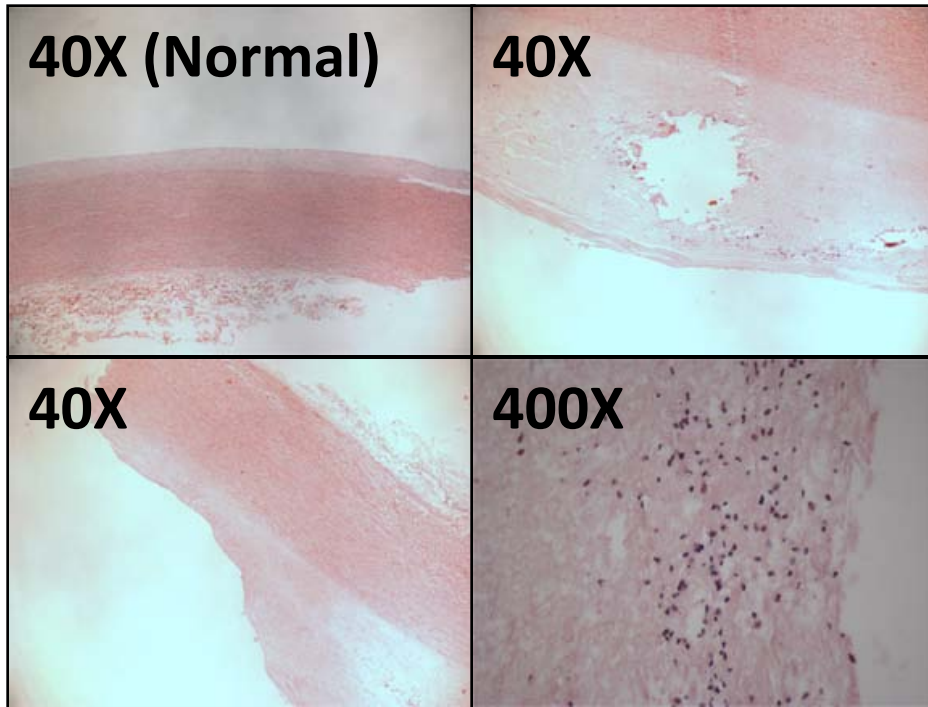
miR155 probe 400X



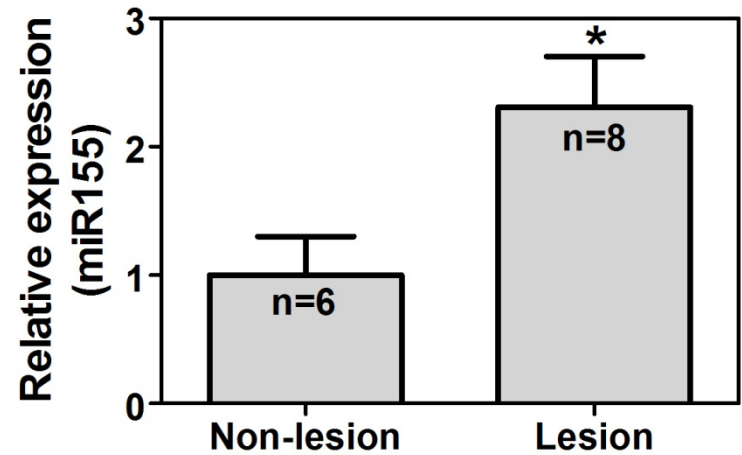
miR155 probe 1000X

Locked nucleic acid in situ hybridization

# miR155 is up-regulated in human atherosclerotic lesions

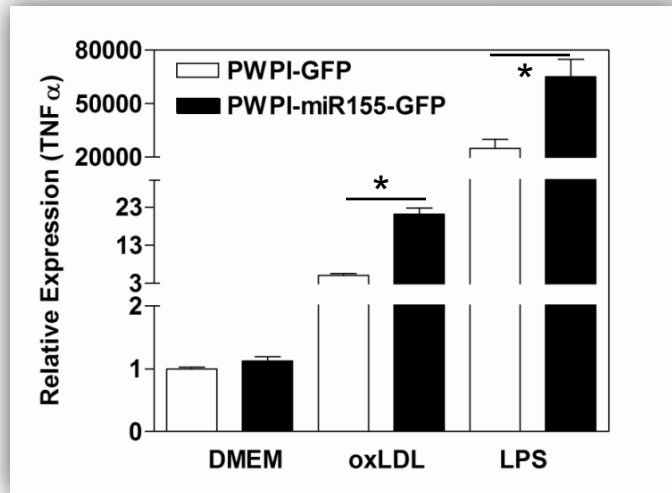
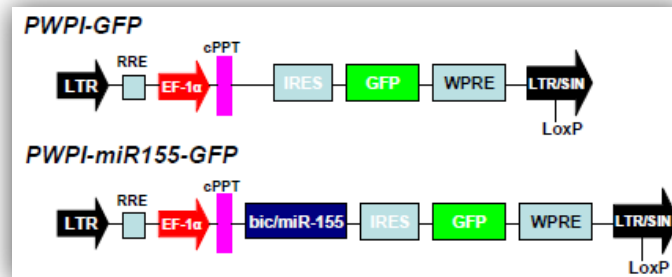


Human aorta atherosclerotic lesions (H&E).

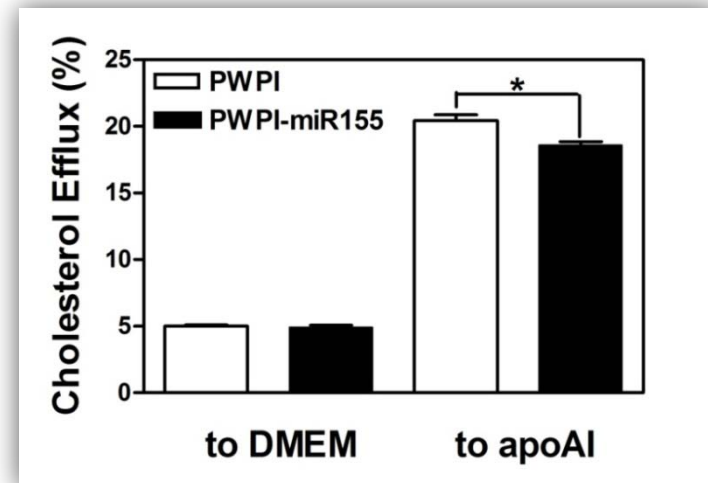


miR155 expression is increased in human aortic atherosclerotic lesions.

# Over-expression of microRNA-155 alters macrophage function



Over-expression of miR155 exaggerates macrophage inflammatory response to oxLDL and LPS.



Over-expression of miR155 impairs macrophage cholesterol efflux to physiological acceptor.

# Conclusion

1. **microRNA-155 participates in macrophage inflammatory responses to atherogenic stimuli.**
2. **microRNA-155 expression is up-regulated in atherosclerotic lesions of mice and humans.**

# Future Studies

1. **To test the hypothesis that macrophage microRNA enhances atherosclerosis in mice. (Bone marrow HPC lentiviral transduction and transplantation)**
2. **To investigate the molecular mechanism through which microRNA-155 participate in the positive feedback loop of macrophage inflammation.**

# Acknowledgements

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