Mechanism of Macrophage Trapping in Atherosclerosis

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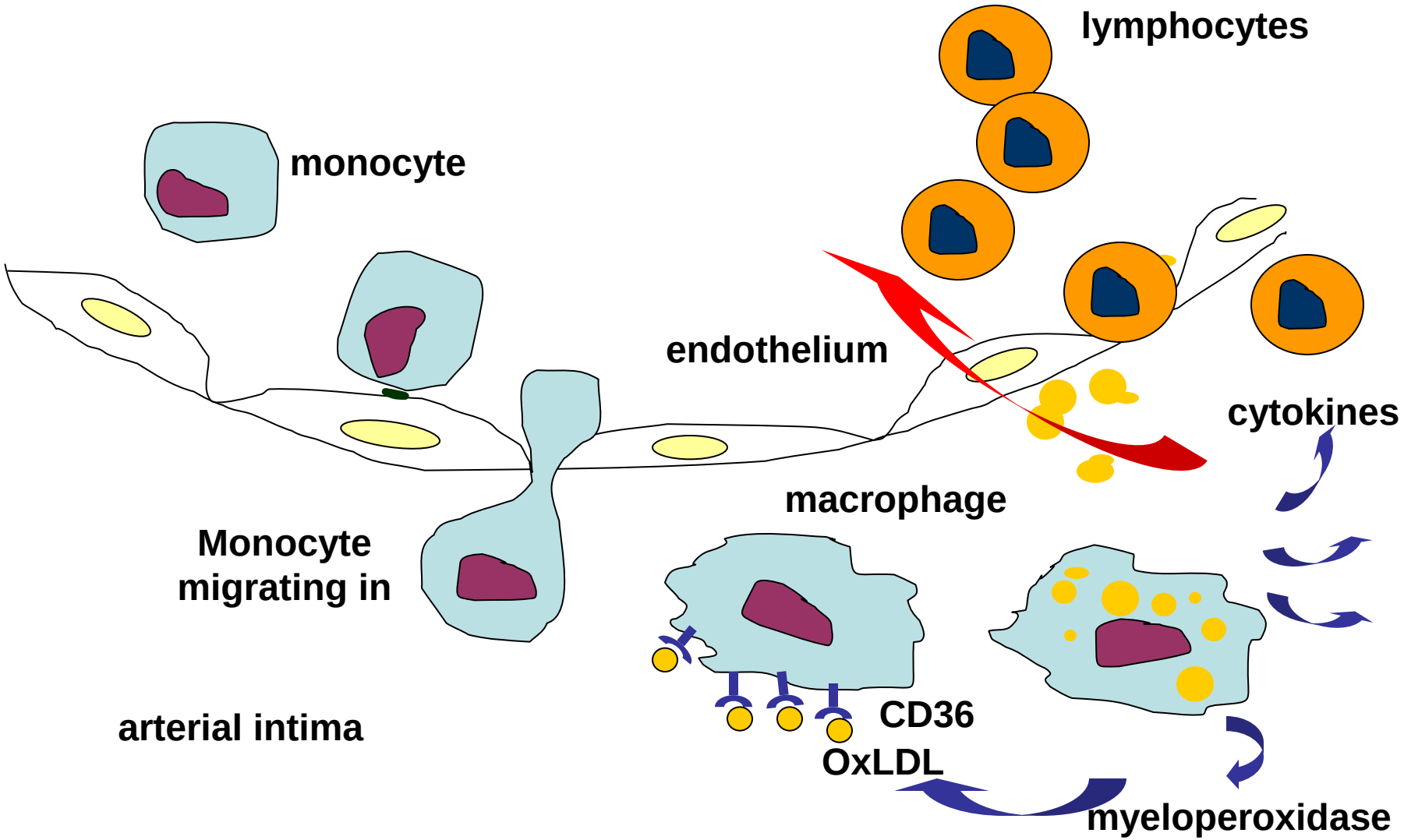
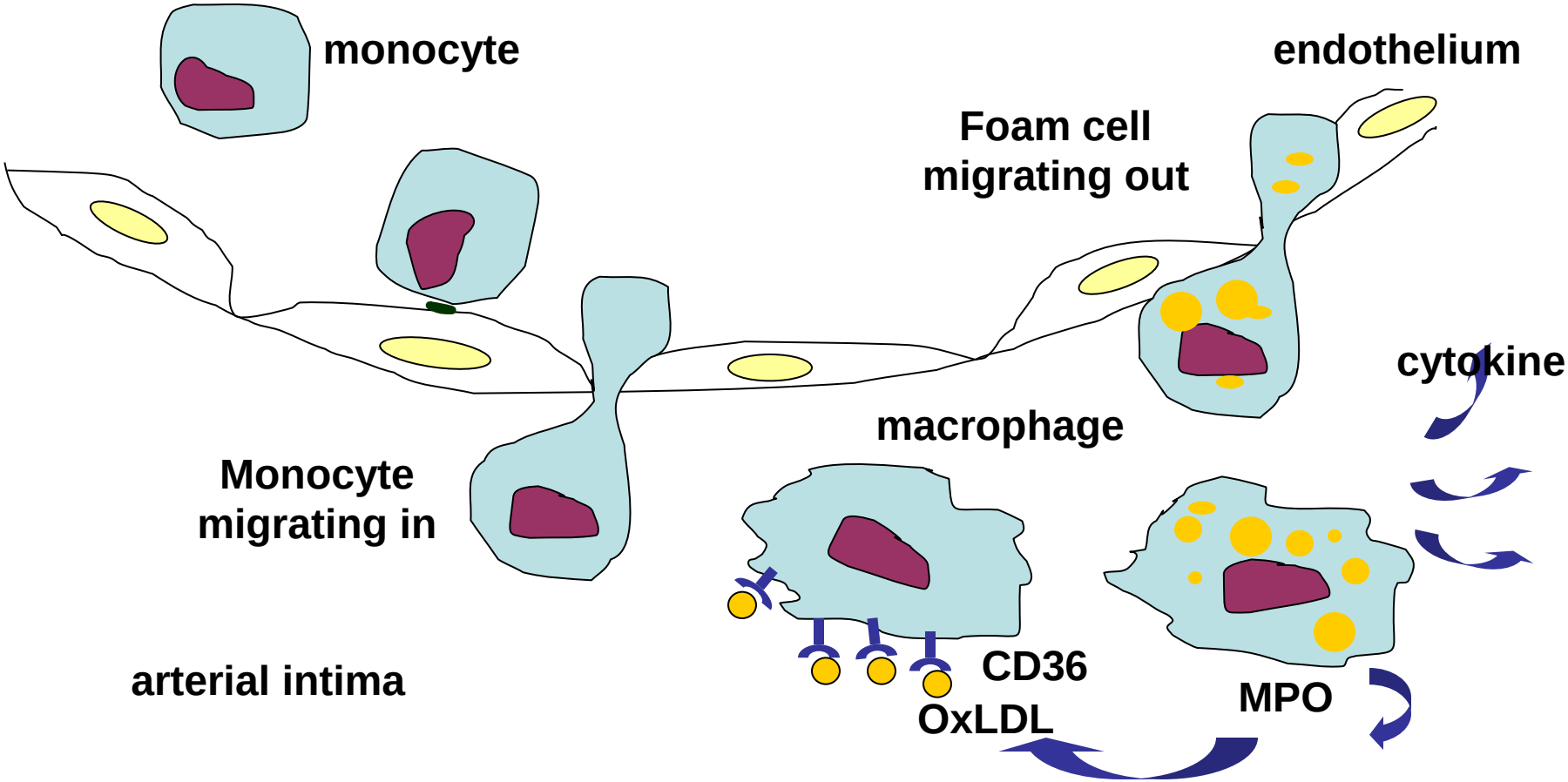
Atherosclerosis



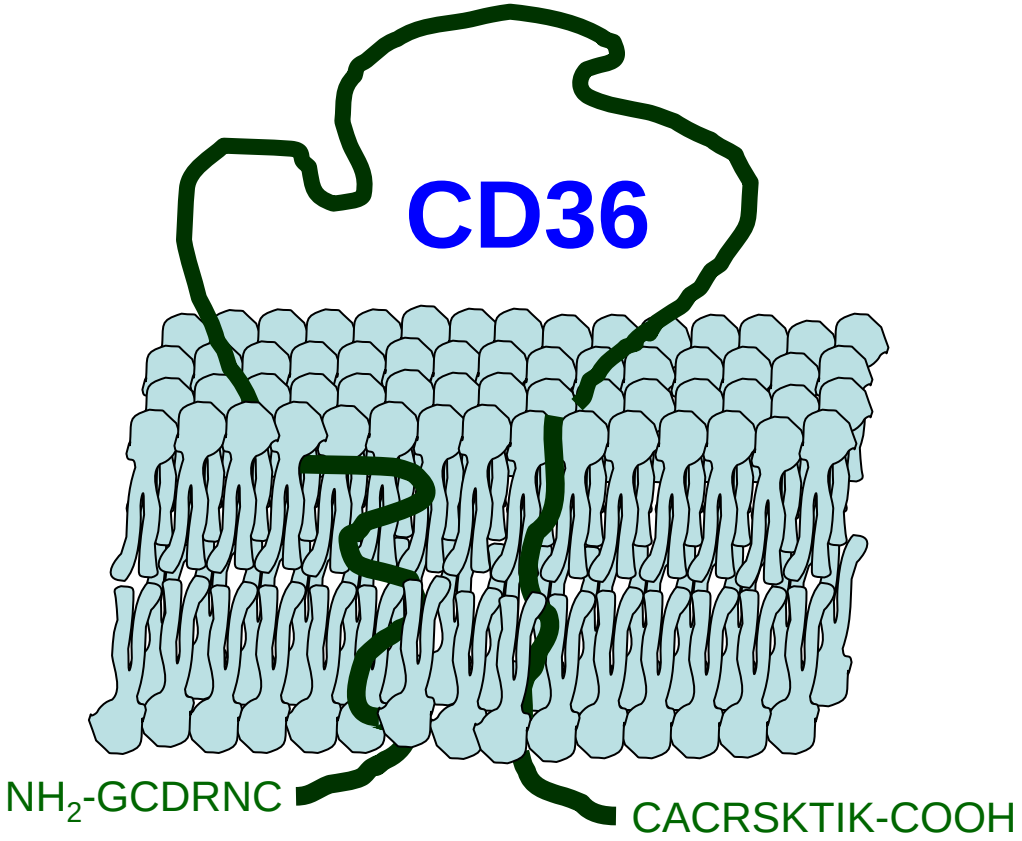
Mobilization of macrophages as a new therapeutic strategy for the treatment of atherosclerosis that reverses the disease



Interaction between oxidized LDL and CD36 modulates macrophage cytoskeletal function and inhibits migration;

A Mechanism of Macrophage Trapping

Oxidized lipoproteins



Atherosclerosis

CD36 in Atherosclerosis

- **Macrophages from CD36 null mice are profoundly defective in uptake of oxLDL and foam cell formation**

- **CD36 null mice demonstrate a dramatic decrease in atherosclerotic lesion development**

In vivo macrophage migration assay

Thioglycolate I.P. injection

4 days

Monocytes come into peritoneal cavity and differentiate to macrophages

oxLDL

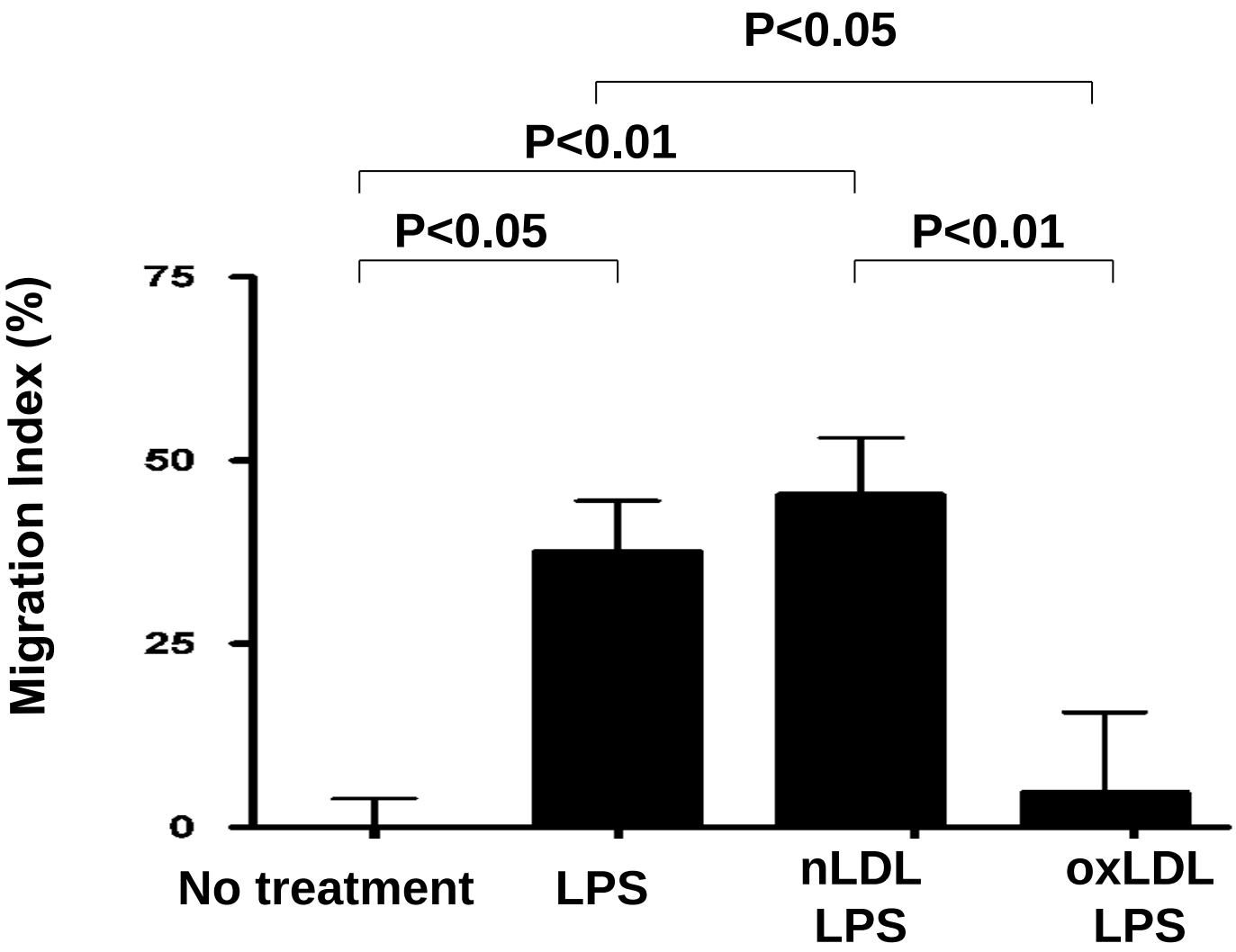
LPS I.P. injection

4 hours

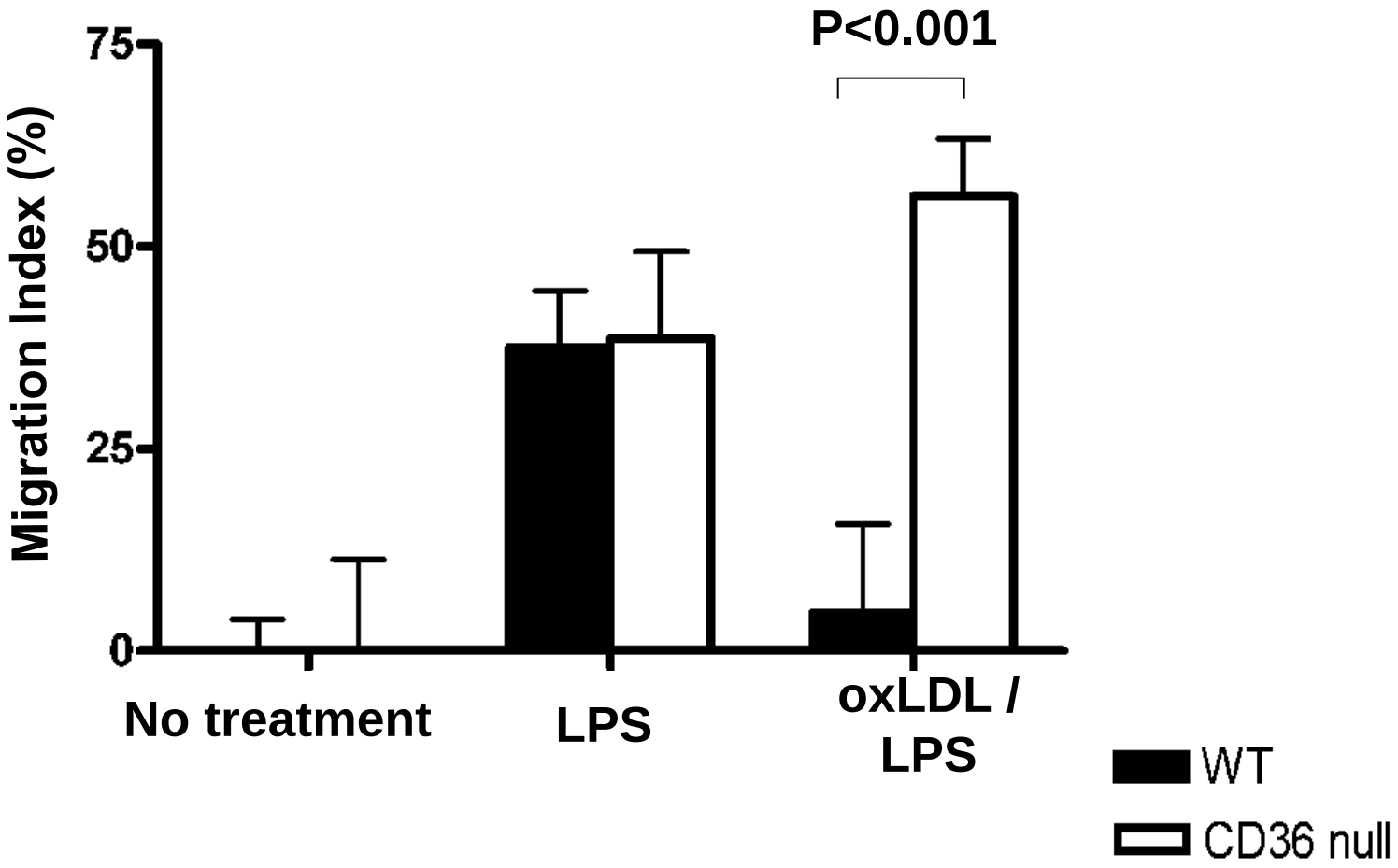
Macrophages migrate out to regional lymph nodes

Peritoneal lavage and count macrophages

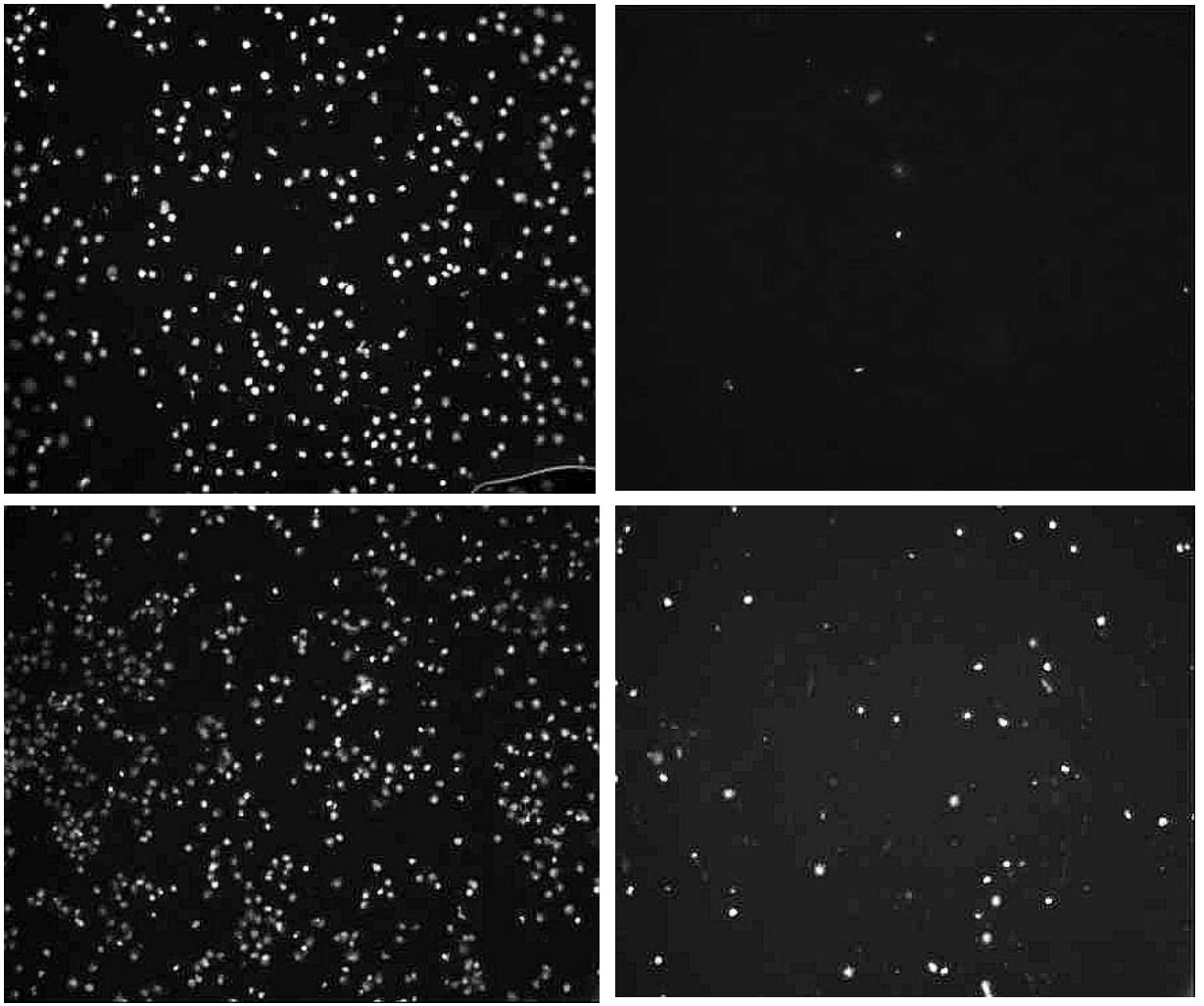
OxLDL inhibits macrophage migration *in vivo*



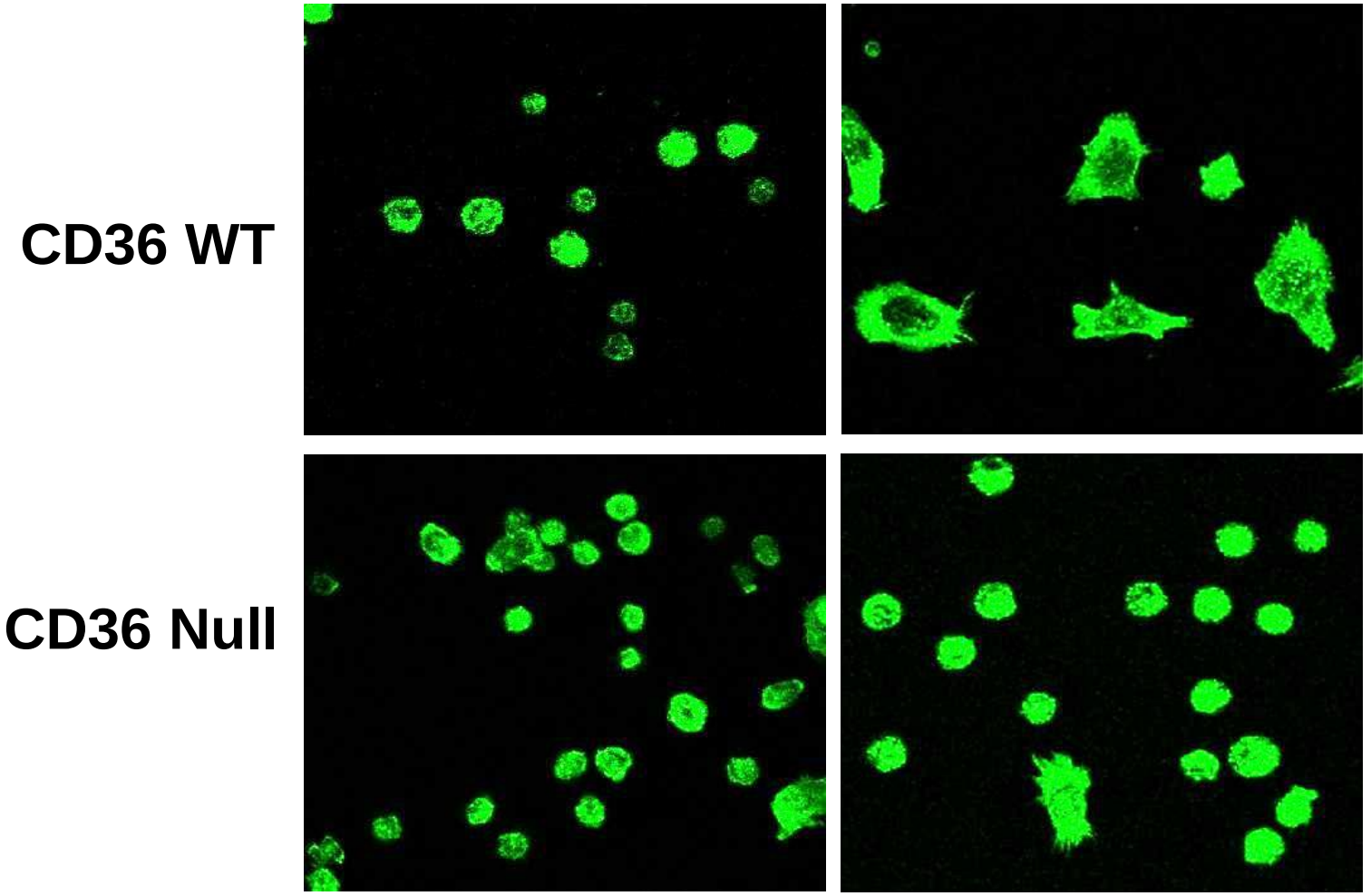
OxLDL inhibition of macrophage migration *in vivo* is CD36-dependent



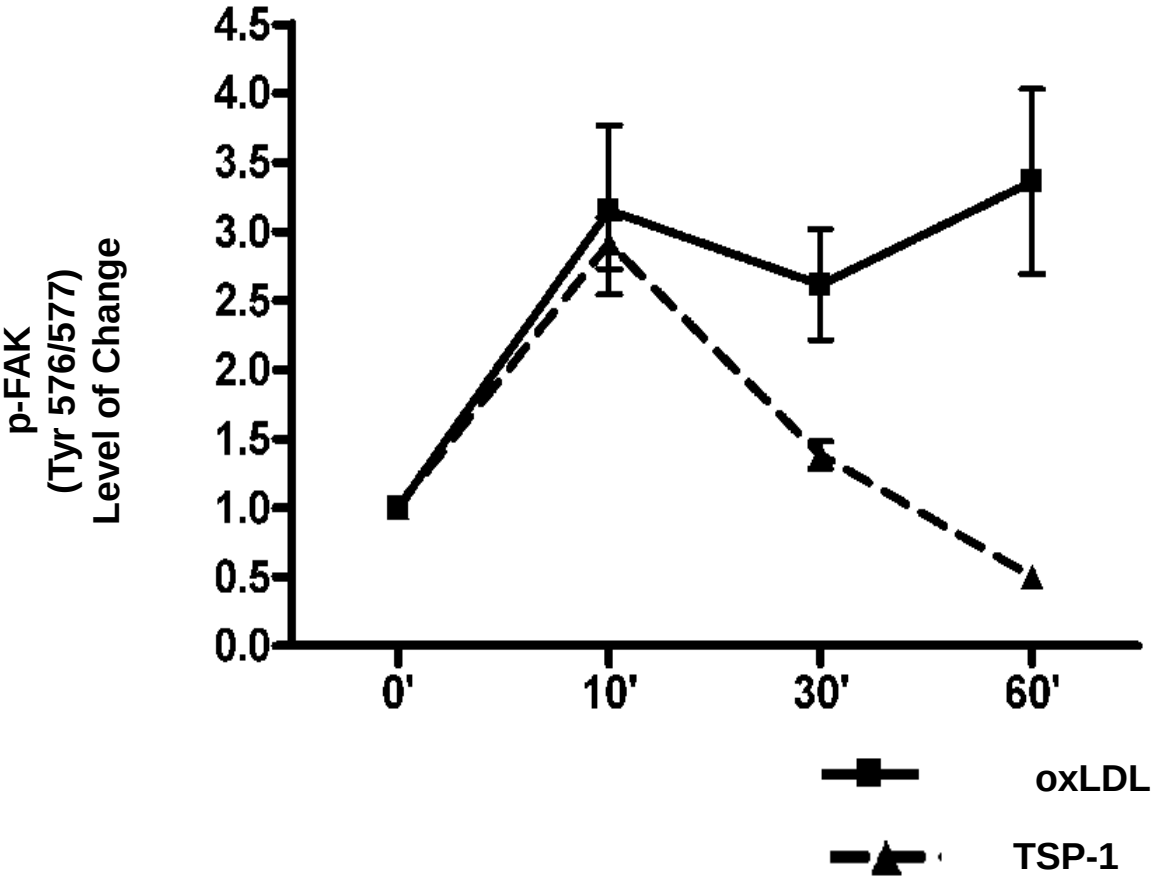
Macrophage migration is inhibited by ox-LDL



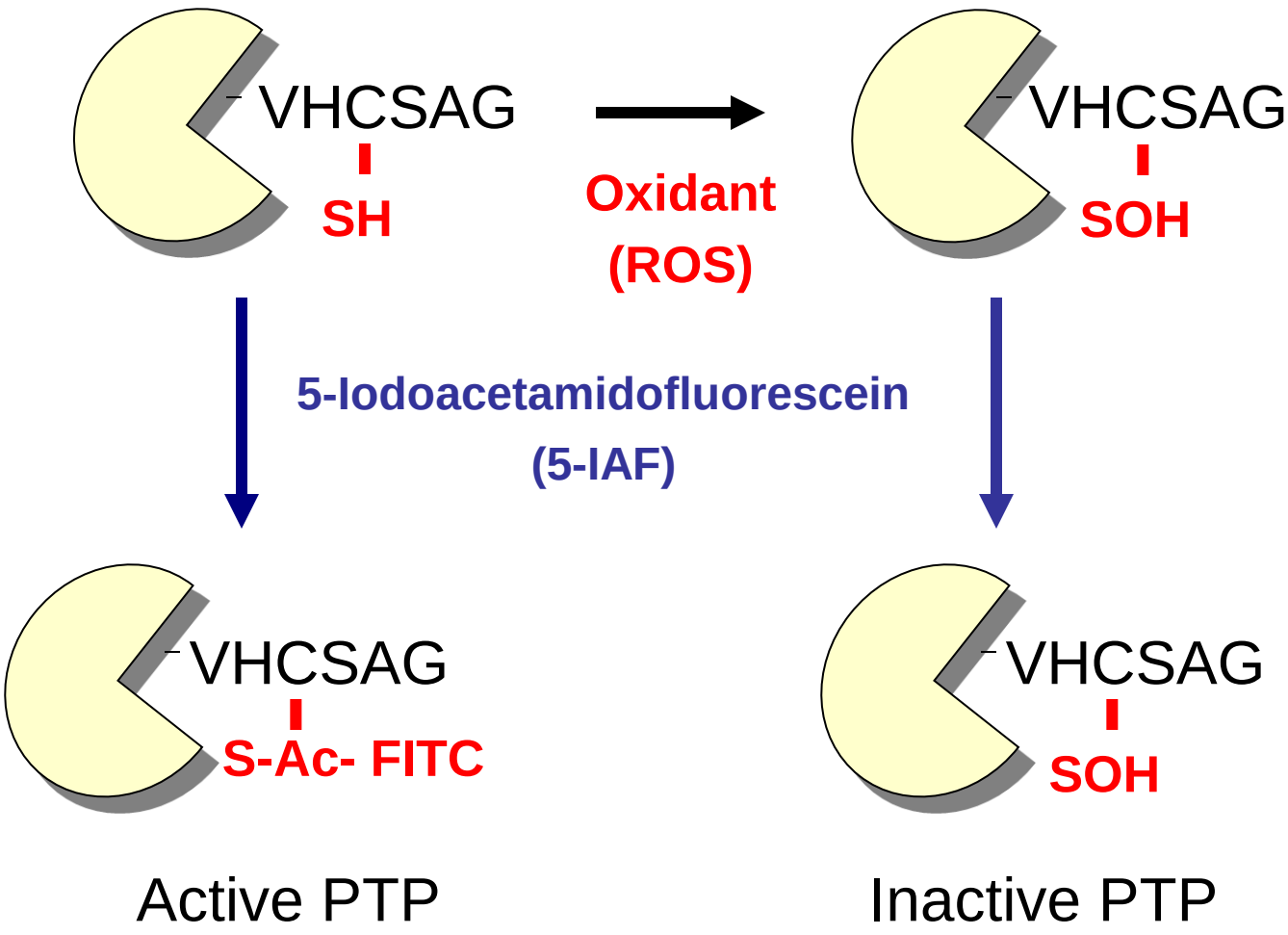
Ox-LDL induces rapid macrophage spreading; CD36 null cells show less spreading in response to oxLDL



OxLDL induces sustained activation of FAK

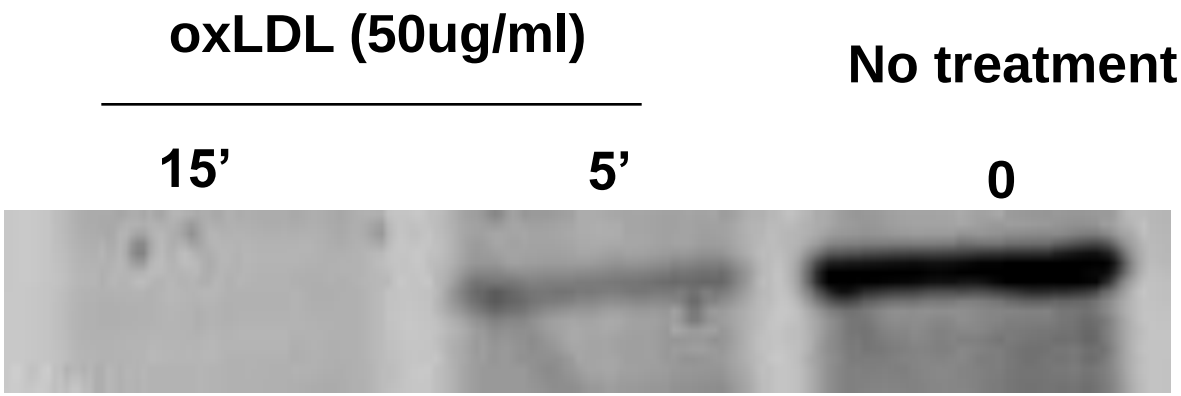


Inactivation of PTP is due to oxidation of the essential cysteine in the active site of PTP

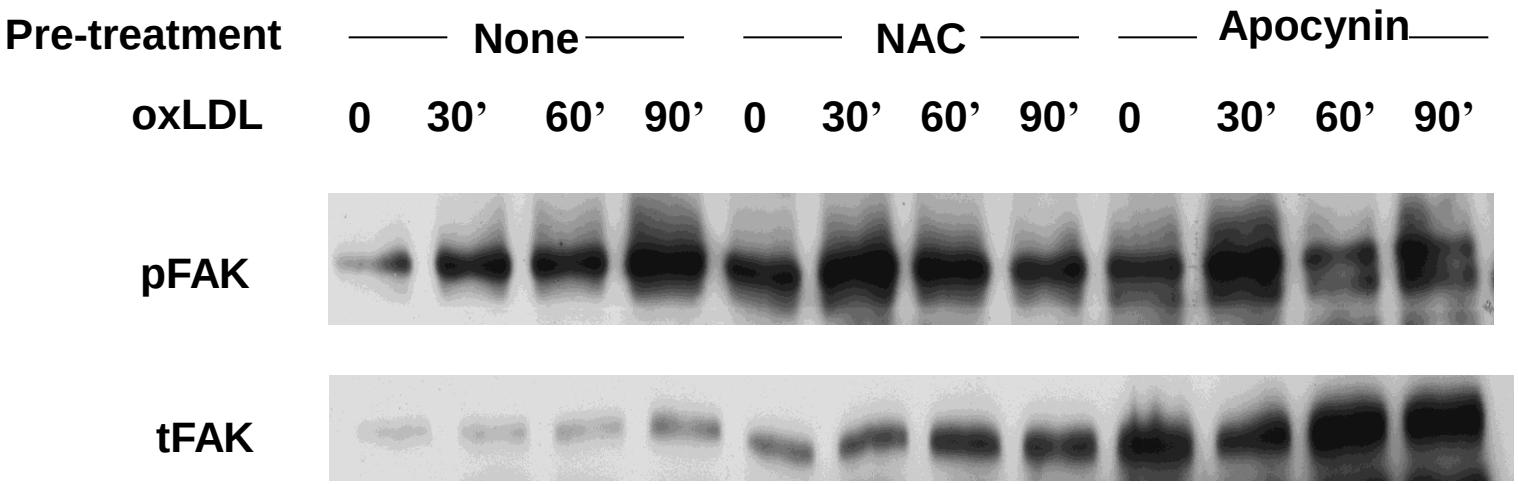


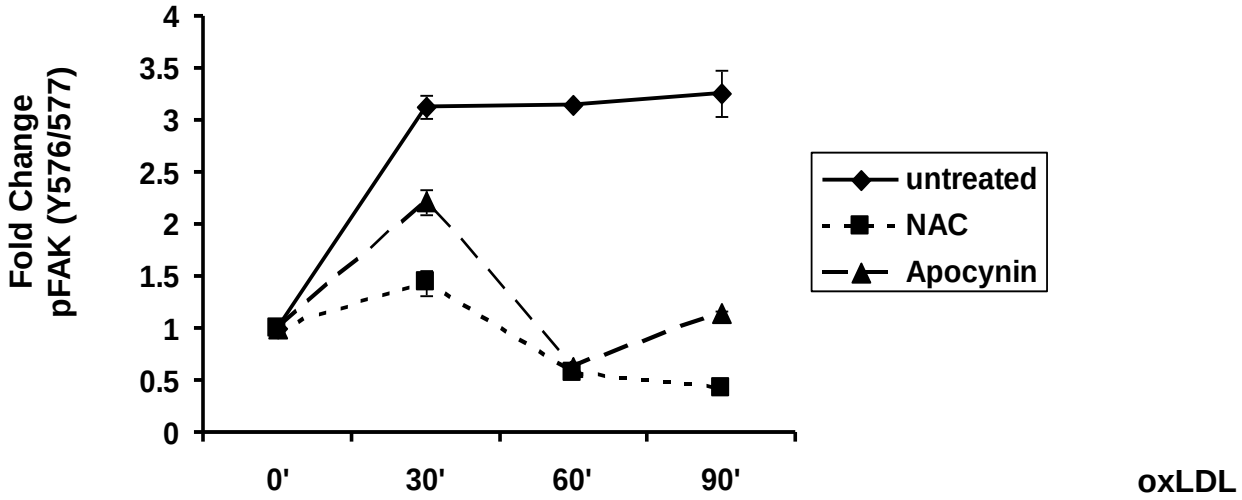
Wu RF, Terada LS, Sci STKE, 2006(332):pl2

OxLDL induces oxidative modification of SHP-2

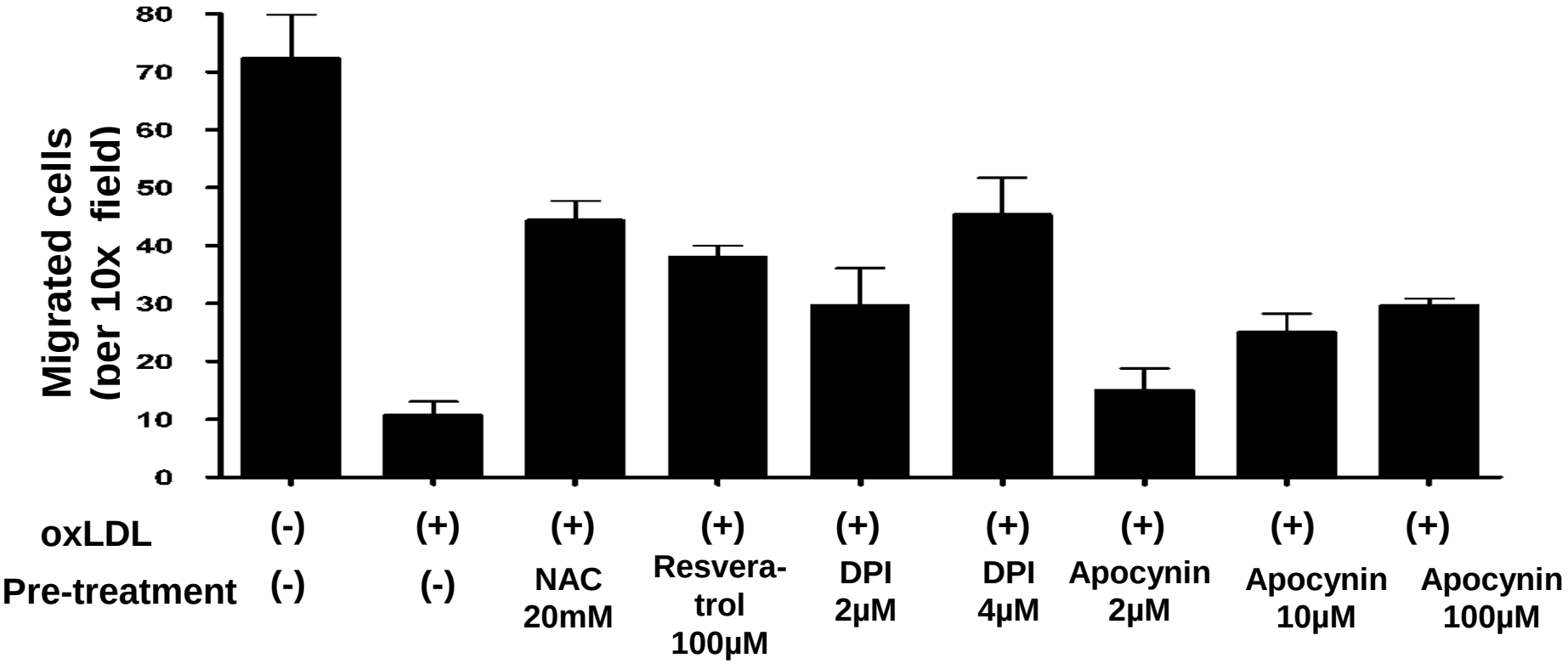


Anti-oxidant and NADPH oxidase inhibitor restore dynamic phosphorylation of pFAK by oxLDL

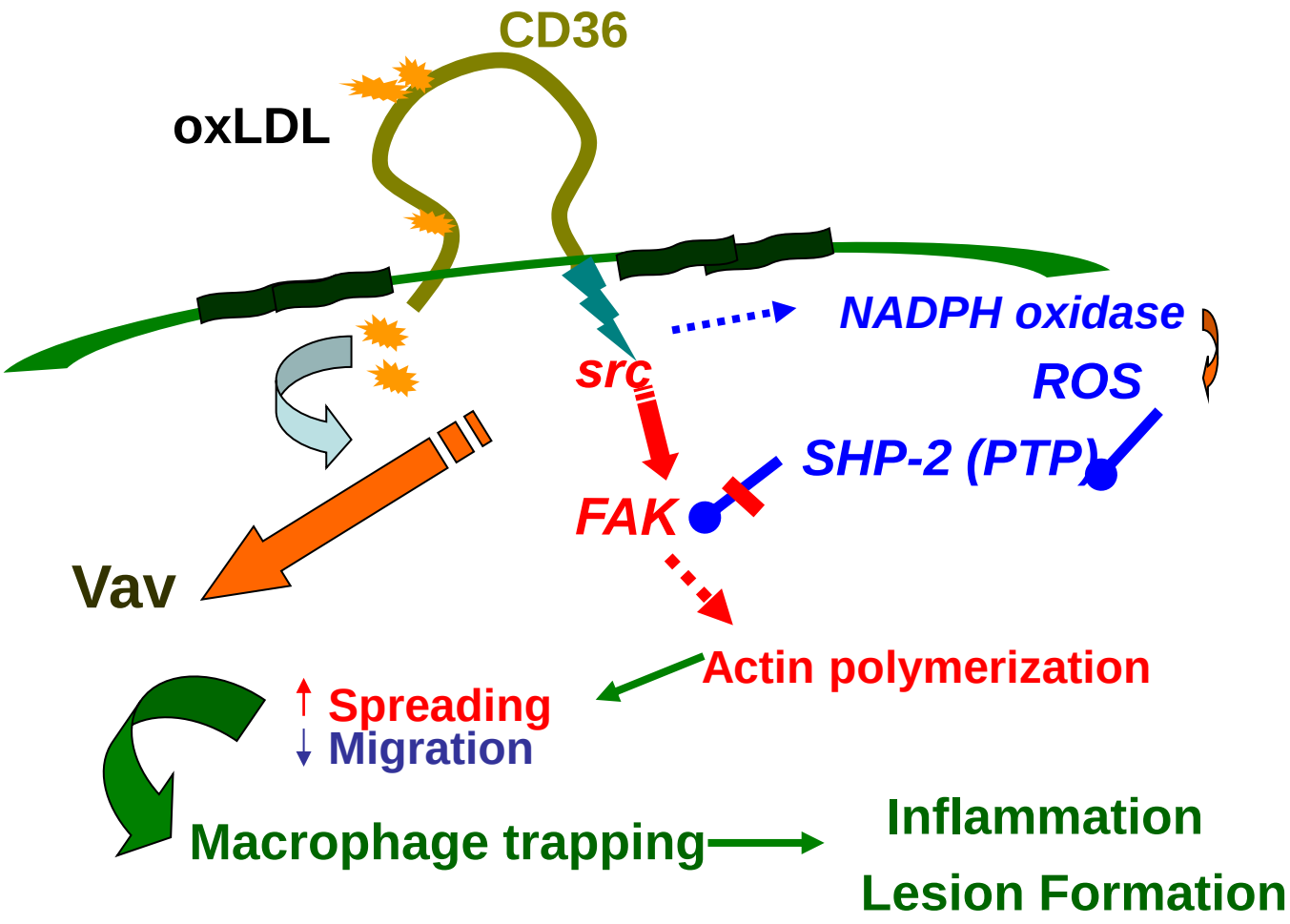




Blockade of ROS generation restores macrophage migration



OxLDL inhibits macrophage migration by CD36-dependent modulation of cytoskeletal function.



Park, Febbraio, Silverstein, J Clin Invest, 119(1): 136-145, 2009

Vav and CD36

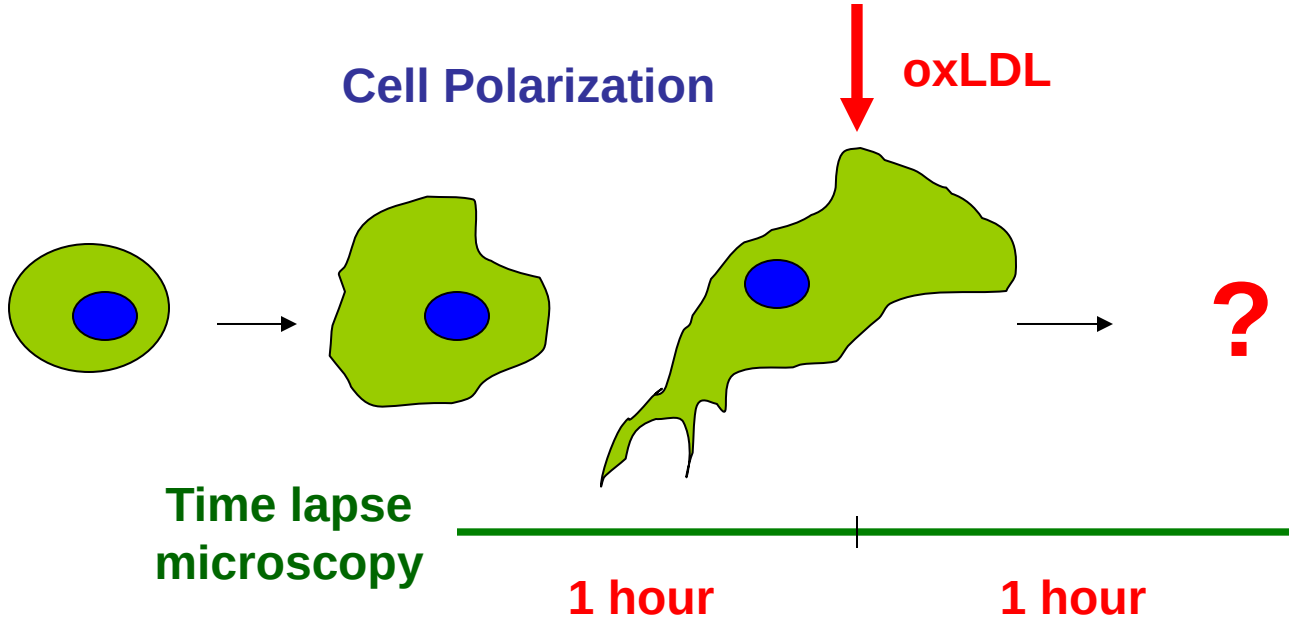
- **Guanine nucleotide exchange factor (GEF)**
- **Activates small MW g proteins, Rac1/RhoA/RhoG**
- **Fibrillar beta amyloid binding to CD36 induces phosphorylation (activation) of Vav in monocytes and microglia**

  (Wilkinson, B. et al. J. Biol. Chem. 281(30), 2006)
- **Ox-LDL / CD36 interaction induces phosphorylation of Vav in murine macrophages**

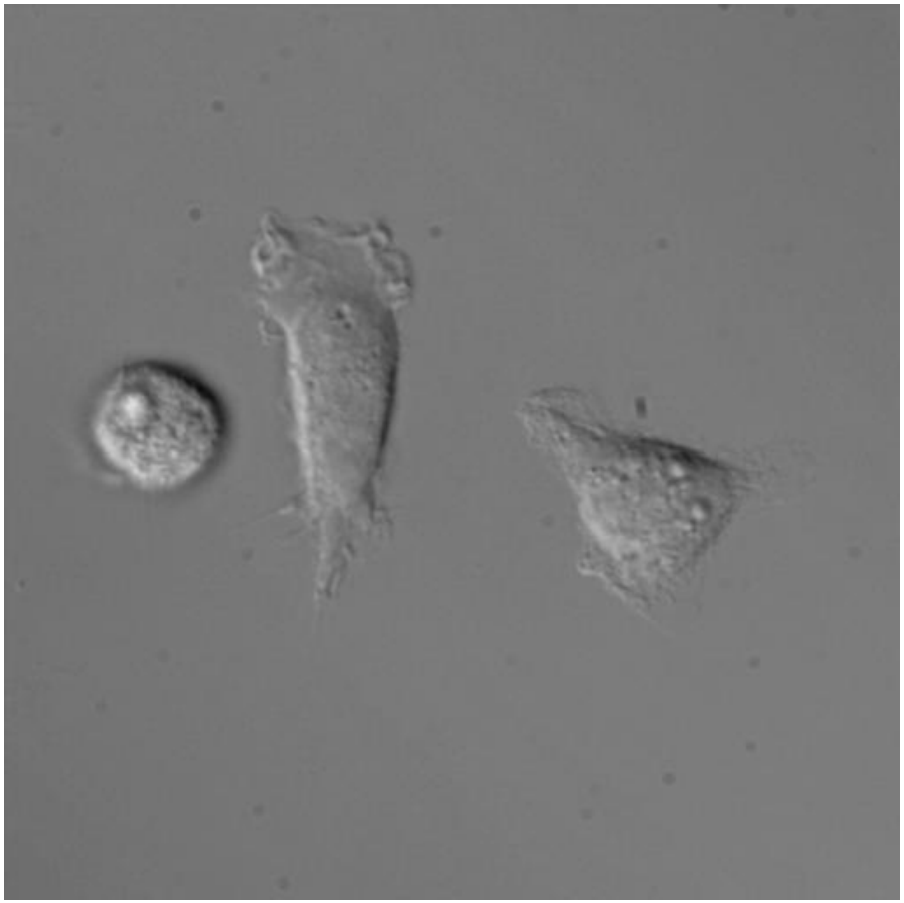
  (Rahaman, O. et al. J Biol Chem, 2011)

Time lapse microscopy to analyze macrophage cytoskeleton

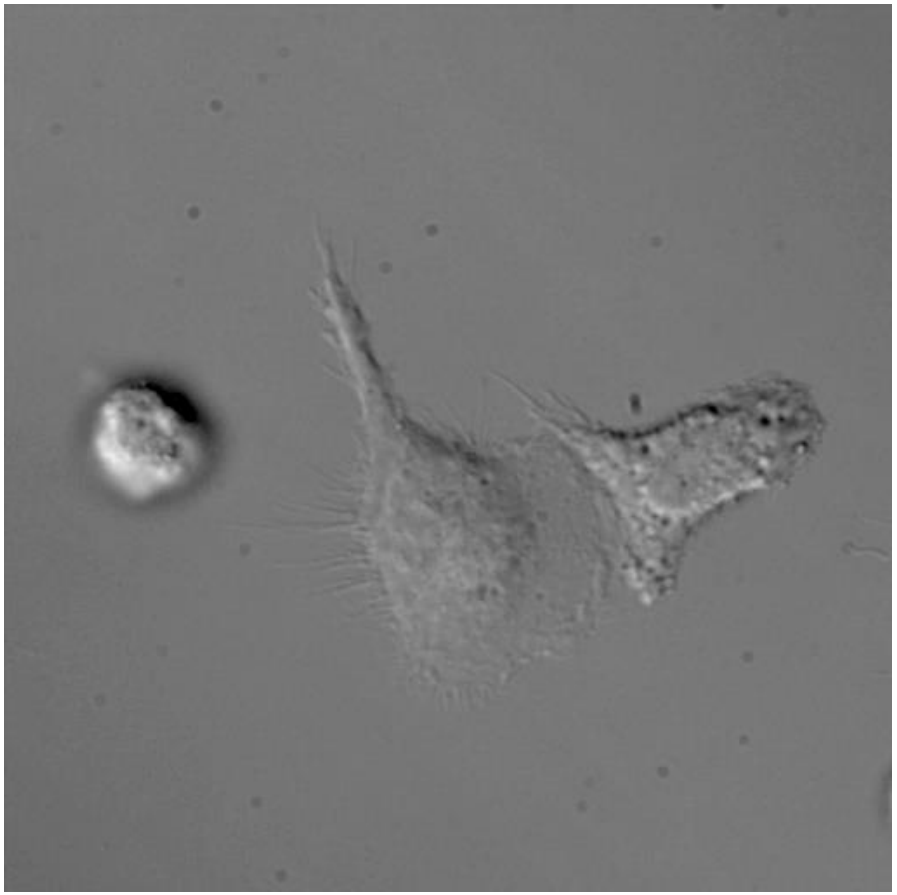
Peritoneal macrophages from wild type, CD36 null, and Vav null mice loaded onto glass coverslips



OxLDL induced loss of cell polarity with lamellipodial retraction, decreased locomotion and decreased dynamic movement

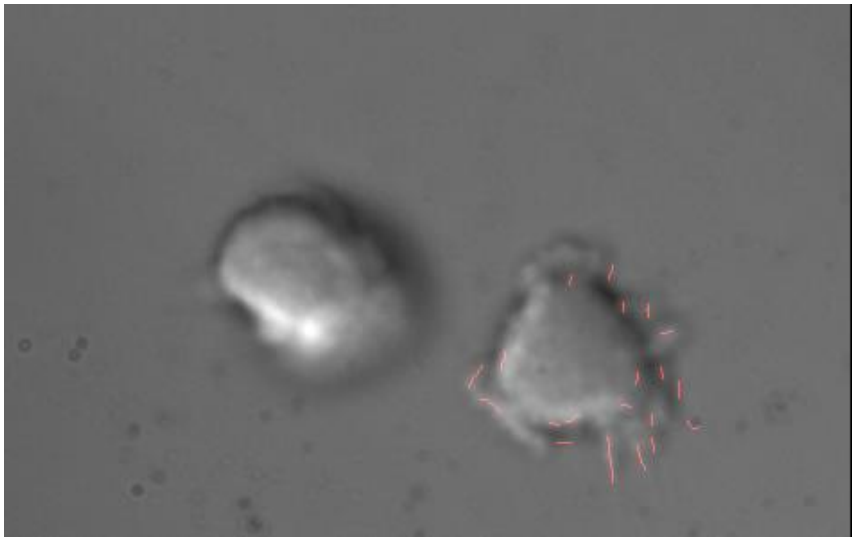


No Treatment



oxLDL

OxLDL effects on macrophage polarity depend on CD36



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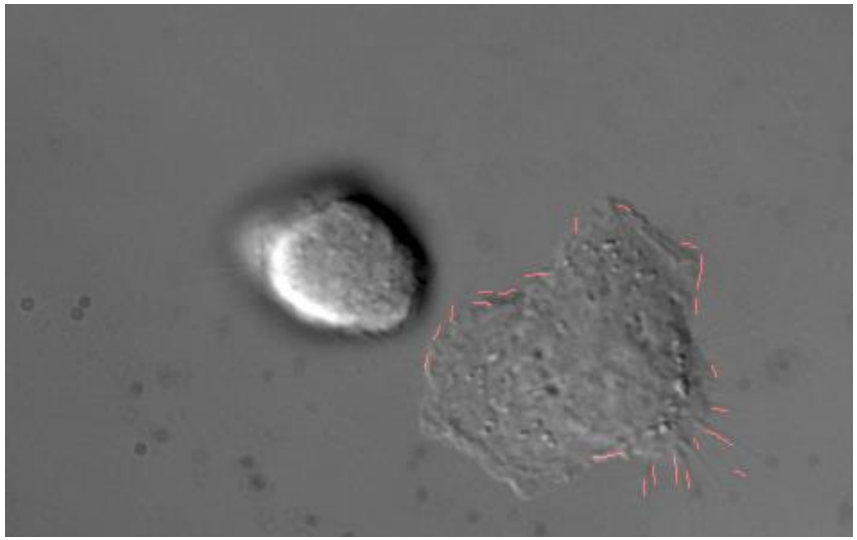


oxLDL

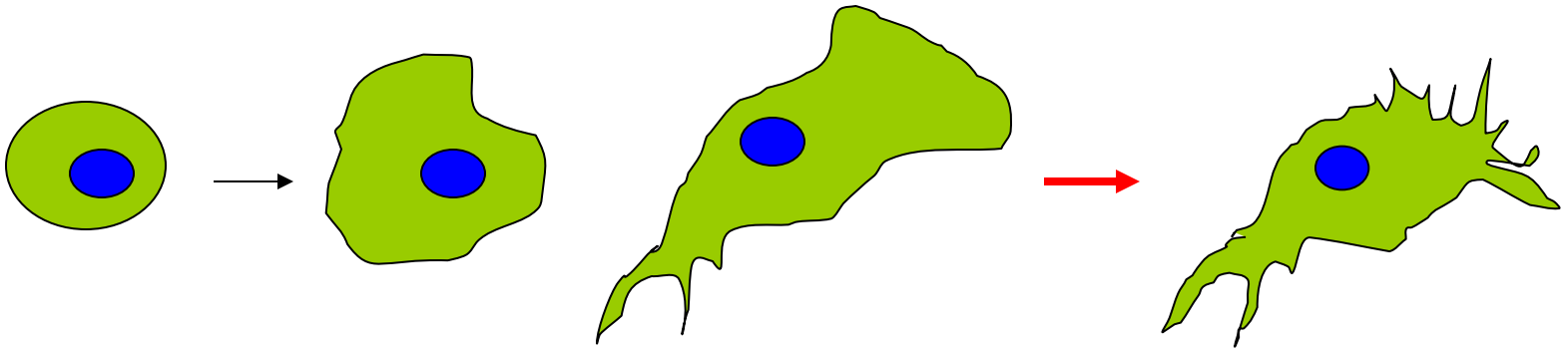
Summary
(Time lapse microscopy)

NO_2LDL → Lamellipodial retraction with retraction fiber formation

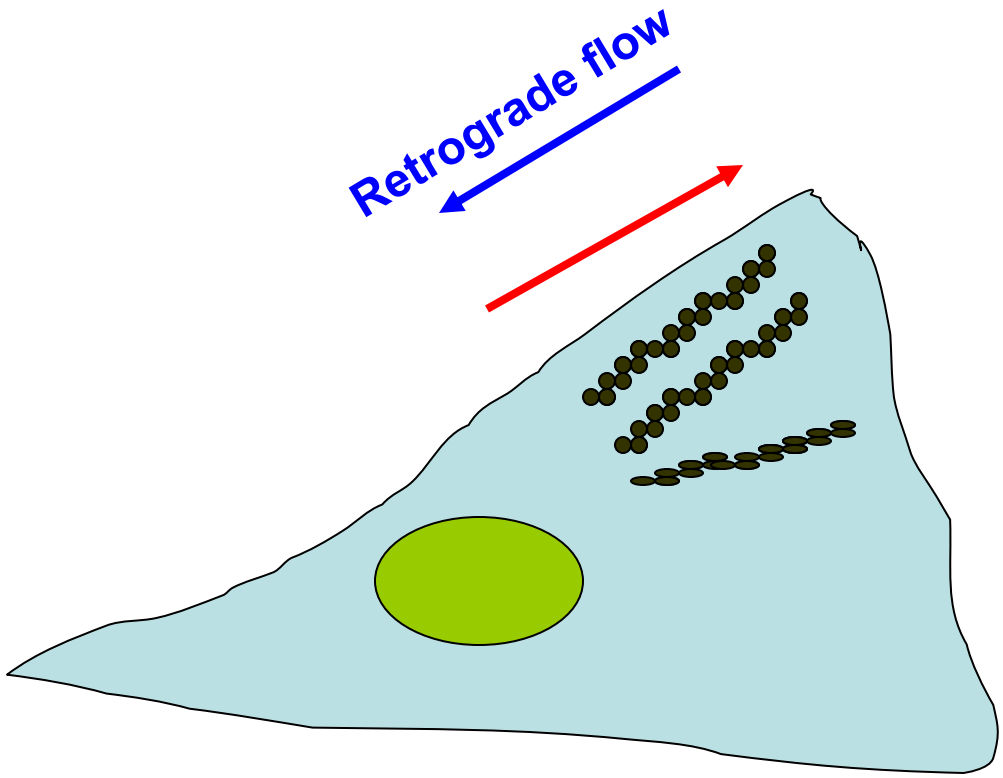
→ Loss of cell polarity

→ Inhibition of cellular locomotion/migration

These effects are CD36 and Vav dependent

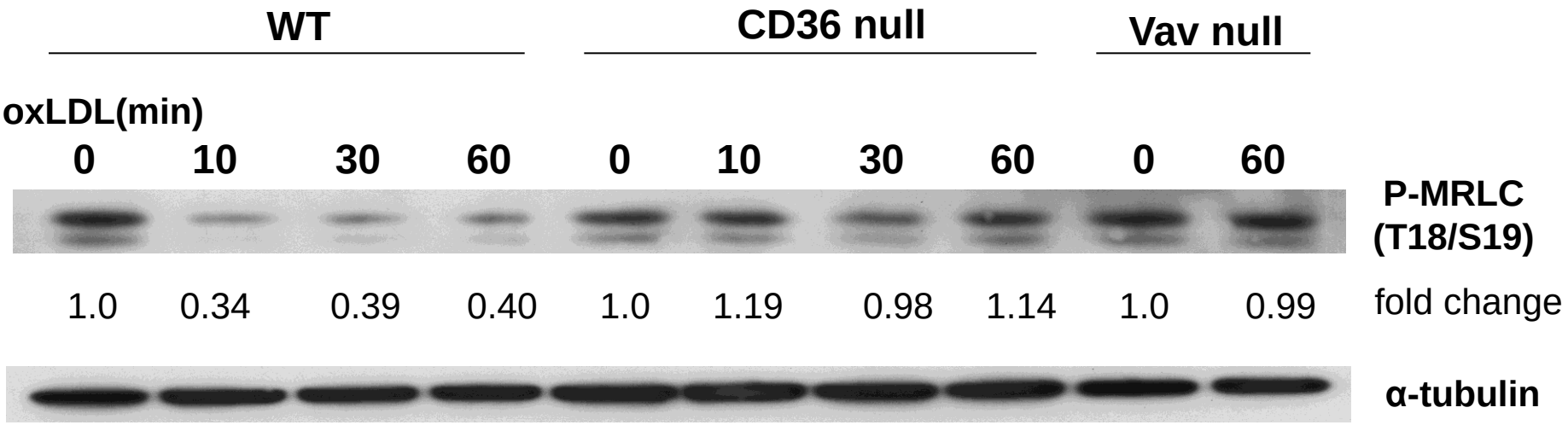


Non-Muscle Myosin II

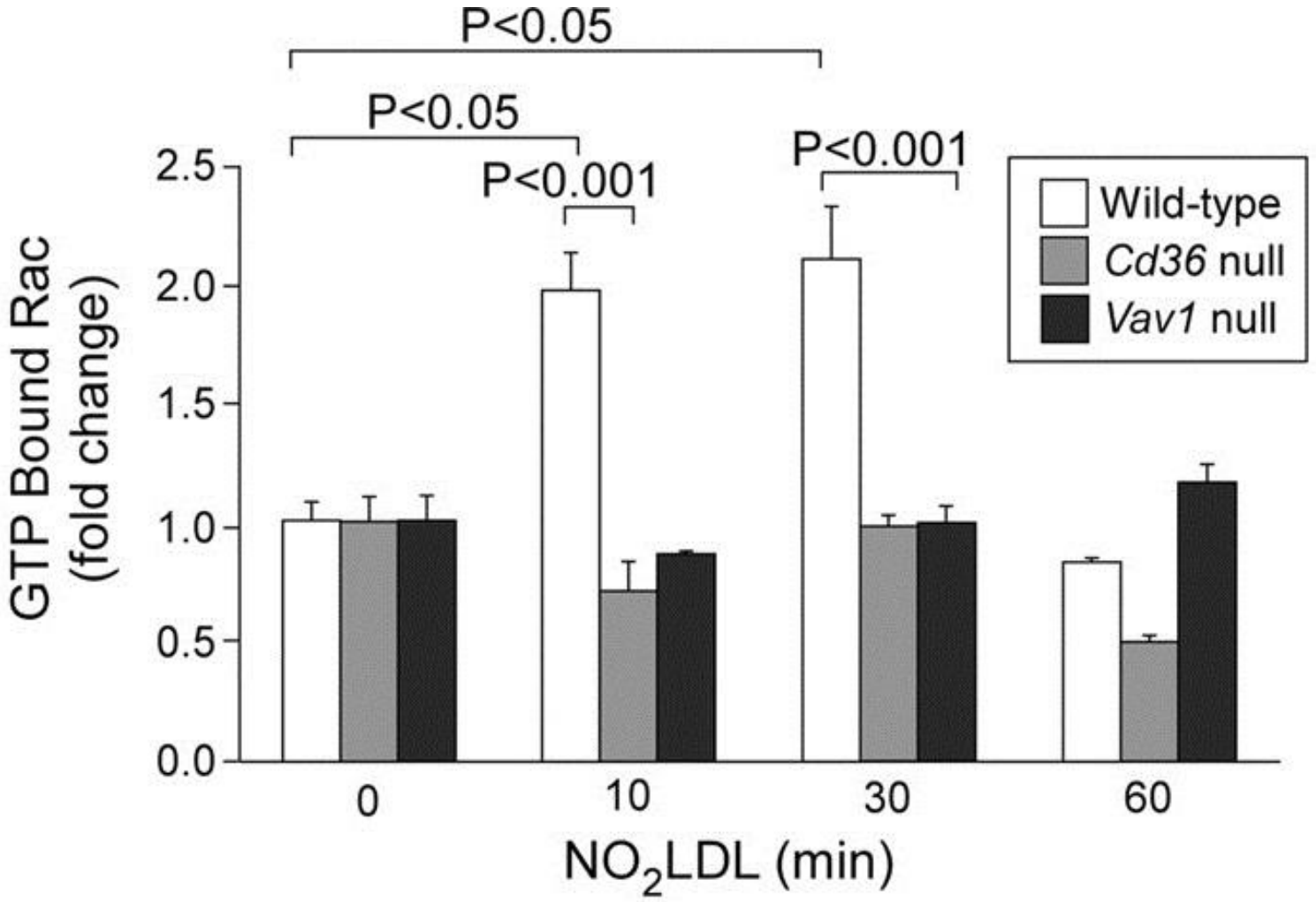


Cell polarity determinant

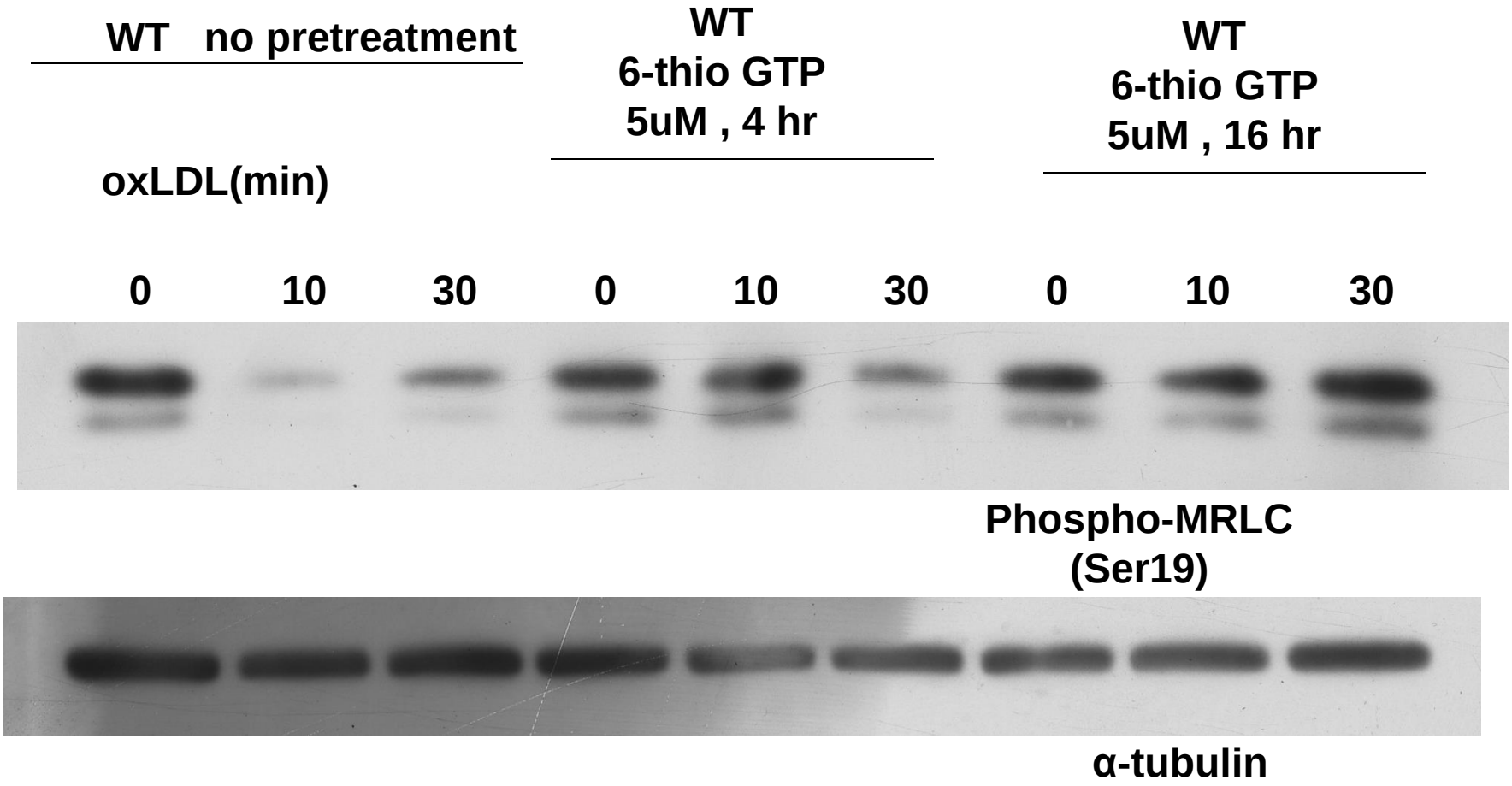
Myosin regulatory light chain phosphorylation is decreased by oxLDL (murine macrophage)



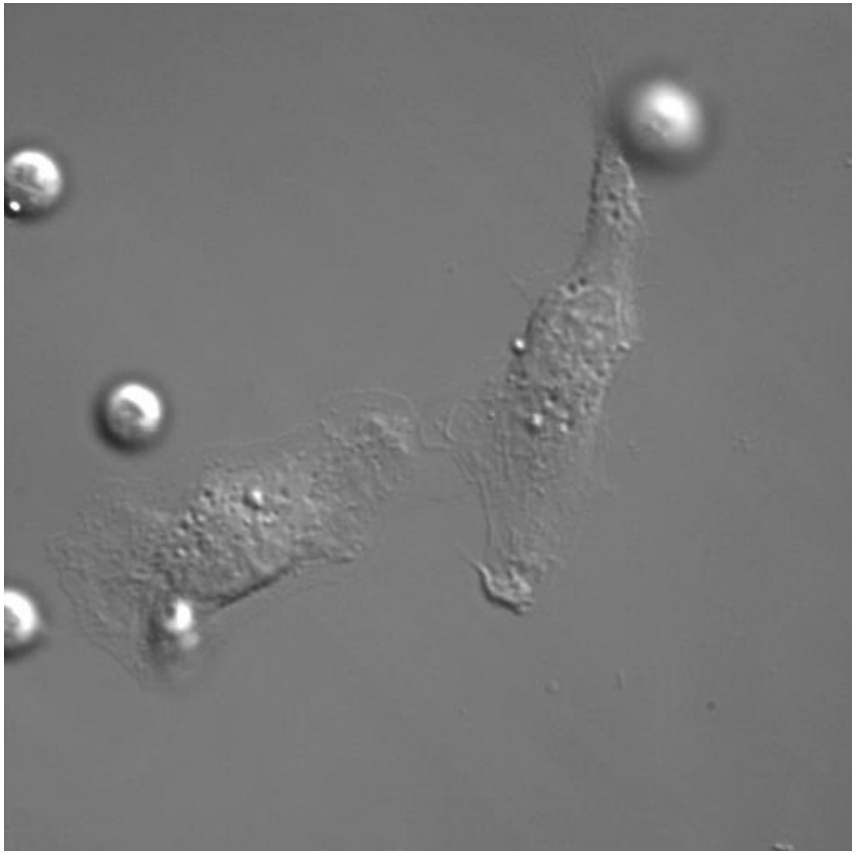
OxLDL induced activation of Rac1-GTPase



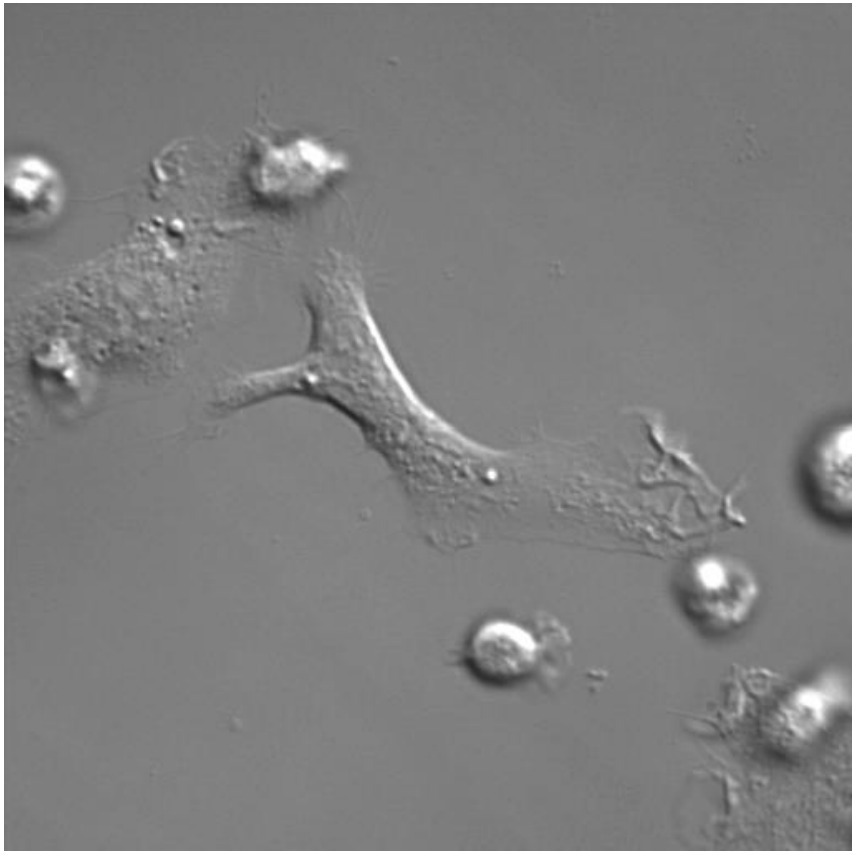
6-thio GTP inhibits MRLC dephosphorylation by oxLDL



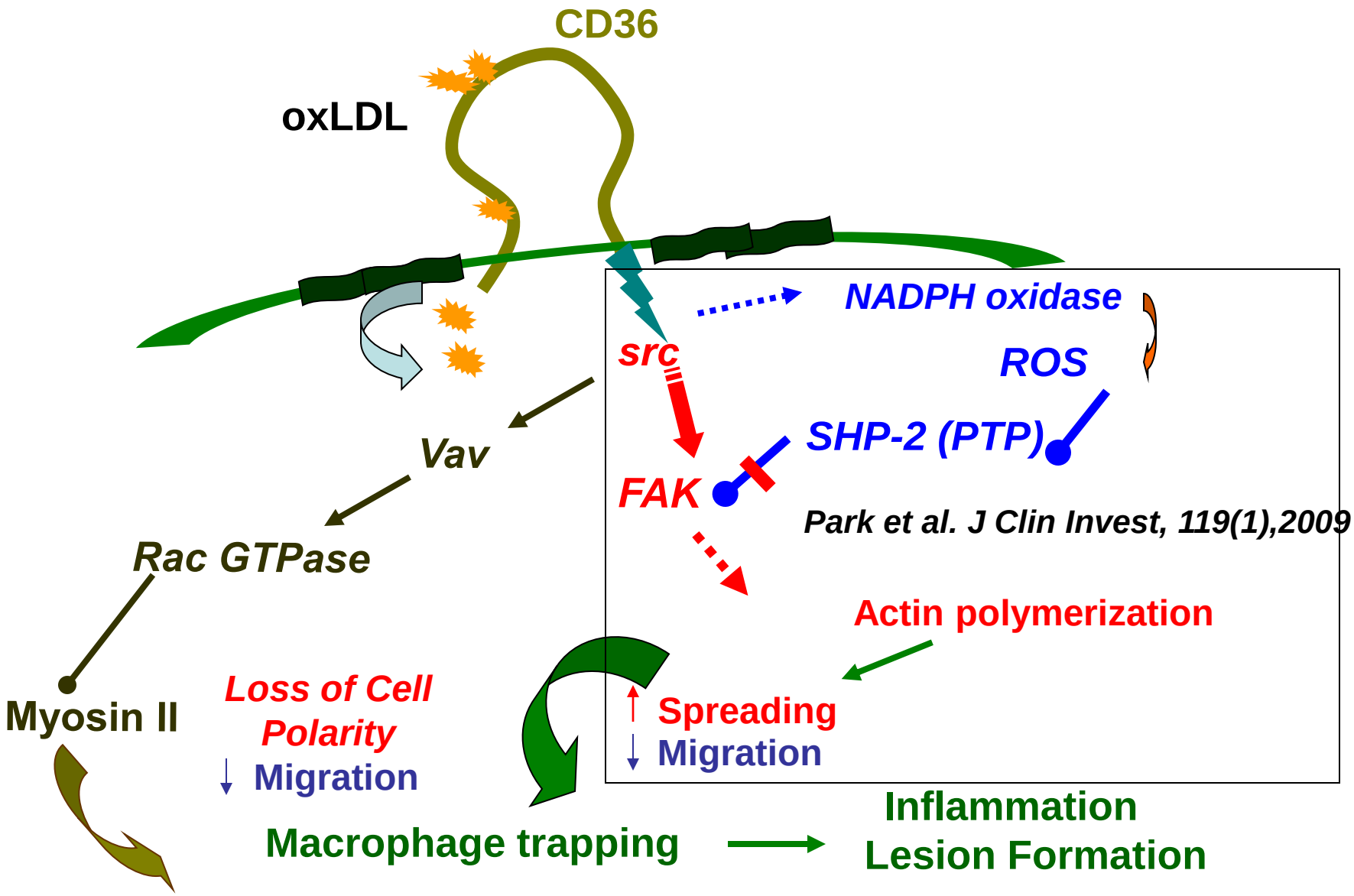
Rac inhibitor, 6-thio GTP blocks the effect of oxLDL



6-thio GTP/ No Tx

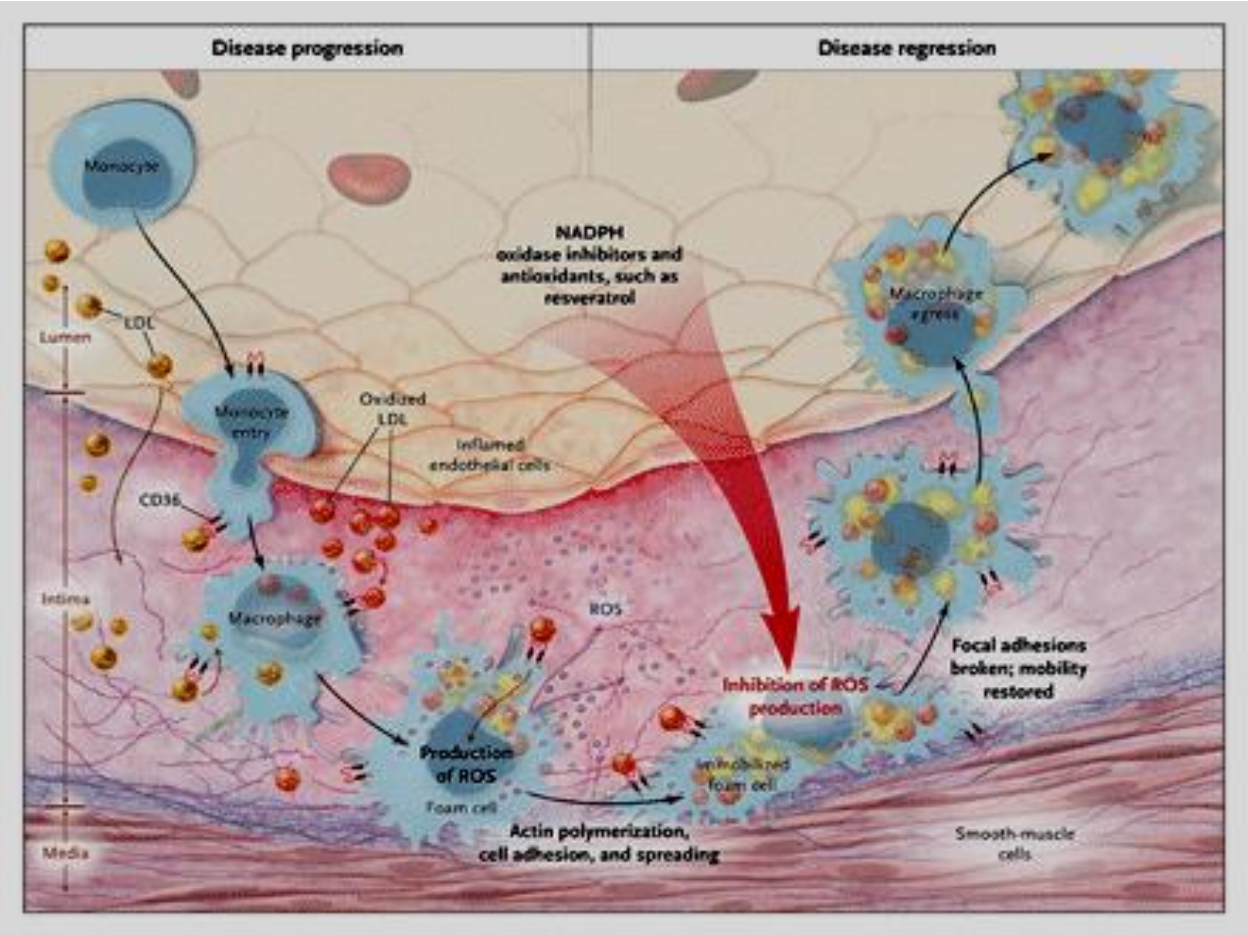


6-thio GTP/ oxLDL



Park et al. Mol Biol Cell, 23(16), 2012

Reversing Atherosclerosis



Linda Curtiss, Reversing Atherosclerosis?, NEJM vol. 360, 1144-1146, 2009

Understanding of the mechanisms of macrophage trapping as well as foam cell emigration may lead to development of novel strategies for the treatment of atherosclerosis

Acknowledgements

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