Modulation of Smooth Muscle Cell Proliferation in Atherosclerotic Plaque by CD98

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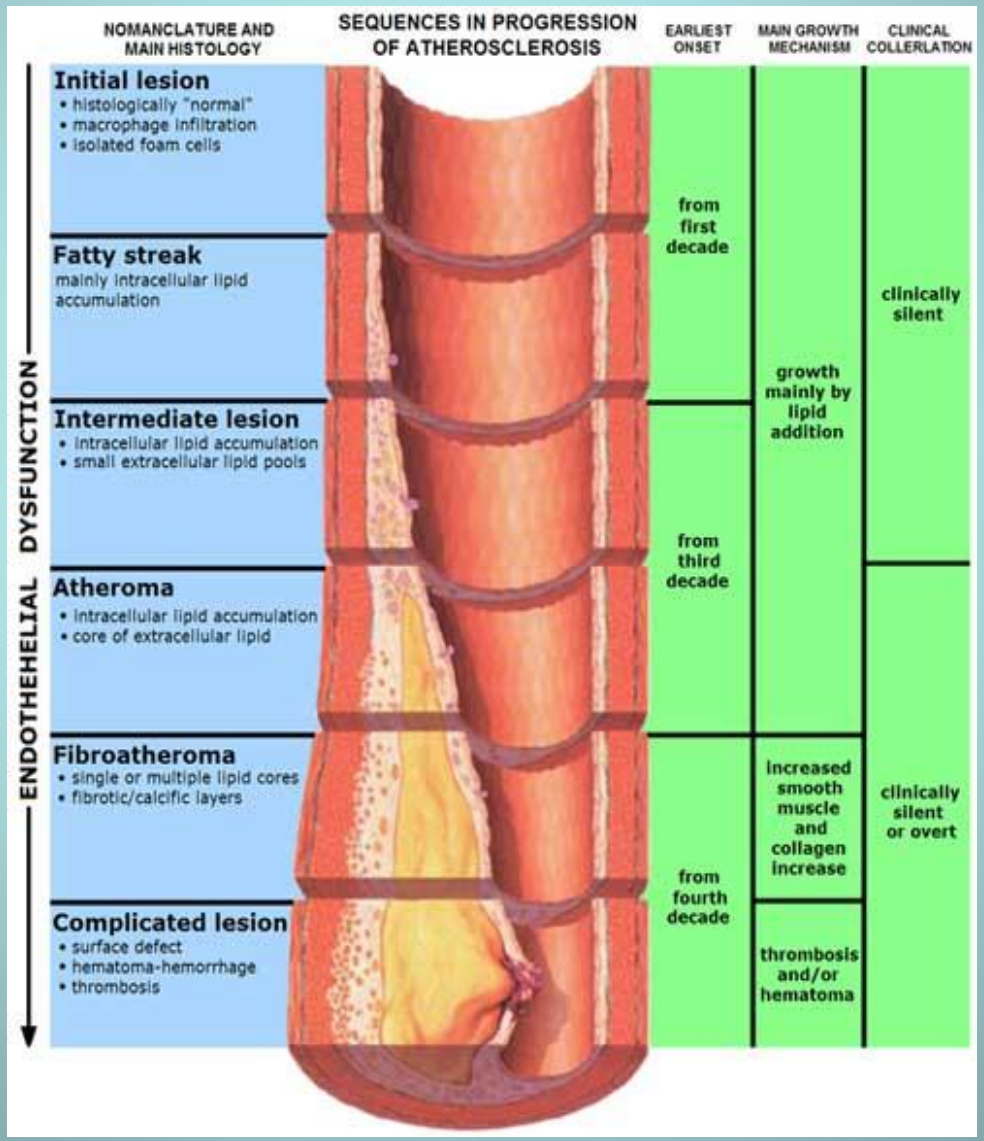
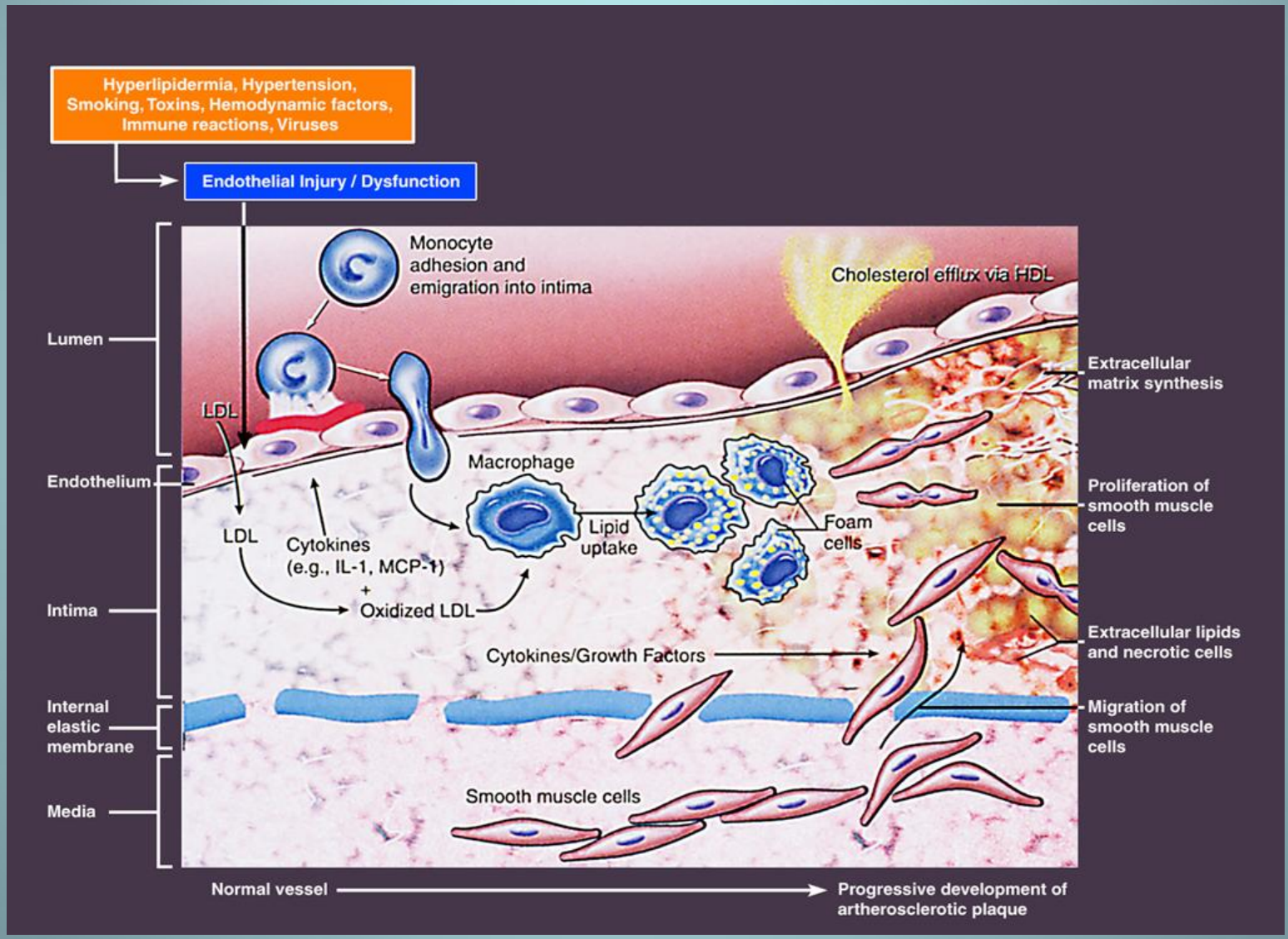
ATHEROSCLEROSIS IS A DISEASE OF INFLAMMATION AND HYPERLIPIDEMIA

- **Intimal thickening that progresses with time**
- **Mononuclear cell infiltrate consisting of monocyte-derived macrophages is very prominent during fatty streak formation**
- **The intimal macrophages and smooth muscle cells are cholesterol loaded**
- **T lymphocytes, natural killer cells and mast cells accumulate during later stages**
- **The plaque contains cholesterol crystals, necrotic core, fibrous cap (collagen fibers, extracellular matrix)**

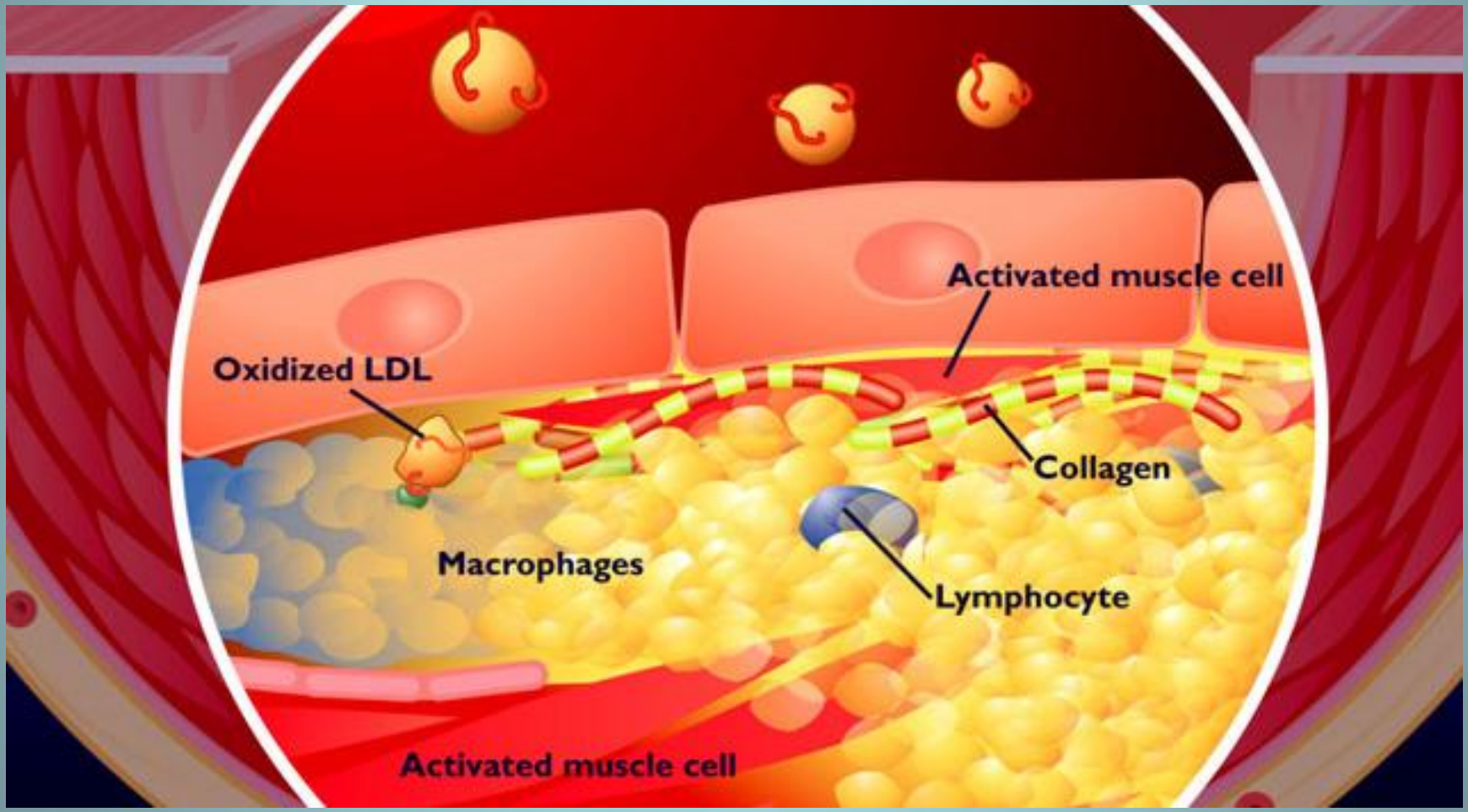
PROGRESSION OF ATHEROSCLEROSIS



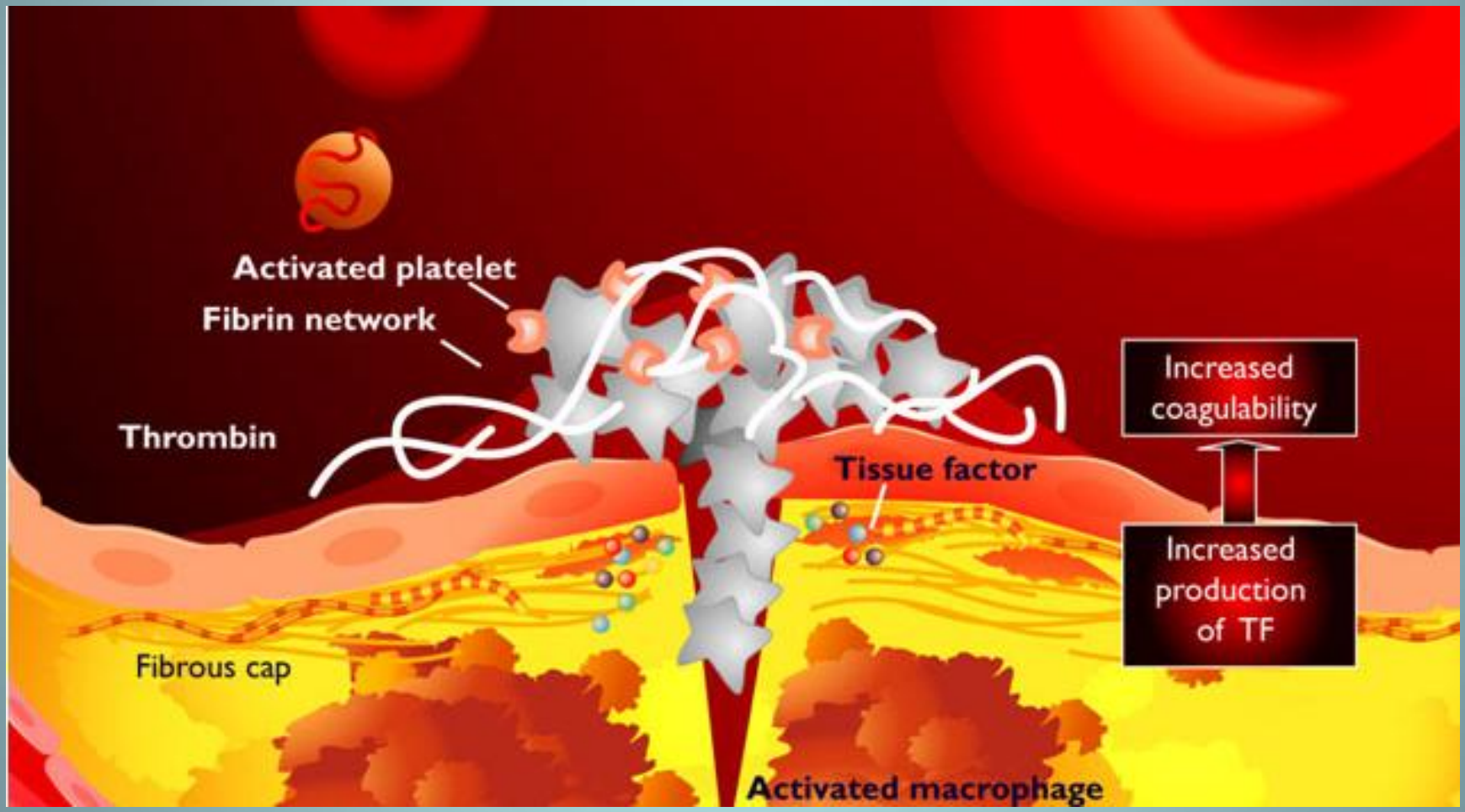
DEVELOPMENT OF ATHEROSCLEROSIS



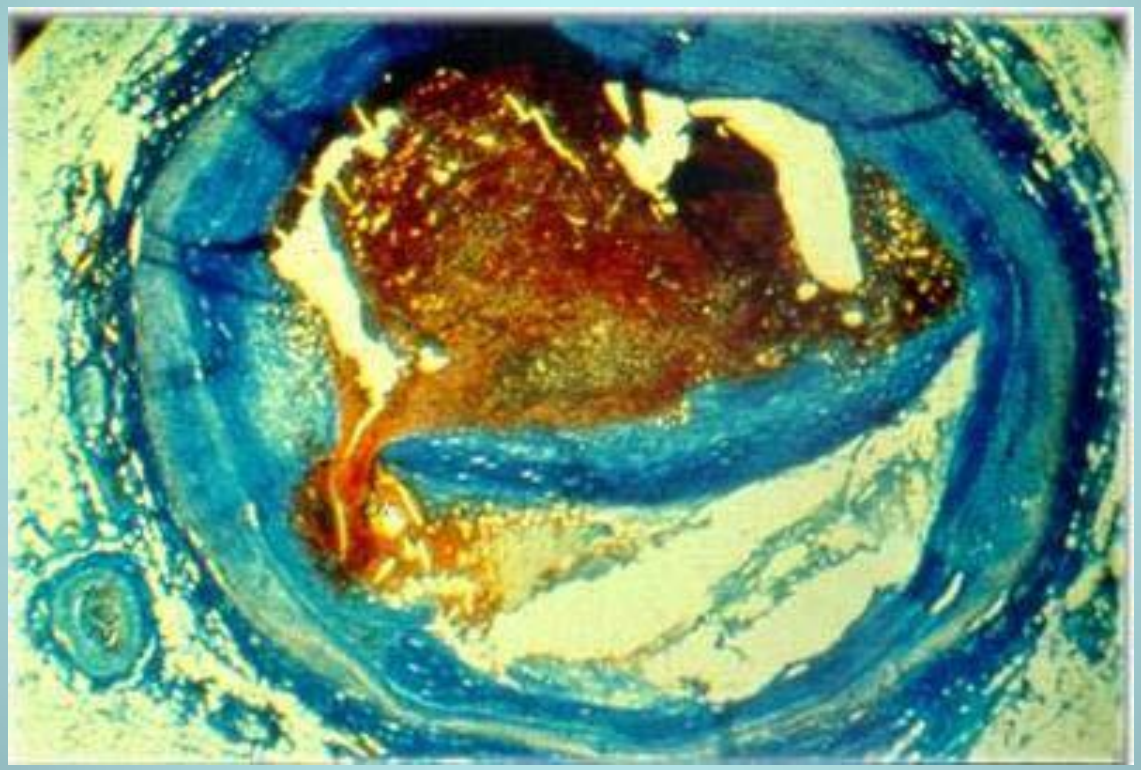
FORMATION OF THE FIBROUS CAP



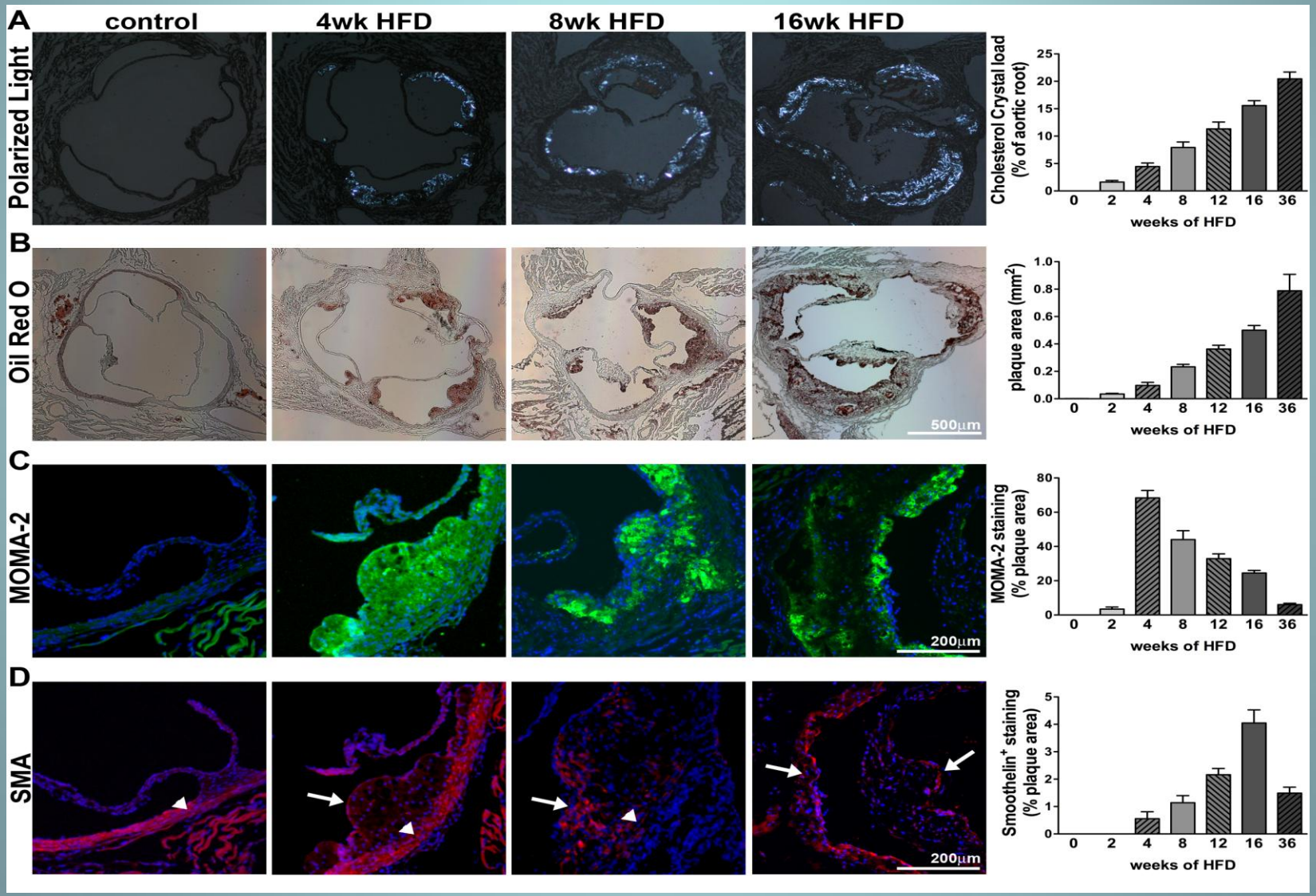
WEAKENED FIBROUS CAP CAN LEAD TO THROMBUS FORMATION



RUPTURED HUMAN ATHEROSCLEROTIC PLAQUE



MORPHOLOGICAL CHANGES OF DEVELOPING ATHEROSCLEROSIS



BACKGROUND INFORMATION: VSMC

- VSMCs exist as 2 main phenotypes:
  - Contractile or differentiated VSMC (vasodilation, vasoconstriction, regulation of blood flow)
  - Synthetic, migratory, proliferative phenotype (intimal vascular lesion formation)

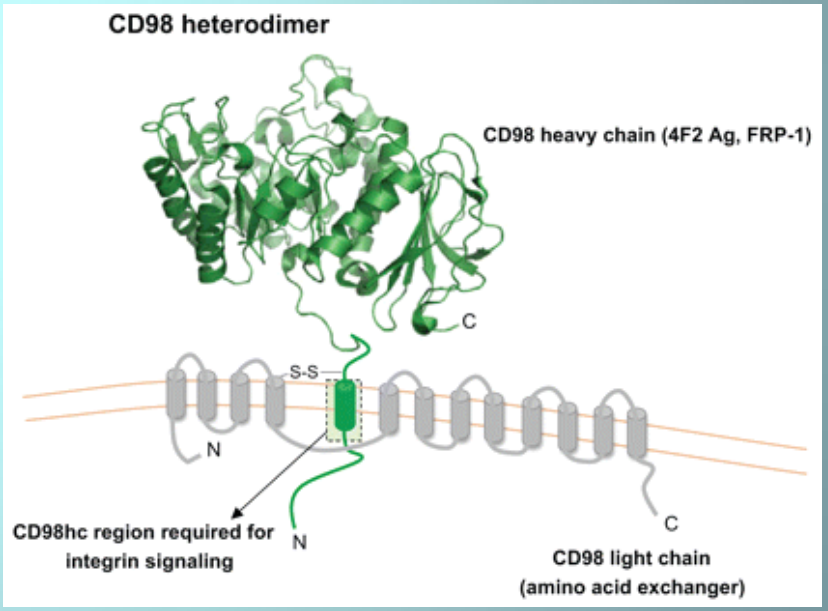
- SMC in lesion are believed to derive from residential medial SMC that undergo phenotypic modulation and migration into intima, where they proliferate, produce ECM and help to form fibrous cap
  - After injury EC, platelets and inflammatory cells produce growth factors and cytokines that alter the phenotype of VSMCs
  - Extracellular ligands bind cell-surface receptors to stimulate VSMC migration, proliferation but also apoptosis and necrosis
    - PDGF is considered to be very important for this process

- SMC as a part of the fibrous cap is associated with plaque stability

BACKGROUND INFORMATION: CD98

- CD98 is a heterodimer of a heavy chain associating with one of several light chains composed of multiple membrane-spanning domains
- CD98 heterodimer functions as an amino acid transporter

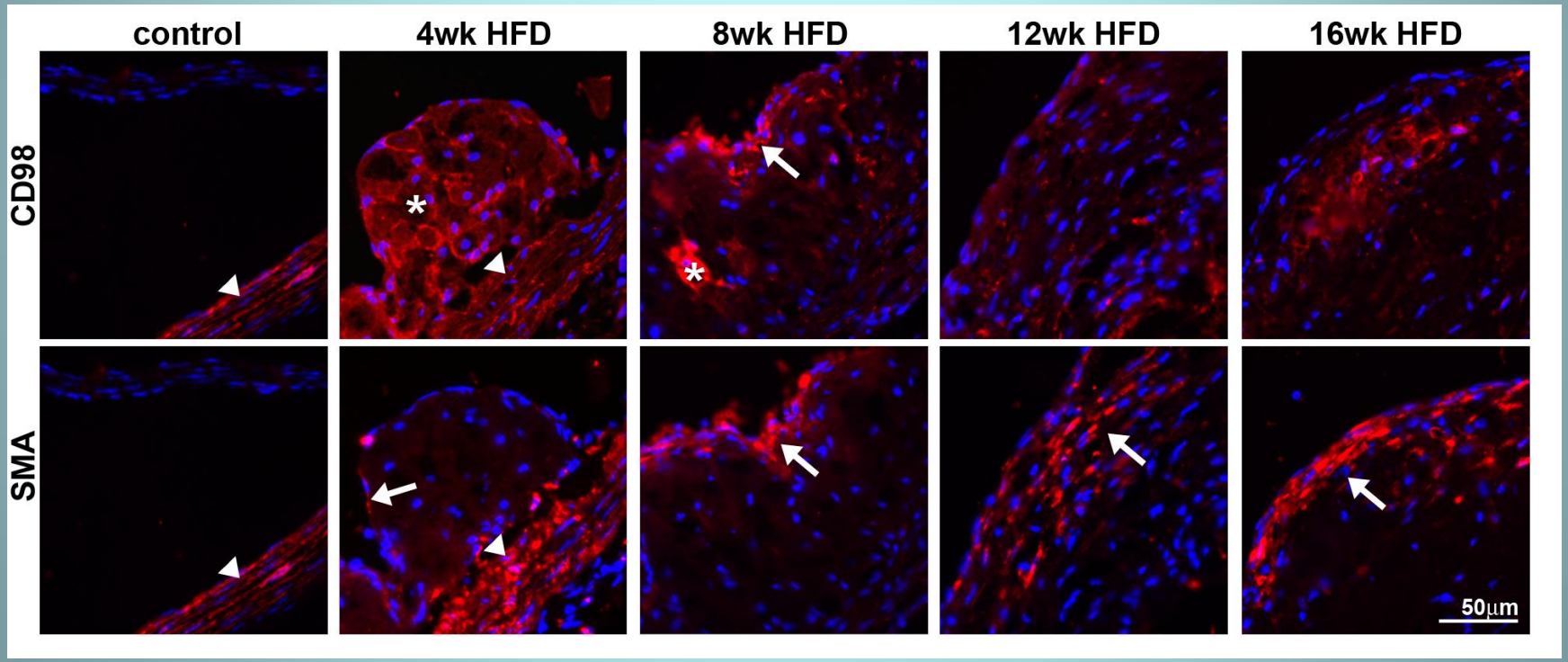
- CD98hc interacts mainly with beta-1 and beta-3 integrins mediating survival, proliferation, migration and even malignant transformation by regulating signaling via FAK, AKT, Src, Rho/Rac, Ras
- Inhibits T-cell proliferation/differentiation (Colitis, Diabetes)
- In Keratinocytes expression over age decreased in highly dividing cells
- SMC knockout of CD98 leads to reduced neointima formation after vascular wire injury



Cantor J M , and Ginsberg M H J Cell Sci 2012;125:1373-1382

EXPRESSION OF CD98 IN DEVELOPING ATHEROSCLEROSIS

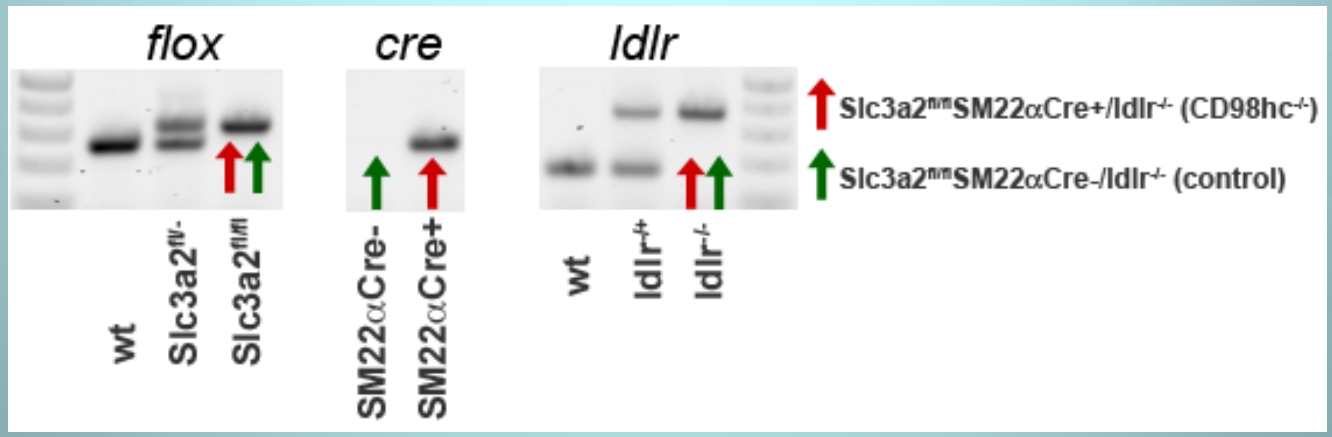
CD98 expression in atherosclerotic plaque:



VERIFICATION OF CD98 AND LDL-R DEFICIENCY

Mouse model

To investigate the role of CD98 expression in SMC on the development of atherosclerosis Slc3A2$^{flox/flox}$ mice crossed with SM22αCre mice were crossed with LDL-R$^{-/-}$ mice



STUDY SCHEME

Atherogenic
diet #94059
(Harlan Teklad)

6 WK Male CD98-/-
LDLR-/- and CD98+/+
LDLR-/- mice

15.8% wt/wt fat
1.25% wt/wt cholesterol

Sacrifice

WK -6

WK 0

WK 8

WK 16

Mice born

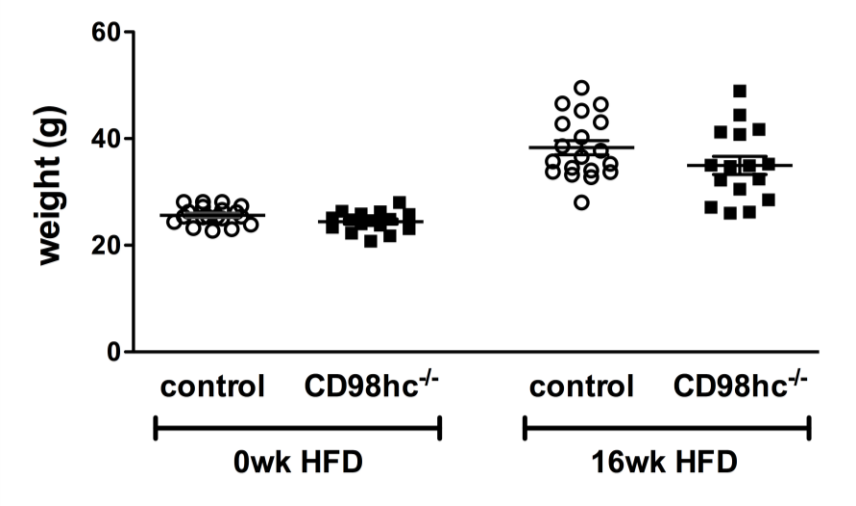
Bleed

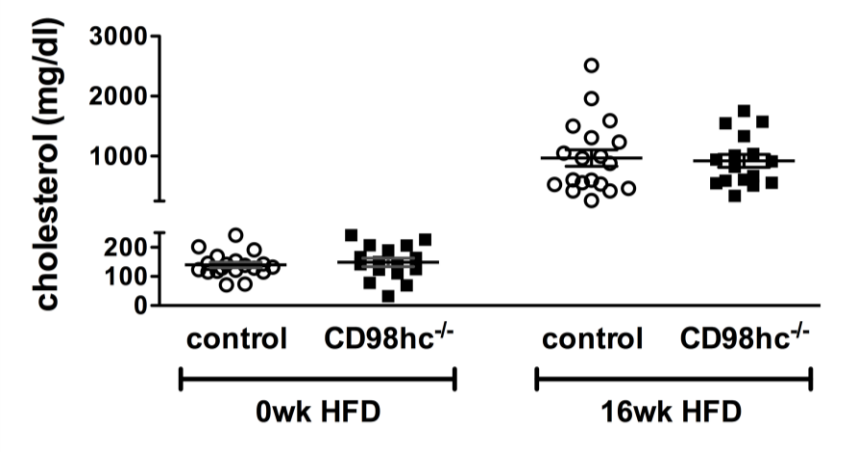
Bleed

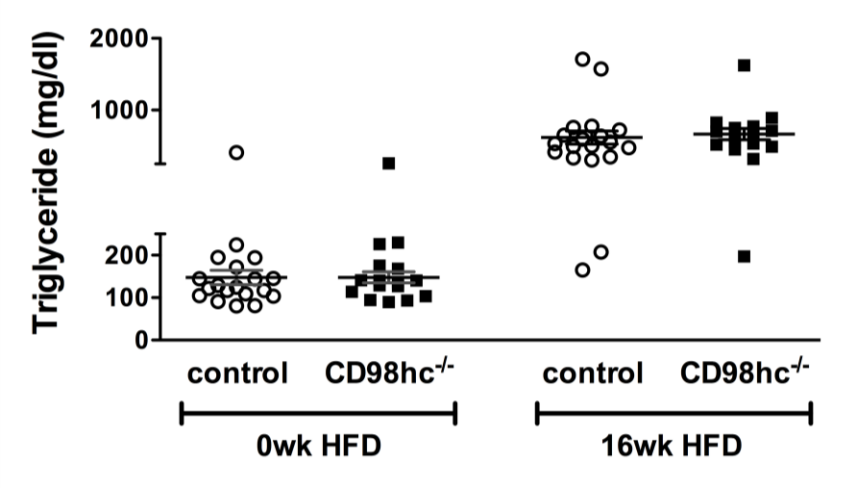
Bleed

WEIGHT AND LIPID LEVELS

16 week atherosclerosis study

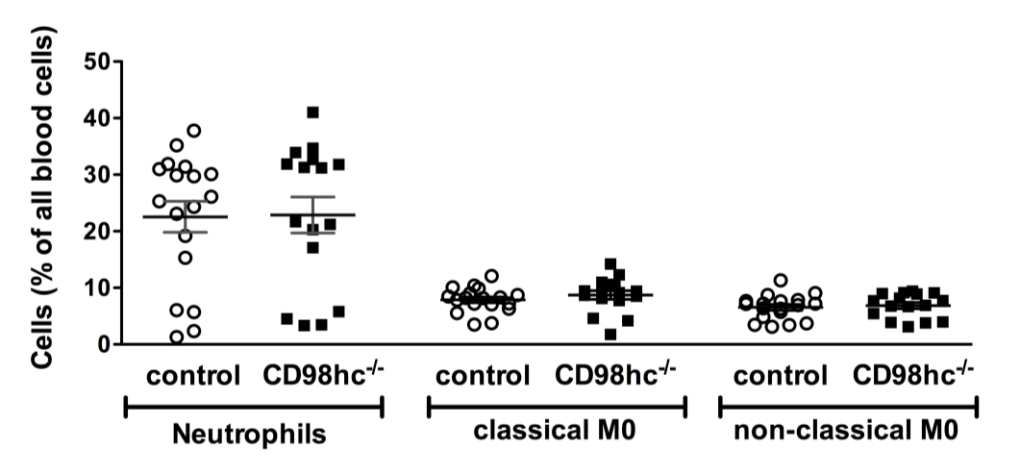


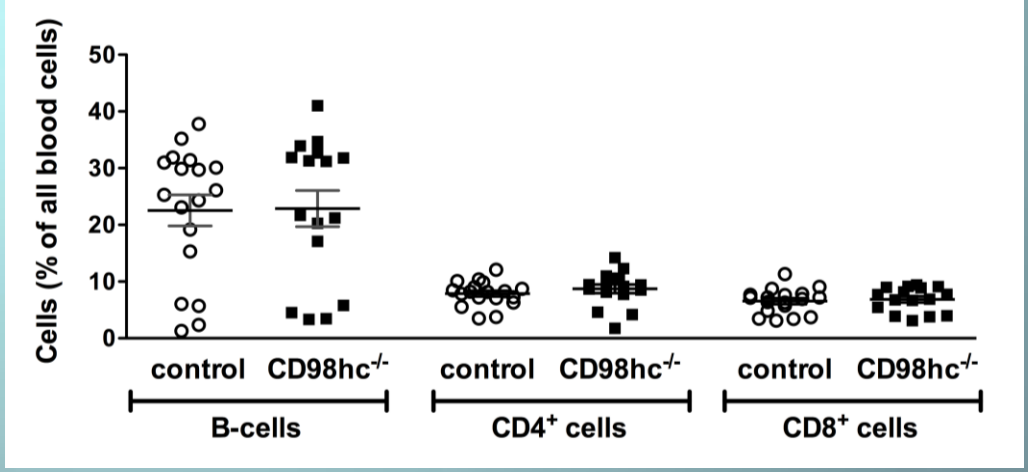




CIRCULATING LEUKOCYTES IN THE MICE

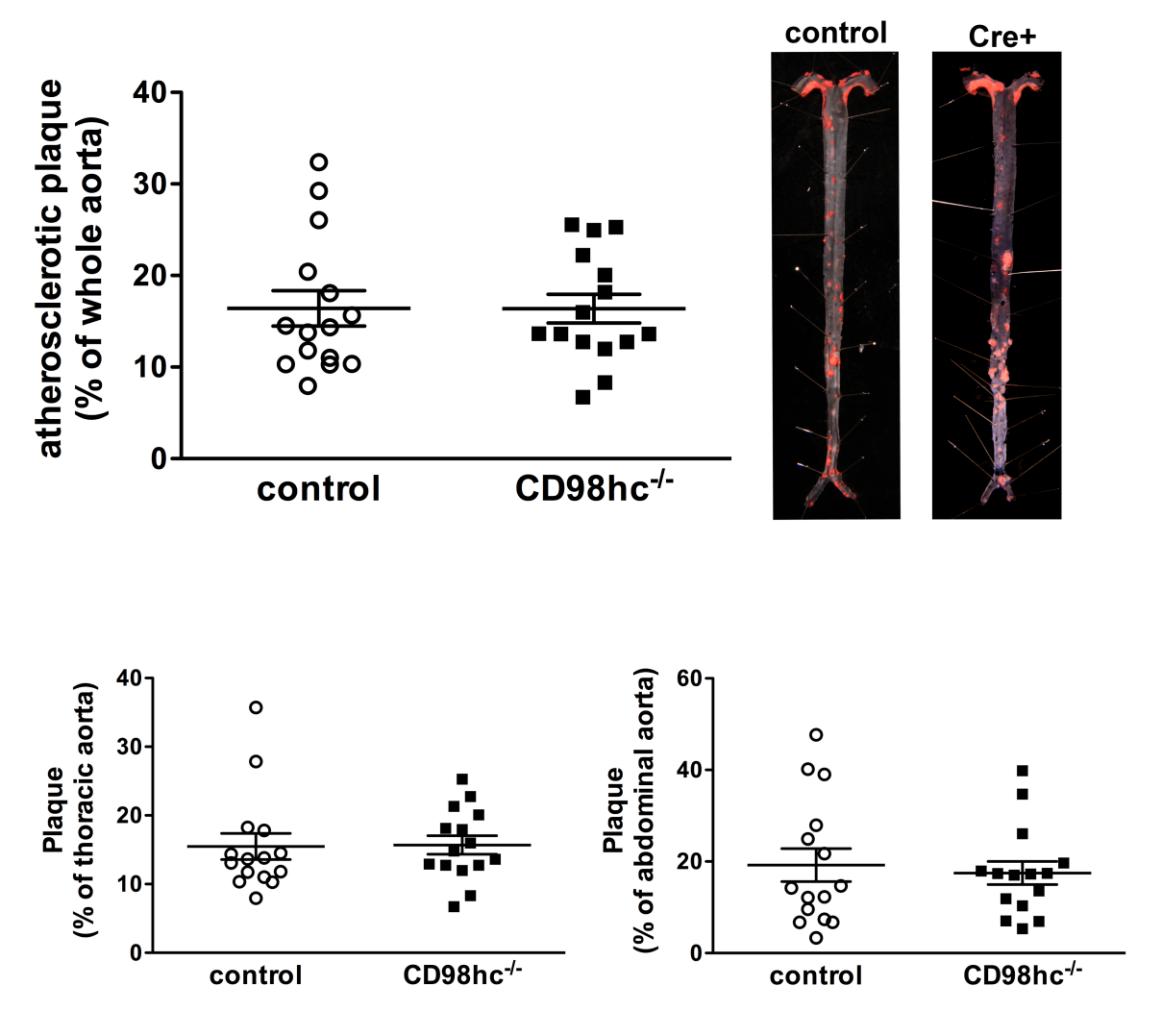
16 week atherosclerosis study





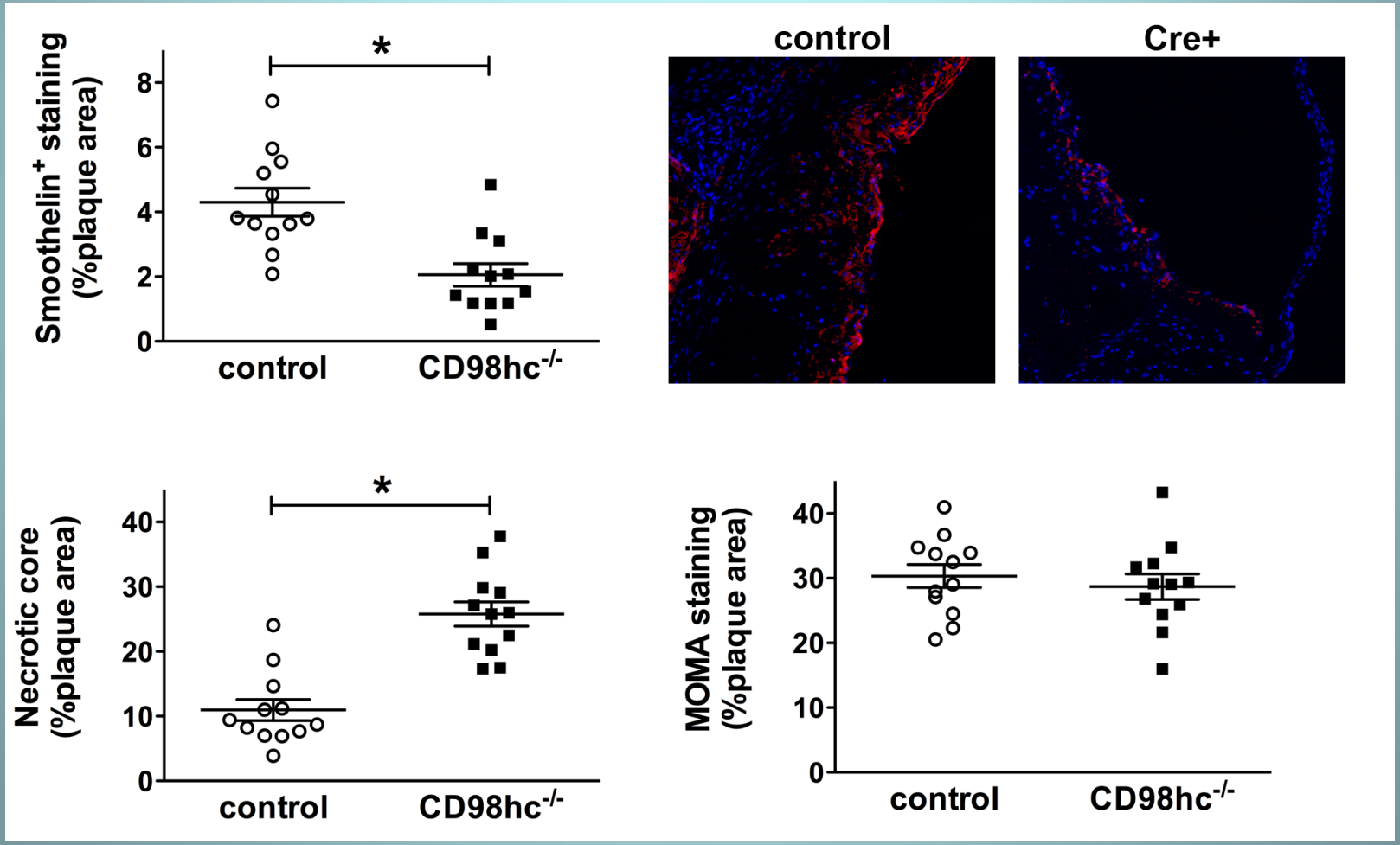
EXTENT OF ATHEROSCLEROSIS IN THE AORTA

16 week atherosclerosis study



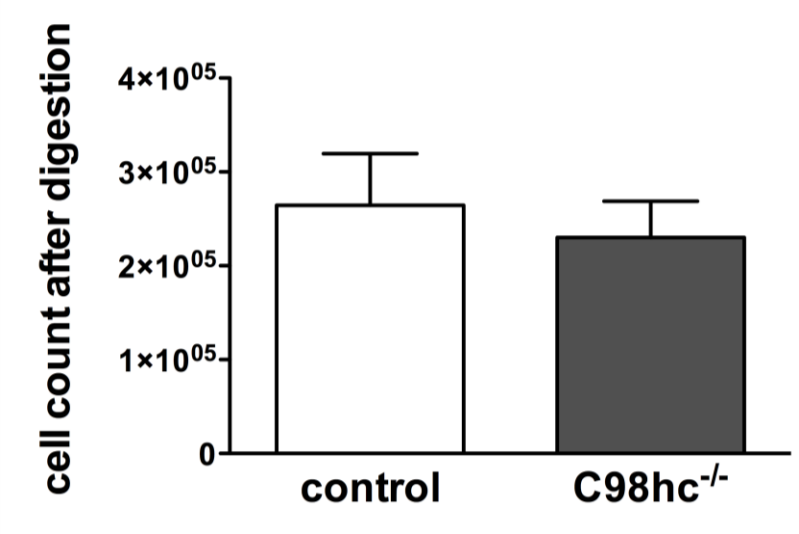
CELLULAR COMPOSITION OF PLAQUES

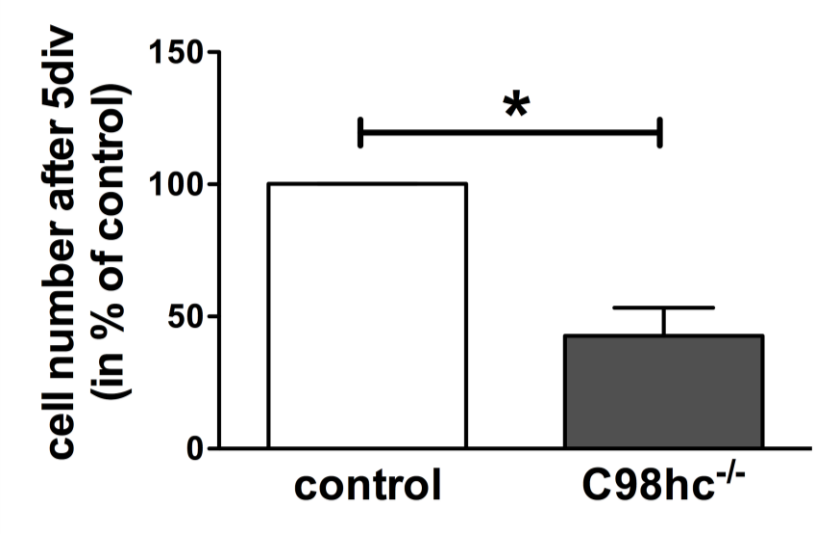
16 week atherosclerosis study



RETARDED PROLIFERATION OF CD98-/- VSMC

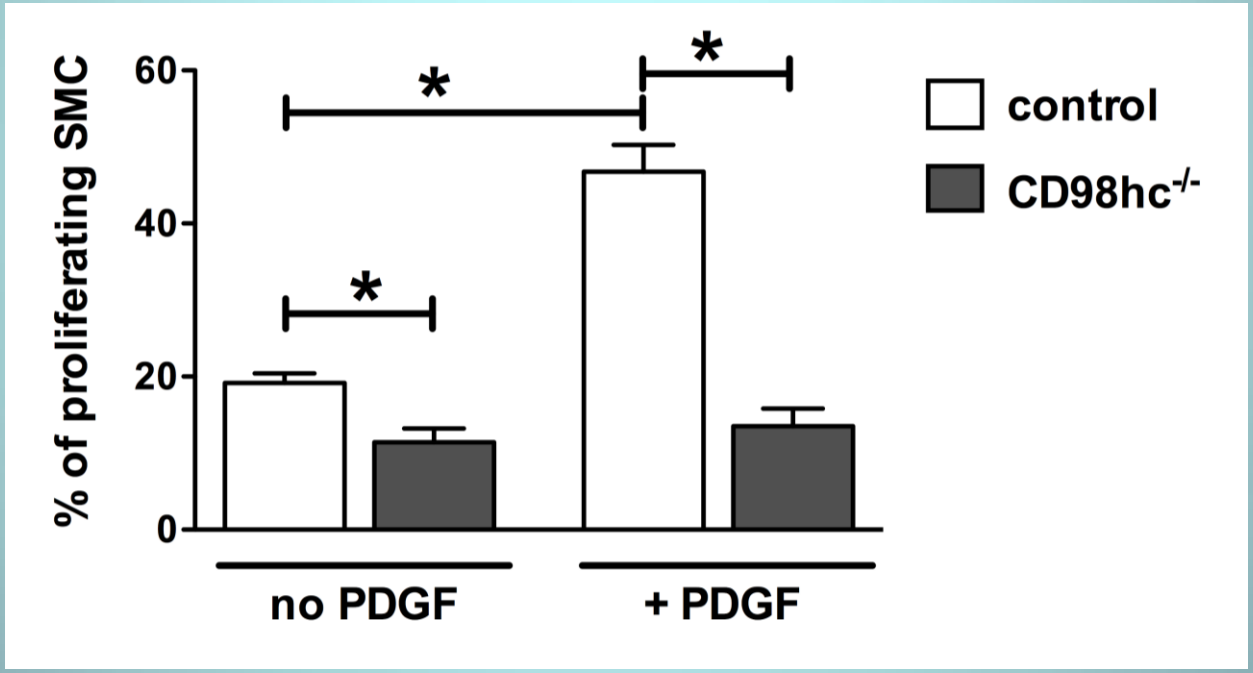
In vitro proliferation experiments:





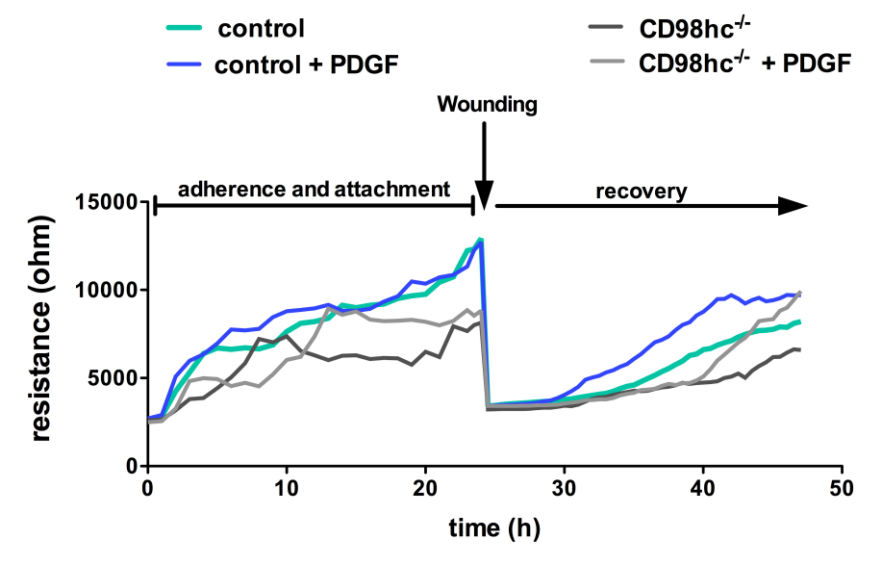
PROLIFERATIVE CHARACTERISTICS OF CD98-/- VSMC

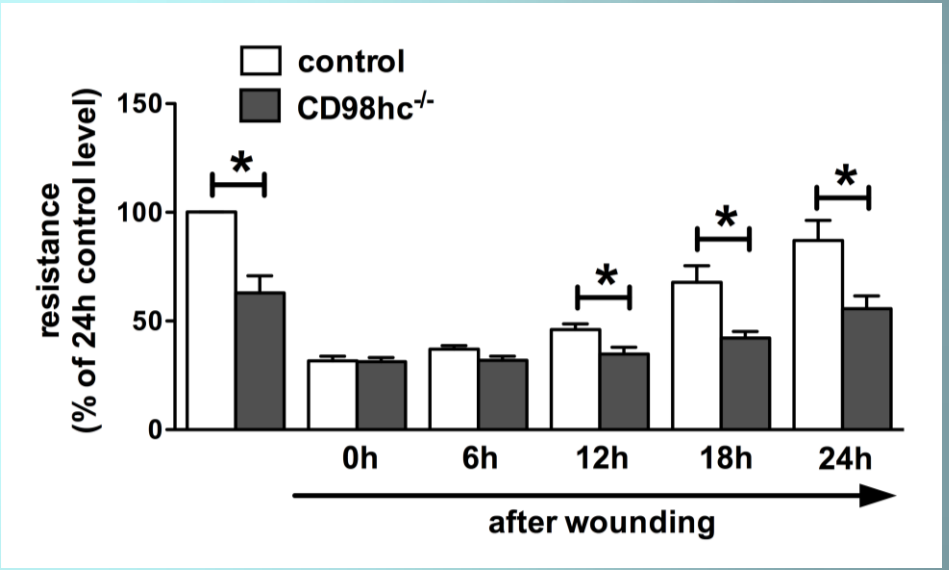
In vitro proliferation - EdU:



PROLIFERATIVE CHARACTERISTICS OF CD98-/- VSMC

In vitro proliferation - ECIS:





SUMMARY

- SMC-CD98hc$^{-/-}$ does not affect cholesterol or triglyceride levels or blood cell composition
- SMC-CD98hc$^{-/-}$ does not affect the extent of atherosclerosis
- SMC-CD98hc$^{-/-}$ does have an effect on atherosclerotic plaque composition due to impaired proliferation of CD98hc$^{-/-}$ SMCs

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Mahalo!

TRANSMISSION ELECTRON MICROSCOPIC IMAGES OF DEVELOPING PLAQUE