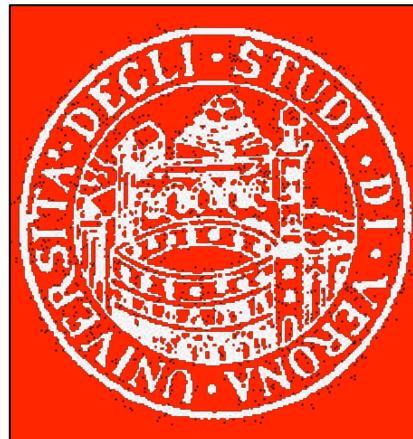


STRESS OSSIDATIVO ED ARTERIOSCLEROSI: RECENTI ACQUISIZIONI

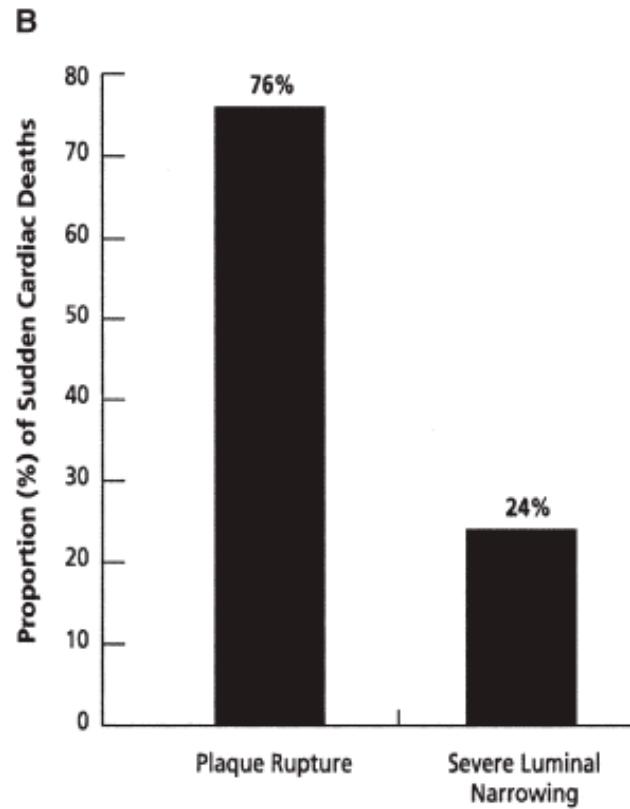
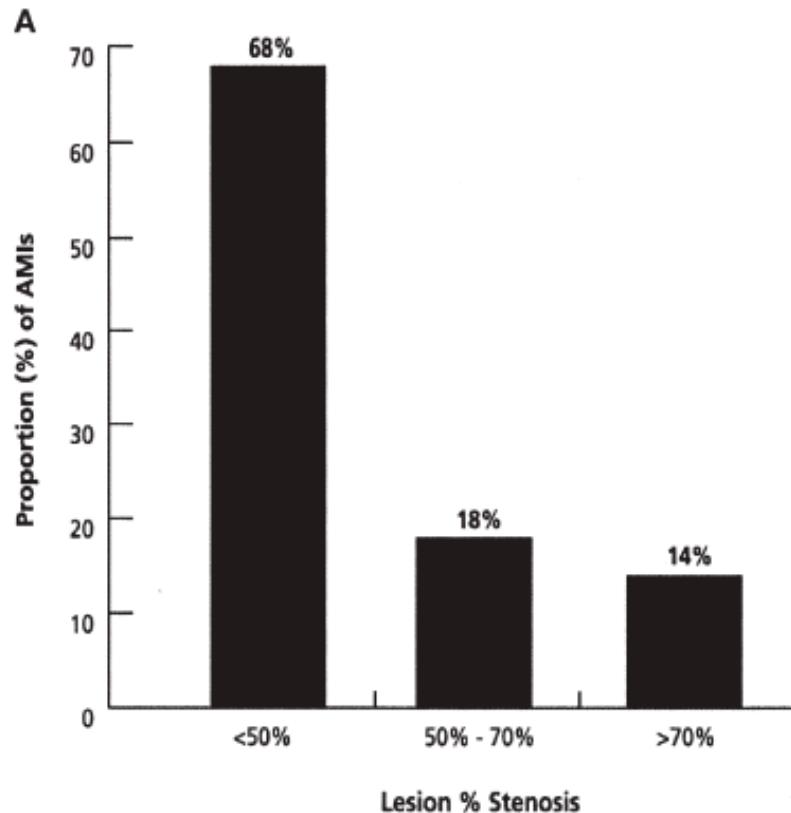
Luciano Cominacini

Dipartimento di Medicina

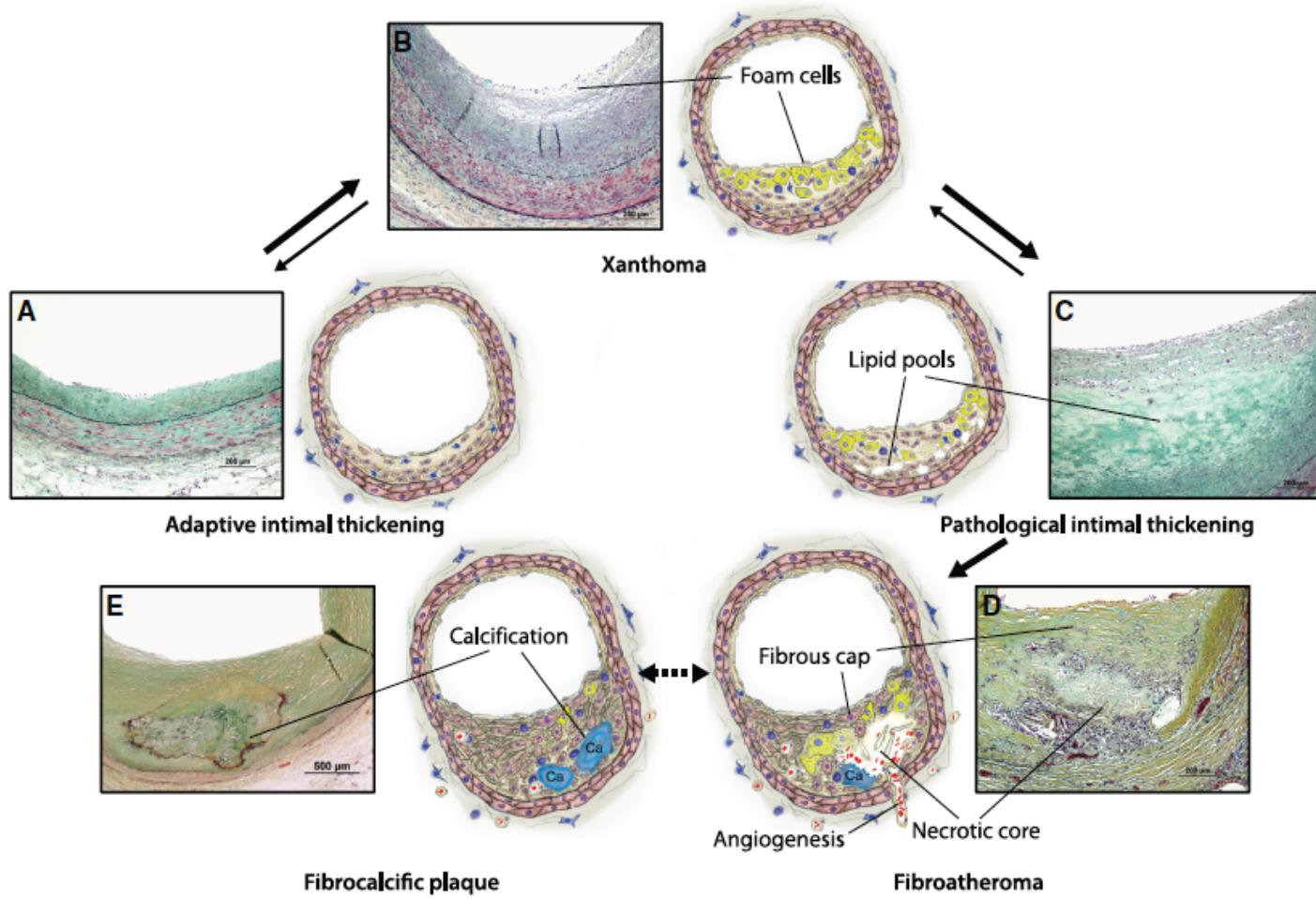
UOC di Medicina Generale e Malattie Aterotrombotiche e Degenerative
Università di Verona



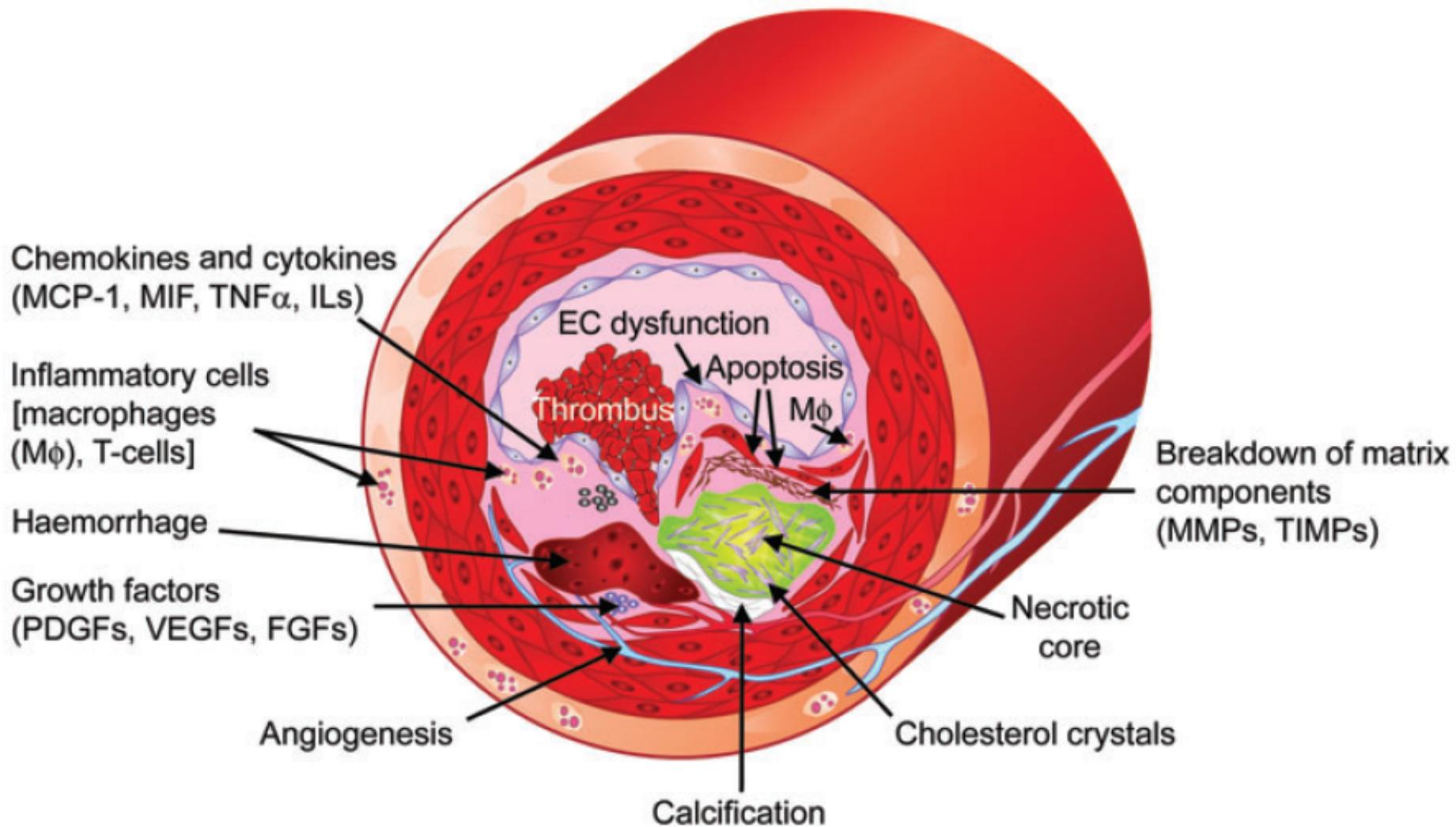
Most acute myocardial infarction present with <50% stenosis and most sudden cardiac deaths are related to thin, fibrous cap and rupture-prone plaques



LESION TYPES OF ATHEROSCLEROSIS AND A PROPOSED SEQUENCE OF THEIR DEVELOPMENT

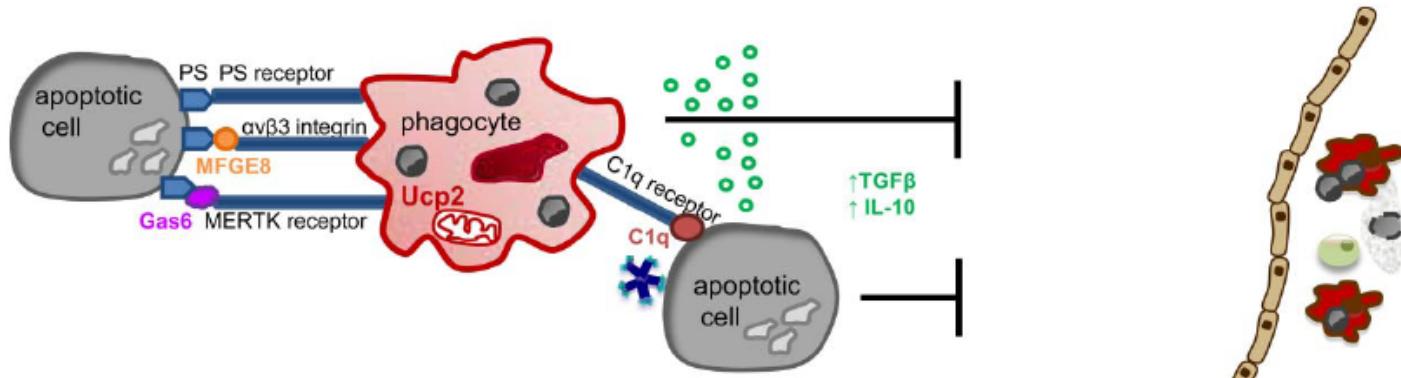


FACTORS CONTRIBUTING TO THE FORMATION OF VULNERABLE PLAQUE

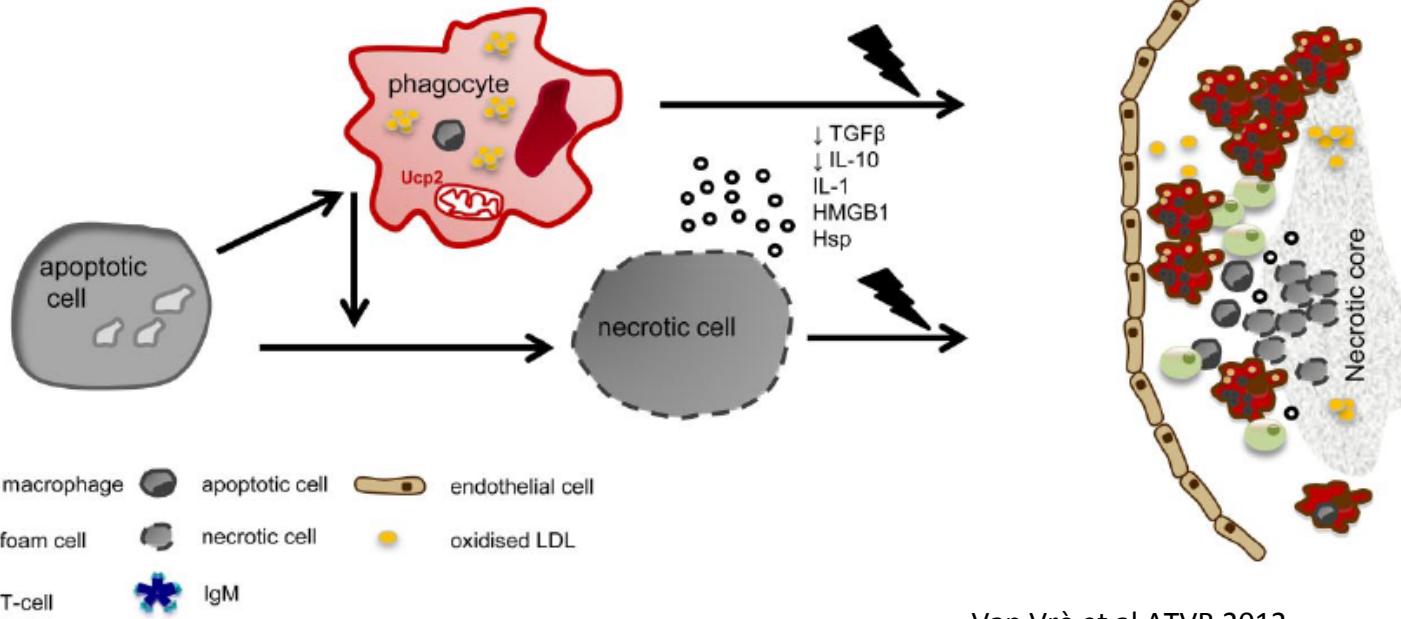


APOPTOSIS AND EFFEROCYTOSIS

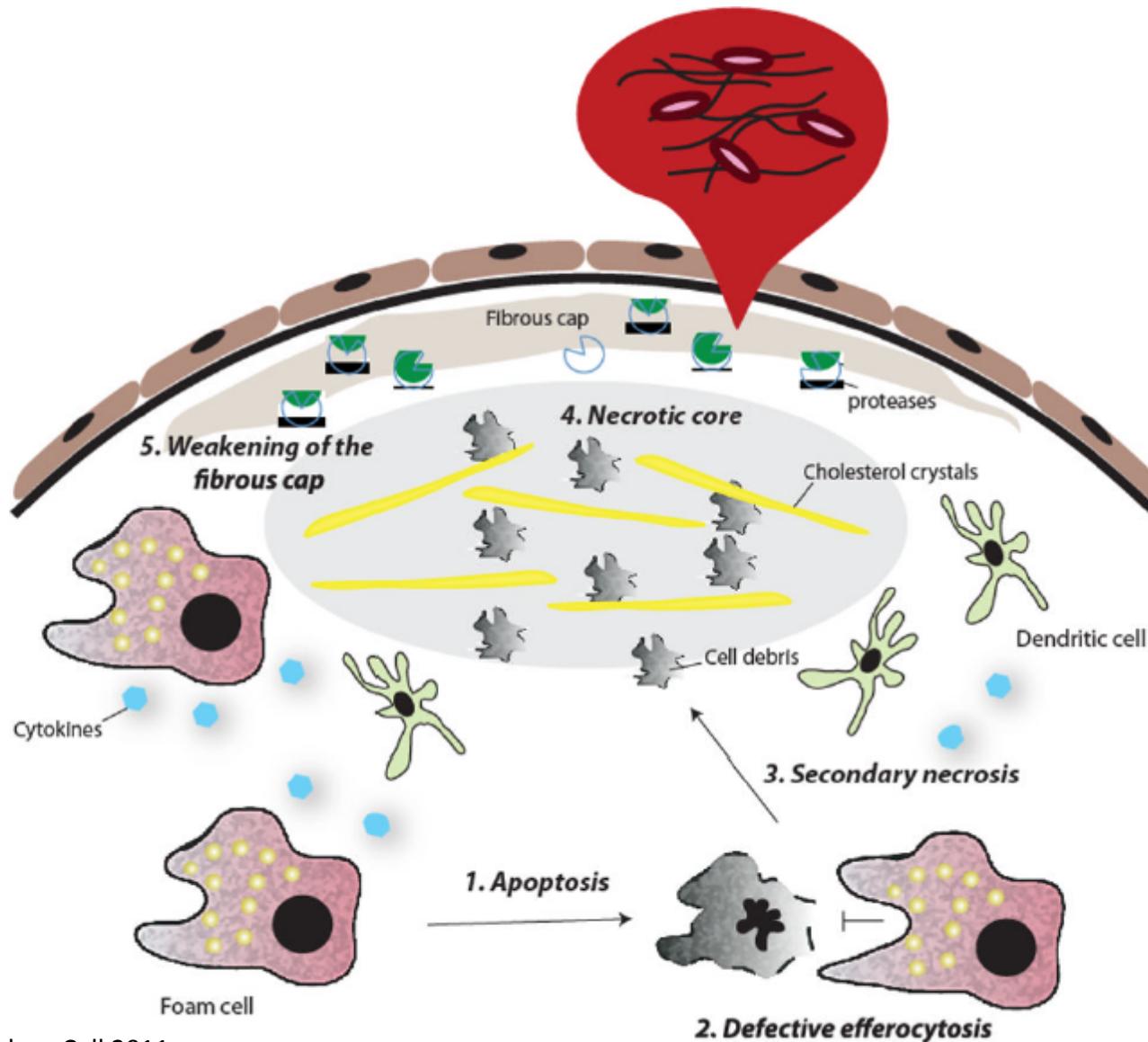
Apoptosis and efficient efferocytosis in early atherosclerosis: protective



Apoptosis and defective efferocytosis in advanced atherosclerosis: detrimental



FORCES IN THE ADVANCED LESION THAT DESTABILIZES THE ATHEROSCLEROTIC PLAQUE



VULNERABLE ATHEROSCLEROTIC PLAQUE

✓ MACROPHAGE APOPTOSIS IN EVOLVING ATHEROSCLEROTIC PLAQUE

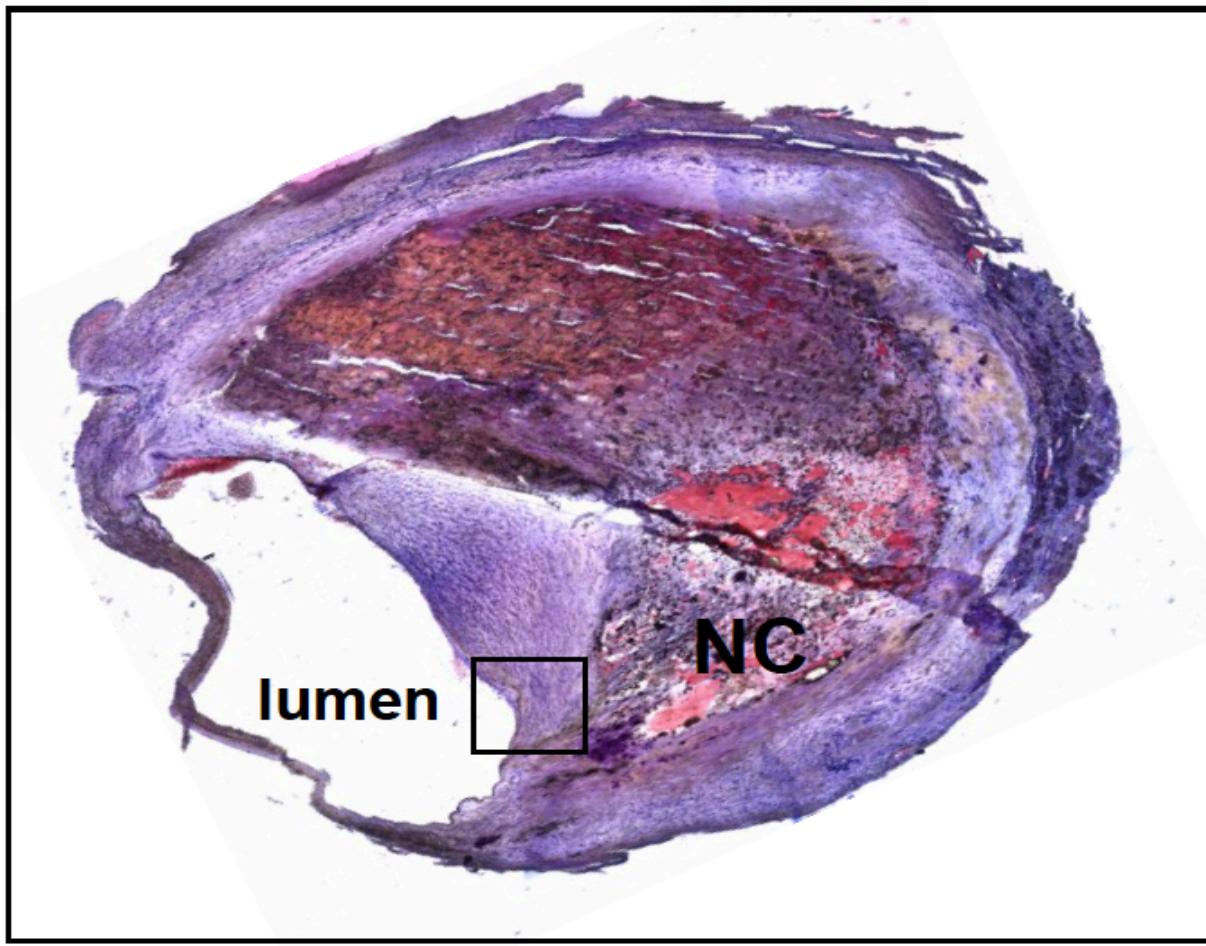
MECHANISMS OF MACROPHAGE APOPTOSIS IN ADVANCED ATHEROSCLEROTIC PLAQUE

ENDOPLASMIC RETICULUM STRESS

ENDOPLASMIC RETICULUM STRESS AND MACROPHAGE APOPTOSIS IN THE VULNERABLE PLAQUE

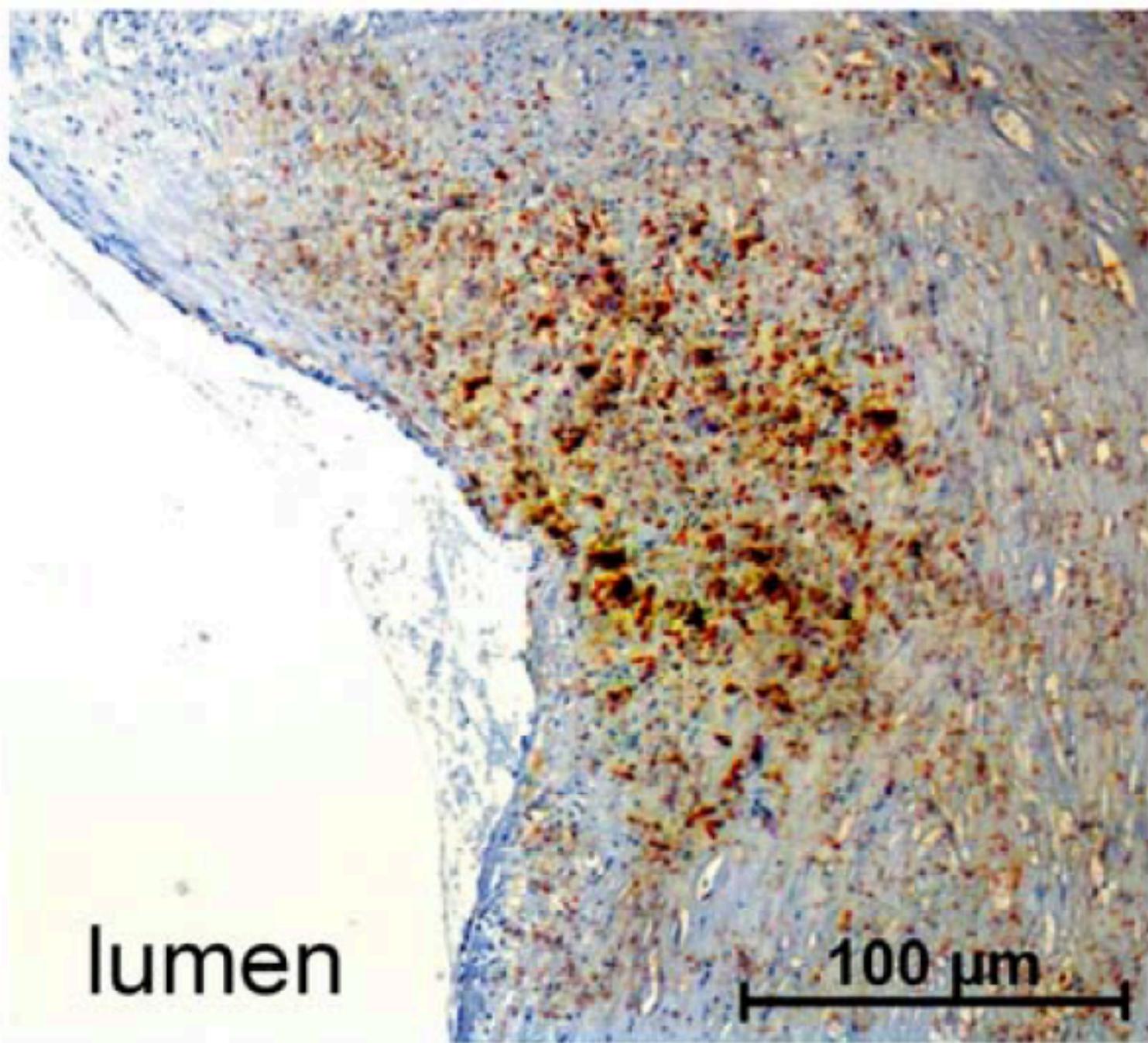
SYNERGISTIC EFFECT OF ER AND OXIDATIVE STRESS ON MACROPHAGE APOPTOSIS IN VULNERABLE PLAQUE

DEFECTIVE EFEROCTYSIS OF APOPTOTIC MACROPHAGES IN VULNERABLE PLAQUE

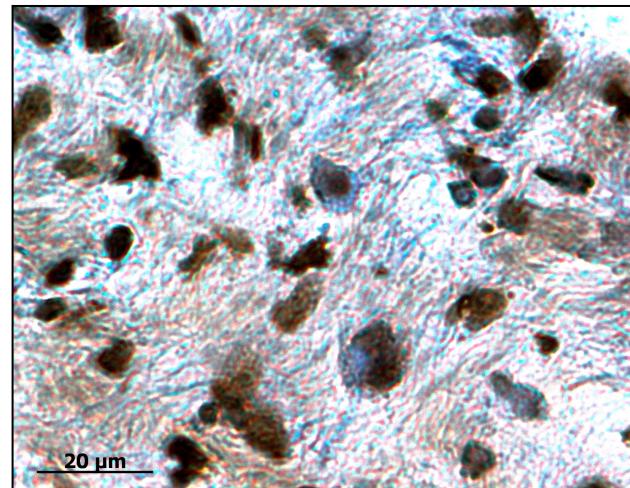
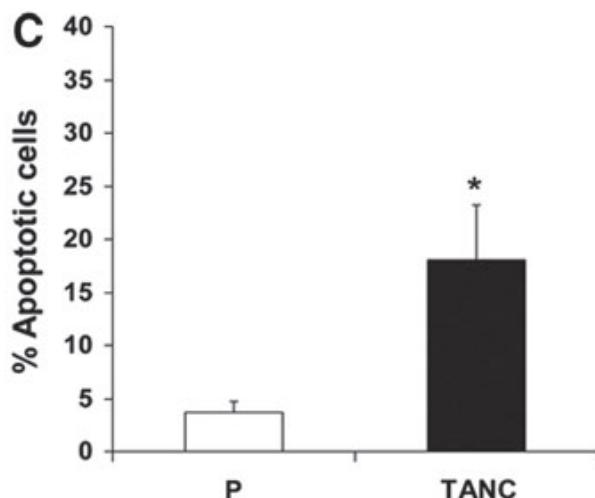
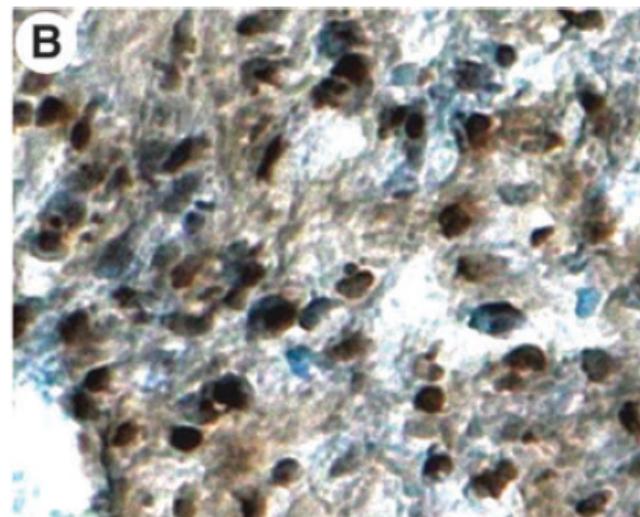
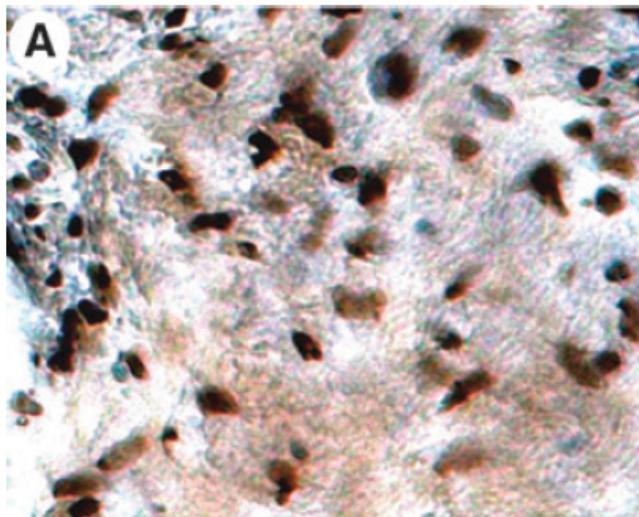


Garbin et al, Card res 2012

A



Apoptotic cells in the periphery (A) and in the tissue around the necrotic core (TANC) (B) of human carotid plaques.



VULNERABLE ATHEROSCLEROTIC PLAQUE

MACROPHAGE APOPTOSIS IN EVOLVING ATHEROSCLEROTIC PLAQUE

- ✓ **MECHANISMS OF MACROPHAGE APOPTOSIS IN ADVANCED ATHEROSCLEROTIC PLAQUE**

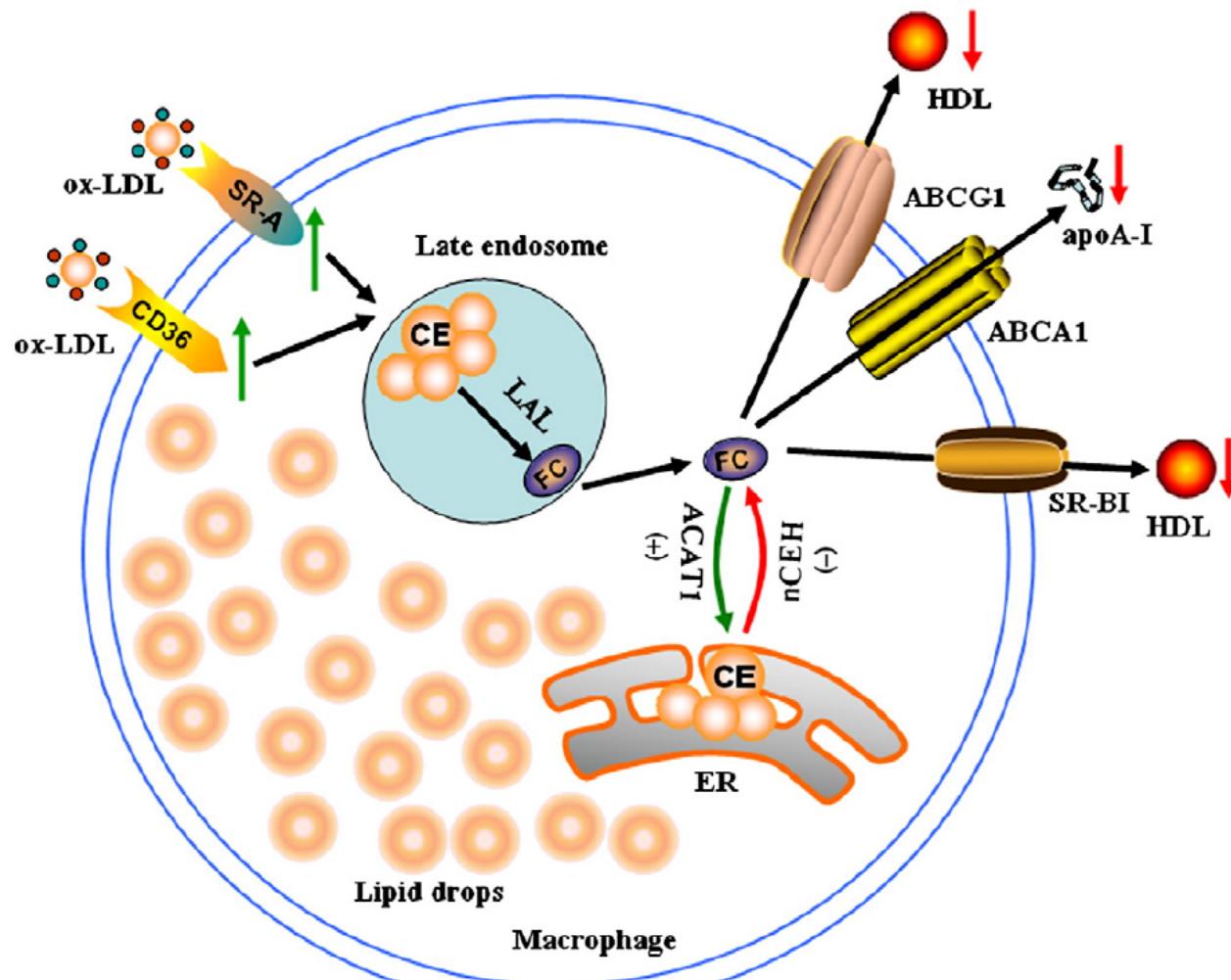
ENDOPLASMIC RETICULUM STRESS

ENDOPLASMIC RETICULUM STRESS AND MACROPHAGE APOPTOSIS IN THE VULNERABLE PLAQUE

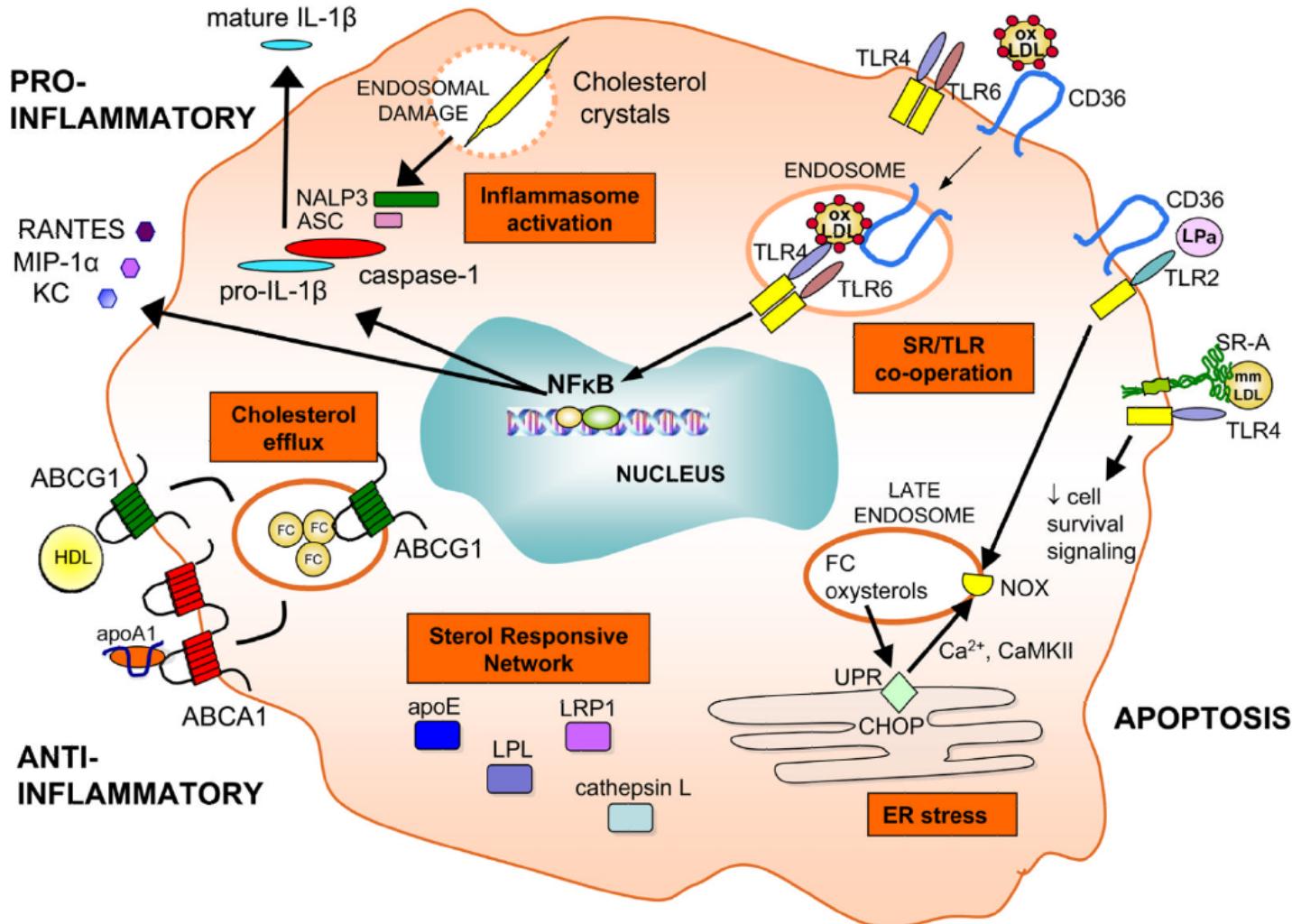
SYNERGISTIC EFFECT OF ER AND OXIDATIVE STRESS ON MACROPHAGE APOPTOSIS IN VULNERABLE PLAQUE

DEFECTIVE EFEROCTYSIS OF APOPTOTIC MACROPHAGES IN VULNERABLE PLAQUE

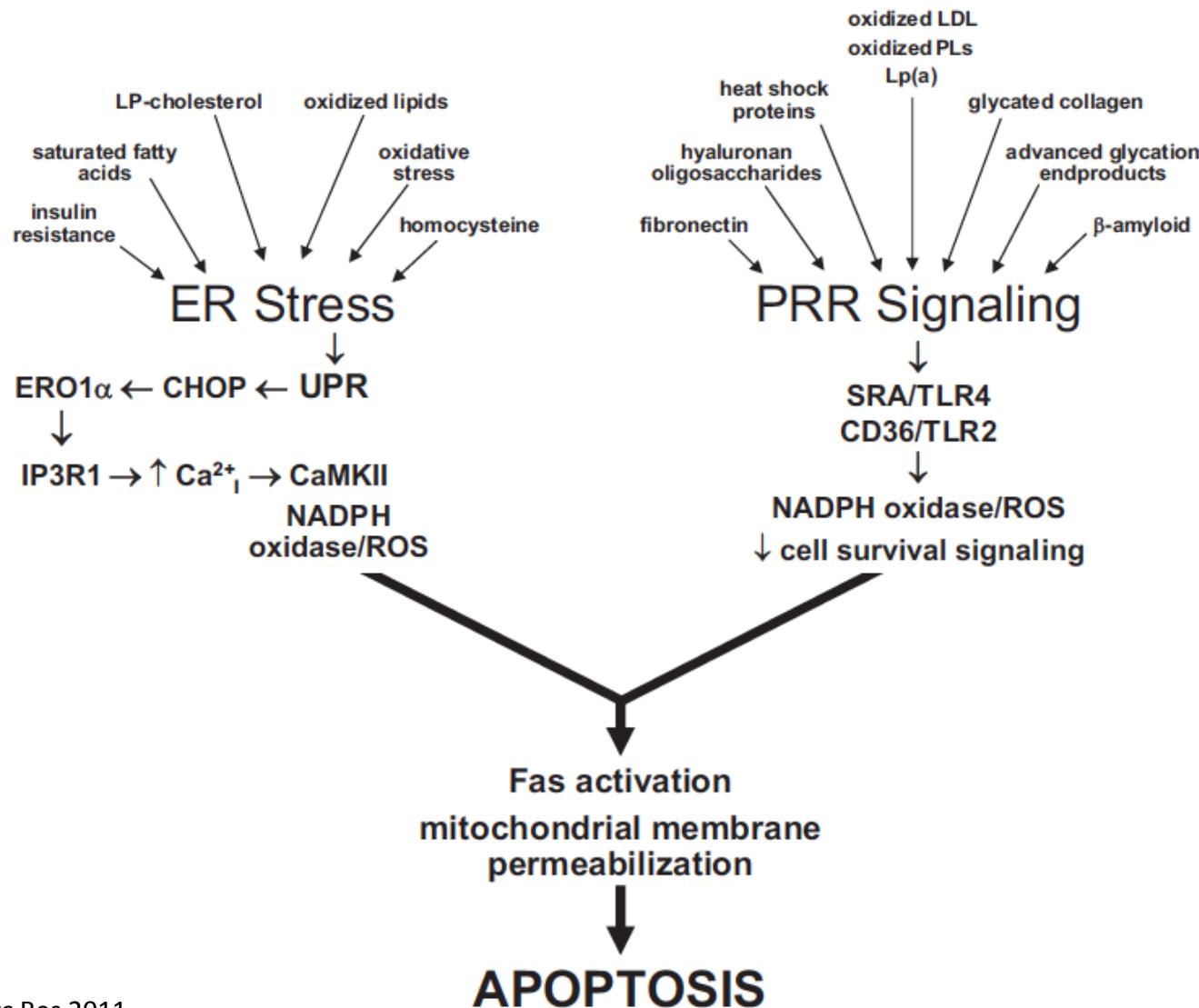
SCHEMATIC REPRESENTATION OF THE MECHANISM INVOLVED IN MACROPHAGE FOAM CELL FORMATION



SIGNALING PATHWAYS ACTIVATED IN THE LESIONAL MACROPHAGE



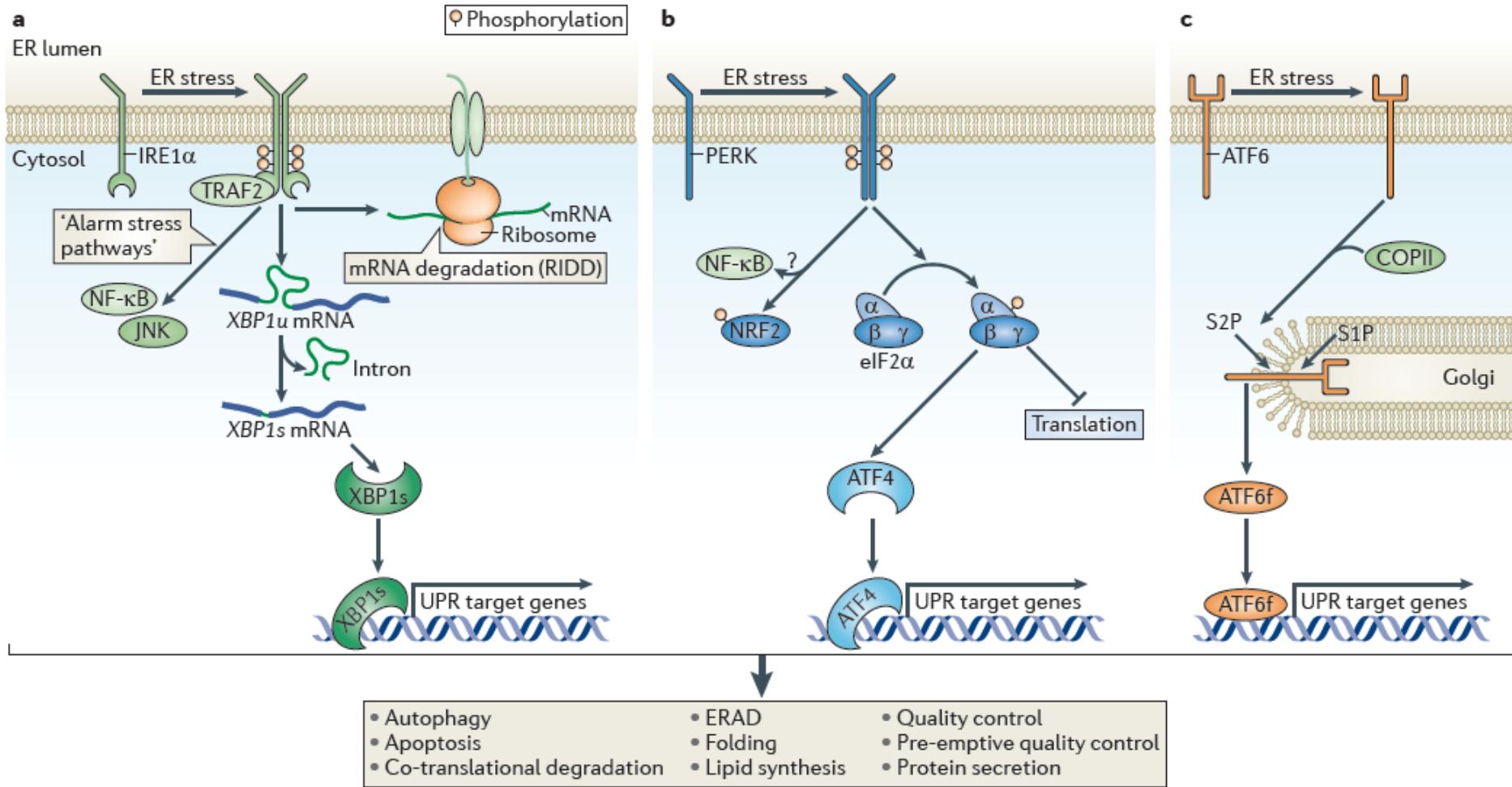
MODEL OF ER STRESS-INDUCED APOPTOSIS IN ADVANCED LESIONAL MACROPHAGES



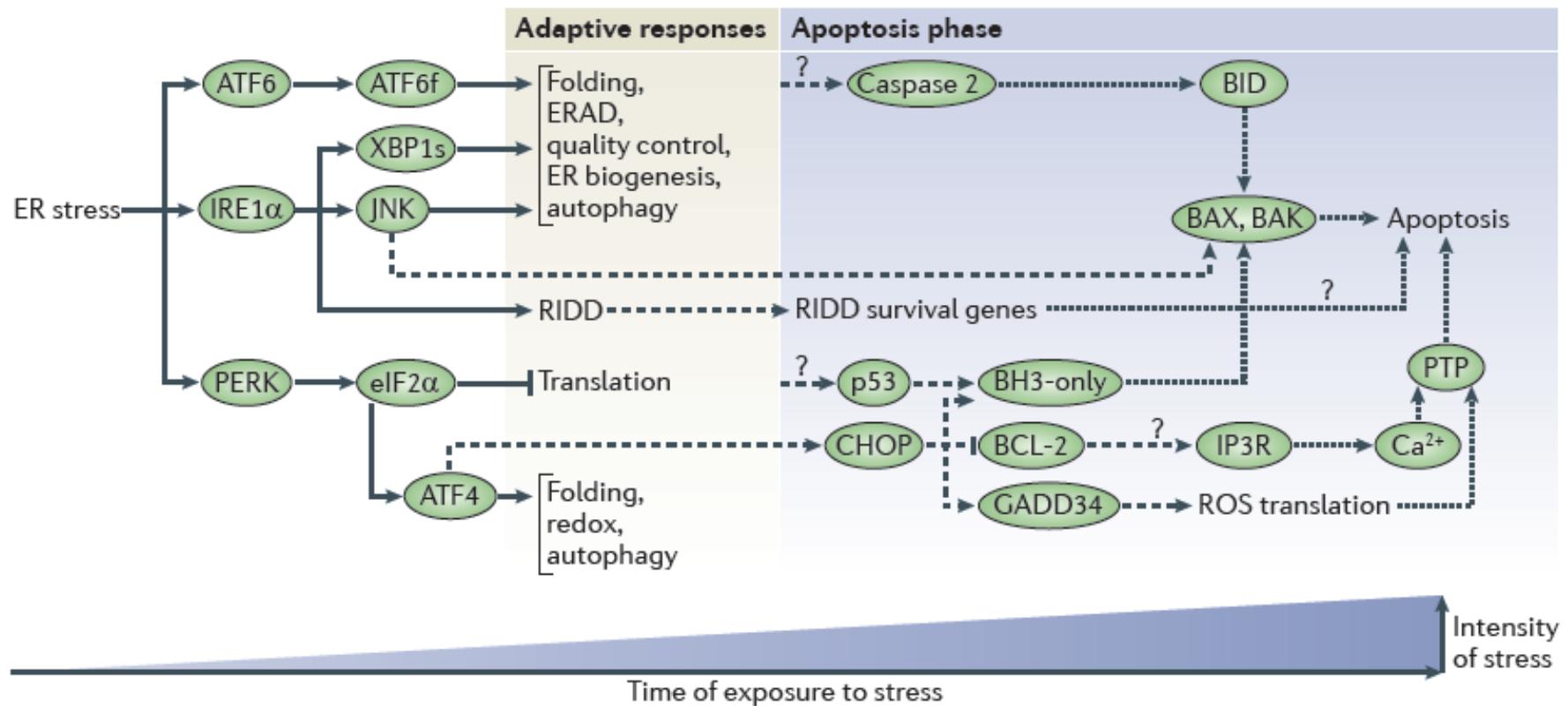
ENDOPLASMIC RETICULUM STRESS

- ✓ In eukaryotic cells, most secreted and transmembrane proteins fold and mature in the lumen of the endoplasmic reticulum (ER). Proteins enter the ER as unfolded polypeptide chains. Their flux into the ER is variable because physiological state of the cell.
- ✓ To handle this dynamic situation, cells adjust the protein-folding capacity of the ER according to their requirements.
- ✓ An imbalance (called ER stress) between the load of unfolded proteins that enter the ER and the capacity of the cellular machinery that handles this load sets the unfolded protein response (UPR)

THE UNFOLDED PROTEIN RESPONSE (UPR) SENSORS



CELL FATE DECISIONS UNDER ER STRESS



VULNERABLE ATHEROSCLEROTIC PLAQUE

MACROPHAGE APOPTOSIS IN EVOLVING ATHEROSCLEROTIC PLAQUE

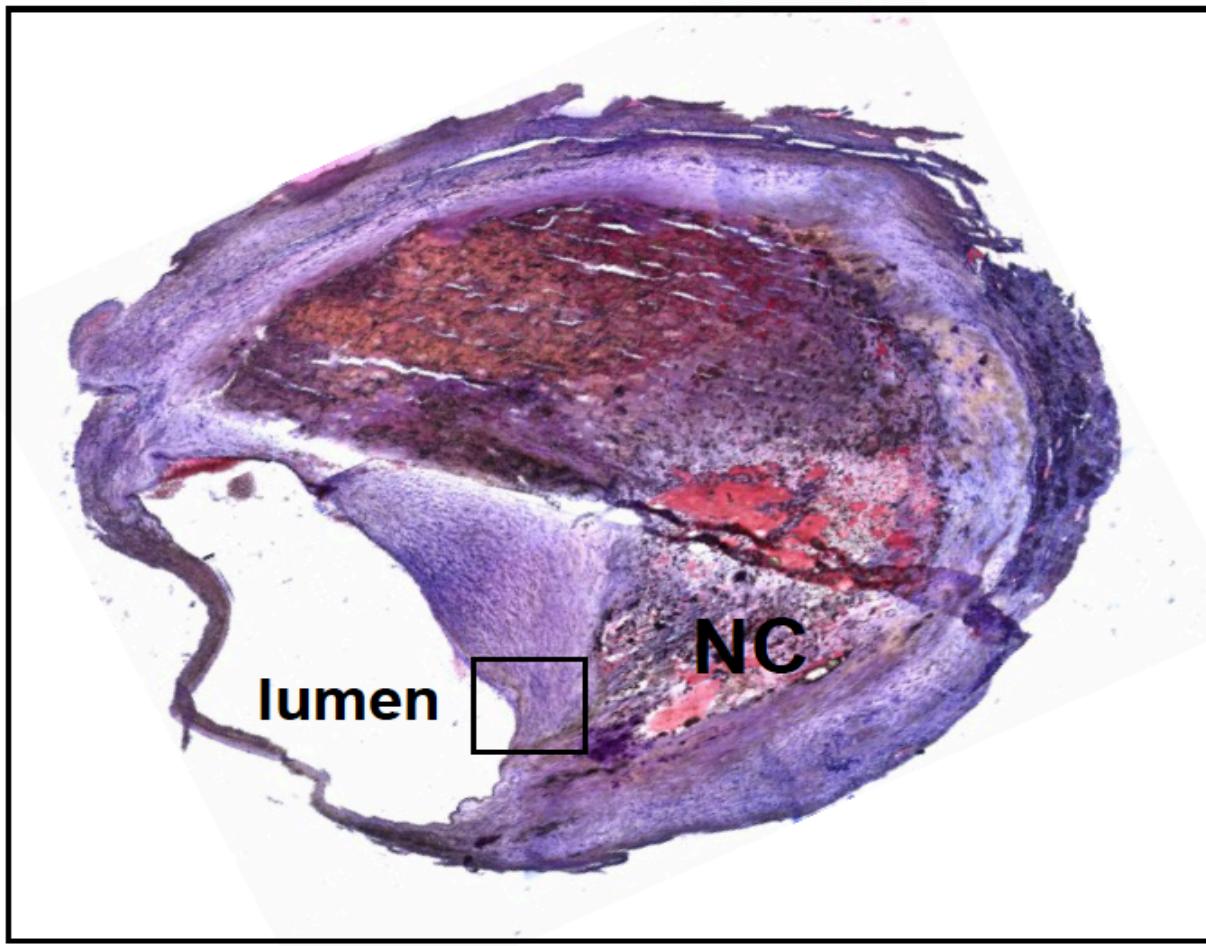
MECHANISMS OF MACROPHAGE APOPTOSIS IN ADVANCED ATHEROSCLEROTIC PLAQUE

ENDOPLASMIC RETICULUM STRESS

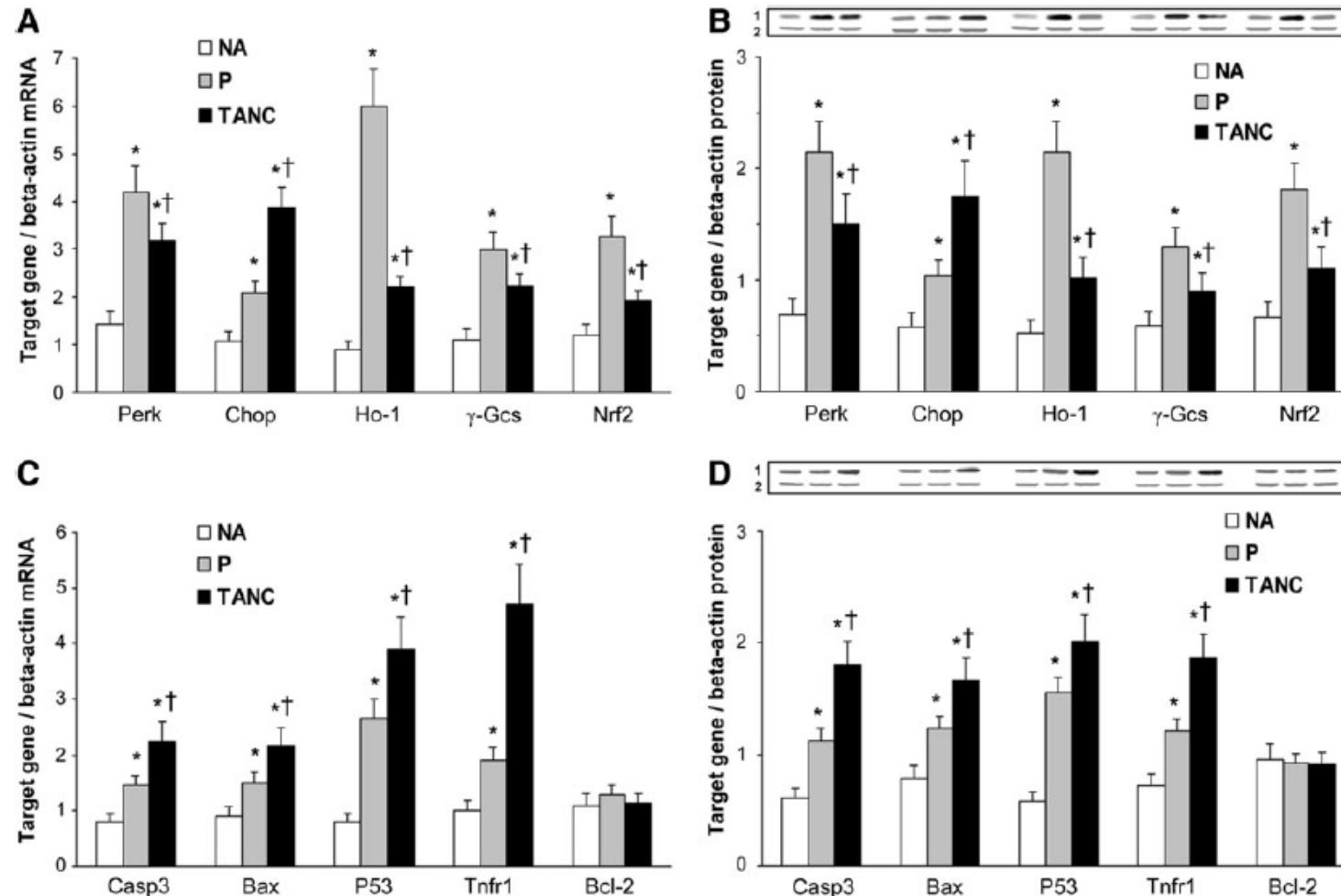
✓ **ENDOPLASMIC RETICULUM STRESS AND MACROPHAGE APOPTOSIS IN THE VULNERABLE PLAQUE**

SYNERGISTIC EFFECT OF ER AND OXIDATIVE STRESS ON MACROPHAGE APOPTOSIS IN VULNERABLE PLAQUE

DEFECTIVE EFEROCYTOSIS OF APOPTOTIC MACROPHAGES IN VULNERABLE PLAQUE

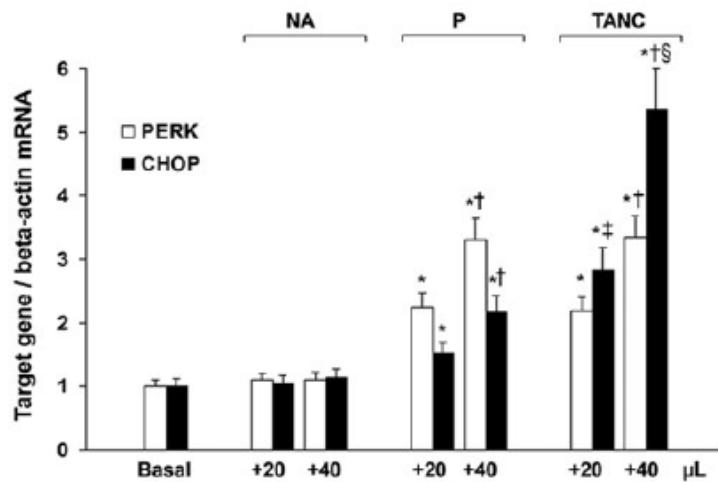


ER STRESS IN HUMAN VULNERABLE CAROTID PLAQUES

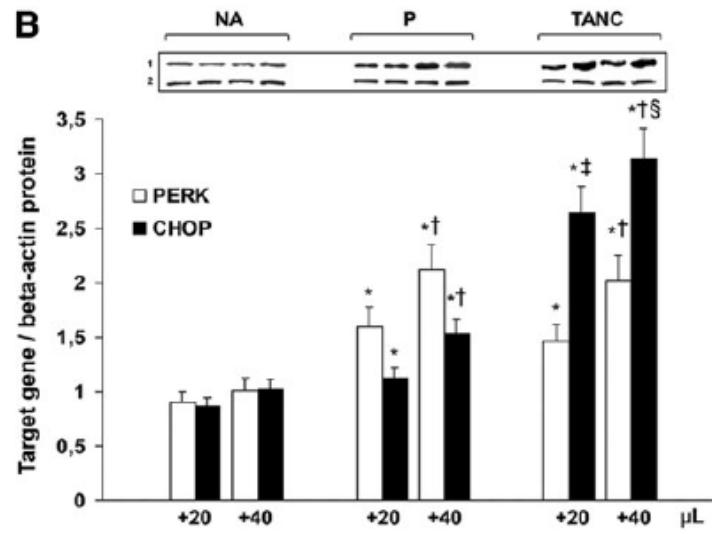


DOSE –RESPONSE EFFECTS OF NA, P AND TANC EXTRACTS FROM HUMAN VULNERABLE CAROTID PLAQUES ON ER GENES IN THP-1 CELLS

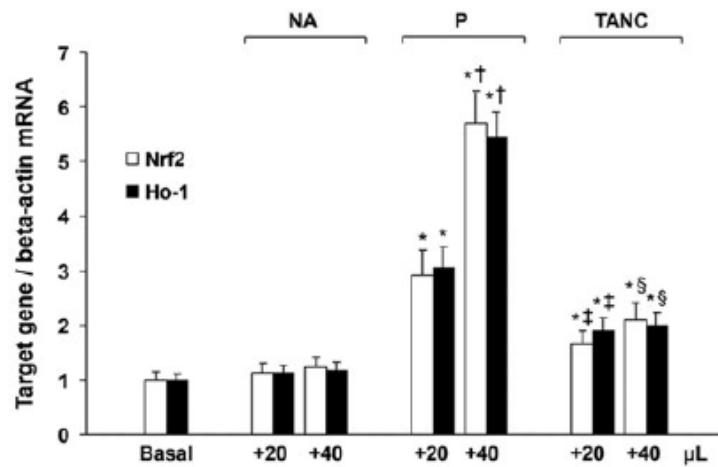
A



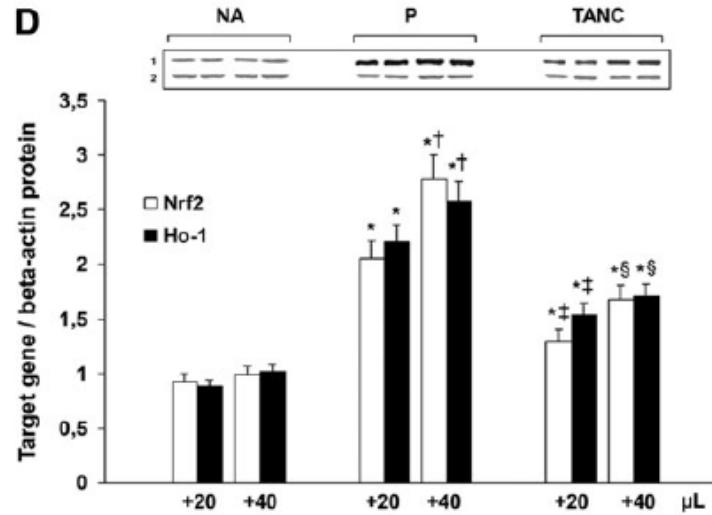
B



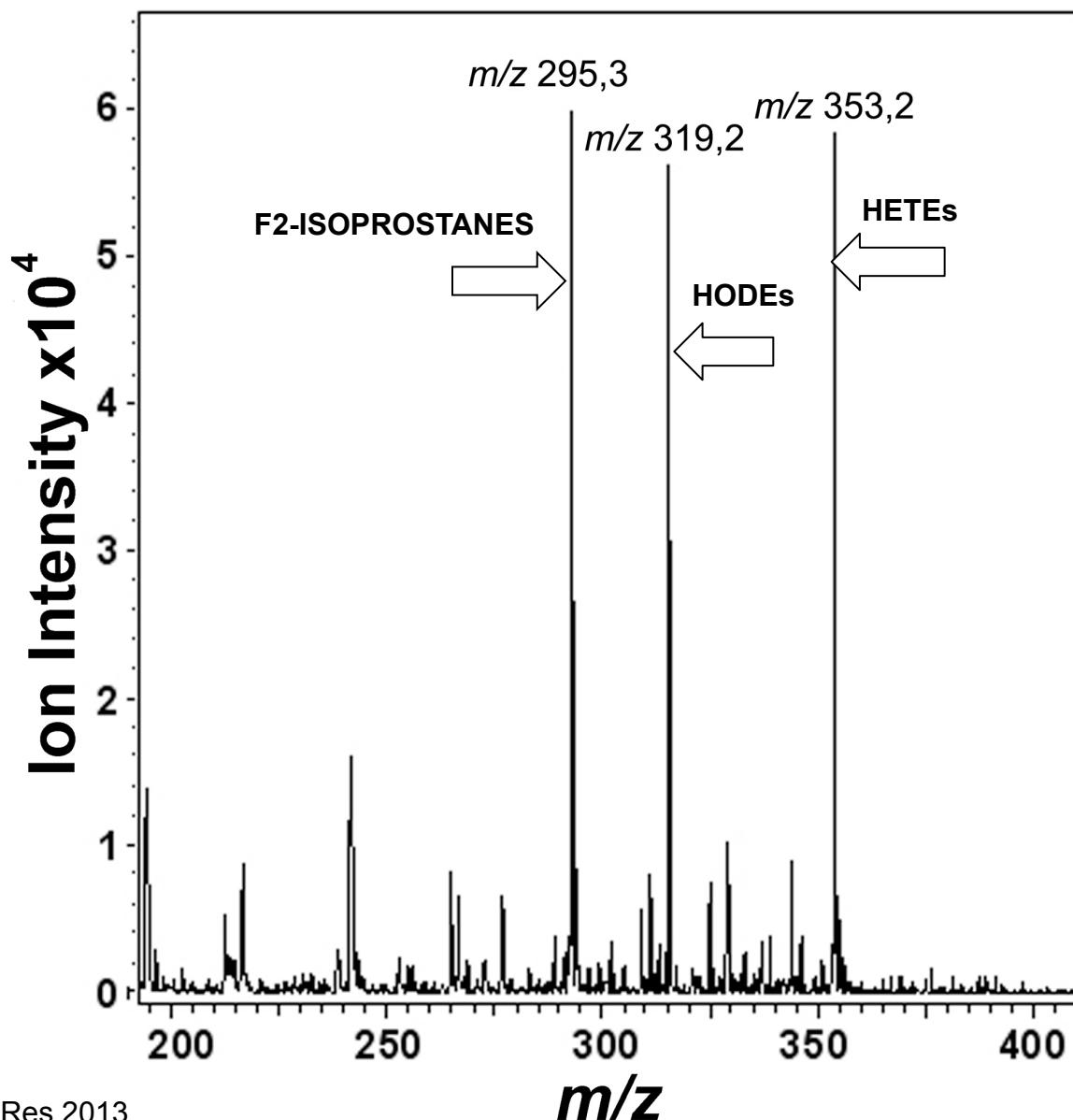
C



D

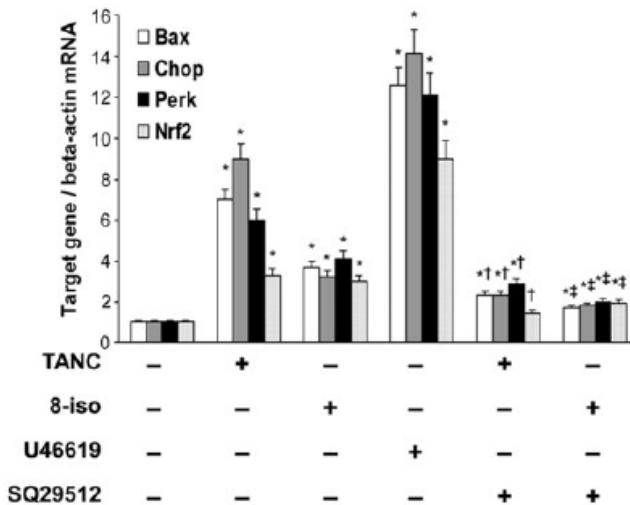


**REPRESENTATIVE MASS SPECTROMETRY ANALYSIS OF TANC
EXTRACT OBTAINED FROM DIRECT INFUSION OF 50 μ L/min OF THE
EXTRACT SOLUTION**

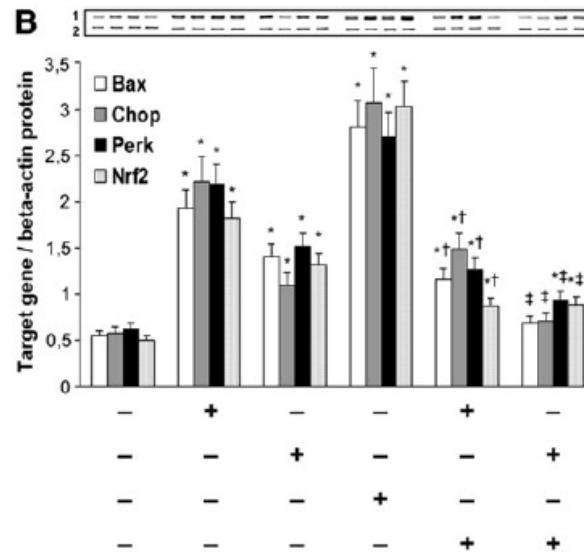


EFFECTS OF TANC, 8-ISO, 9-HODE AND 15-HETE AND OF TP AND G2A RECEPTOR ANTAGONISTS ON ER STRESS-RELATED GENES IN THP-1 CELLS

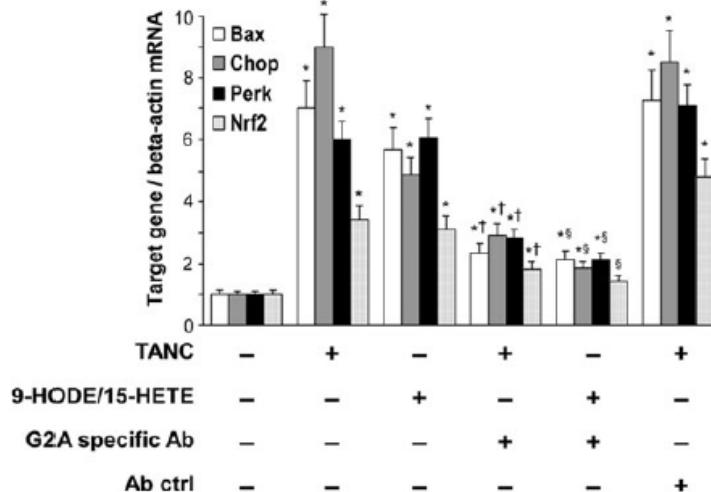
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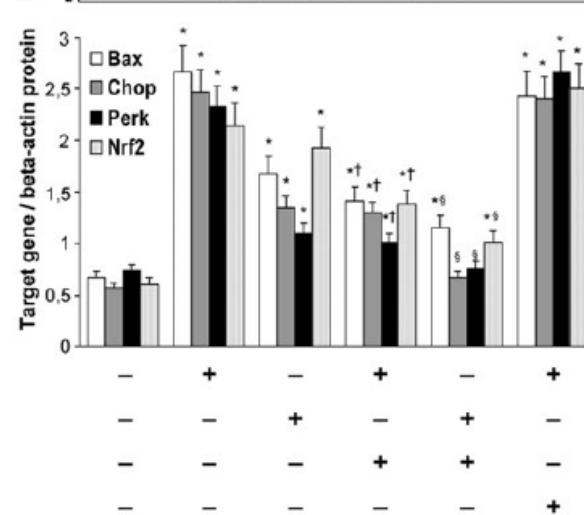
B



C



D



VULNERABLE ATHEROSCLEROTIC PLAQUE

MACROPHAGE APOPTOSIS IN EVOLVING ATHEROSCLEROTIC PLAQUE

MECHANISMS OF MACROPHAGE APOPTOSIS IN ADVANCED ATHEROSCLEROTIC PLAQUE

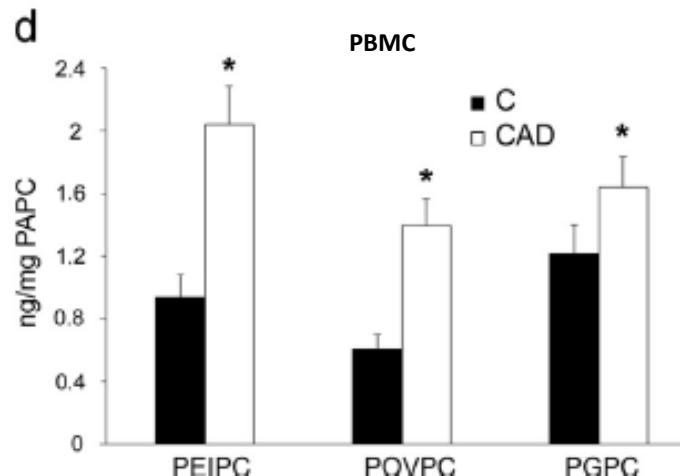
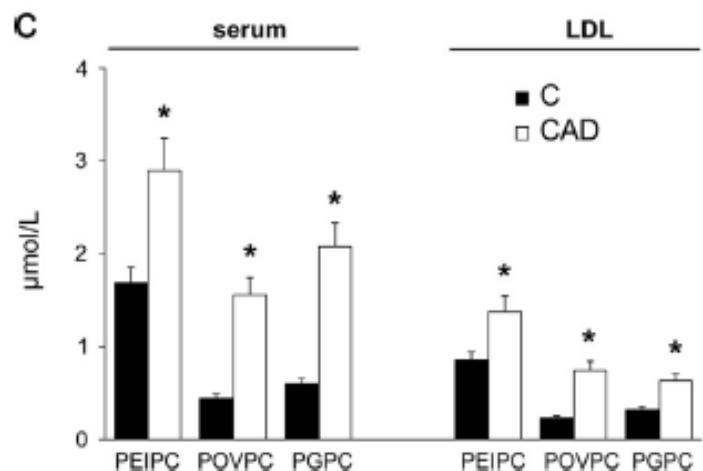
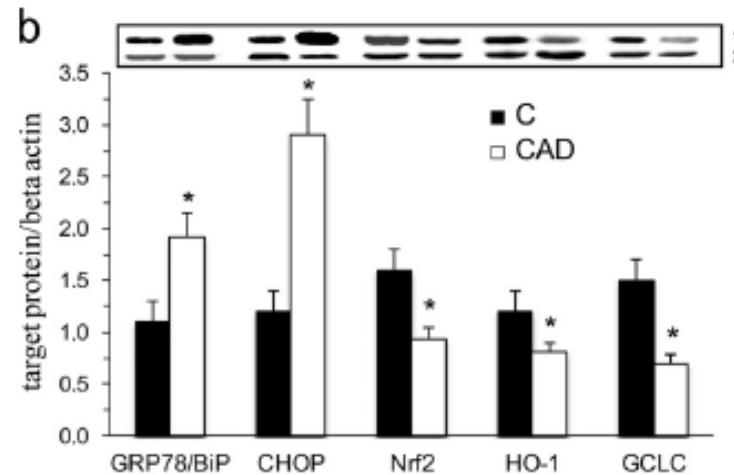
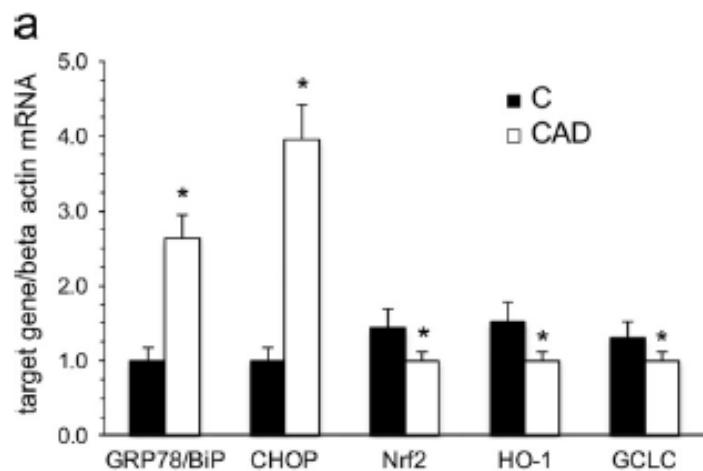
ENDOPLASMIC RETICULUM STRESS

ENDOPLASMIC RETICULUM STRESS AND MACROPHAGE APOPTOSIS IN THE VULNERABLE PLAQUE

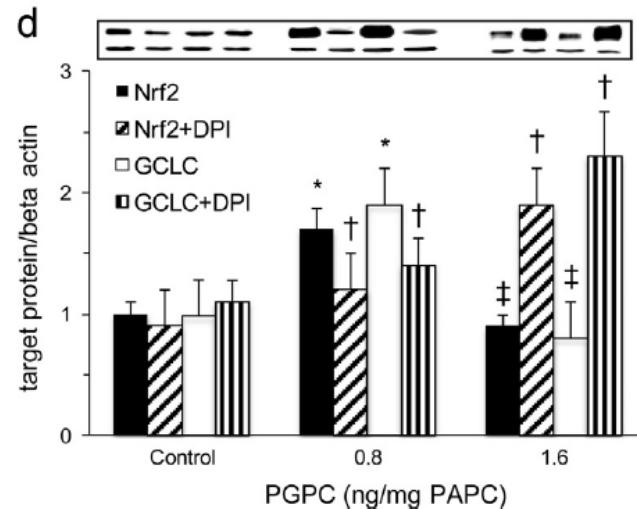
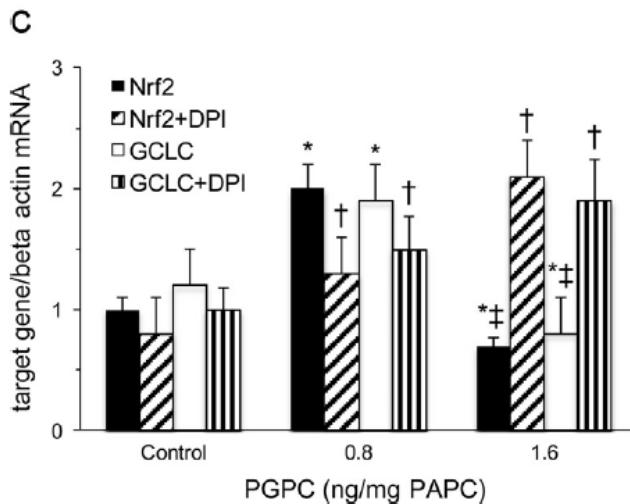
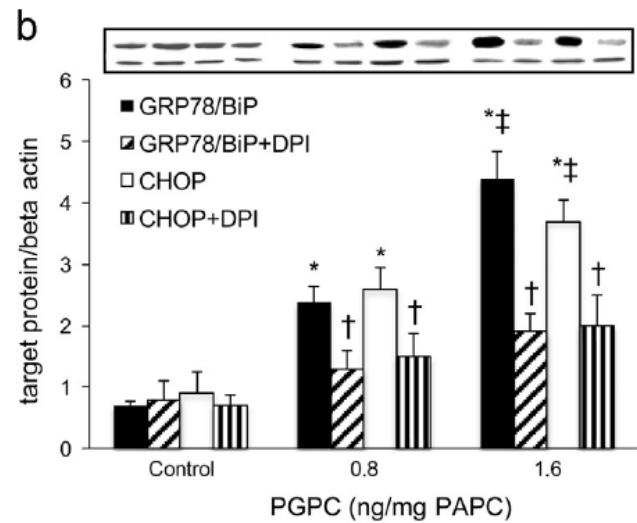
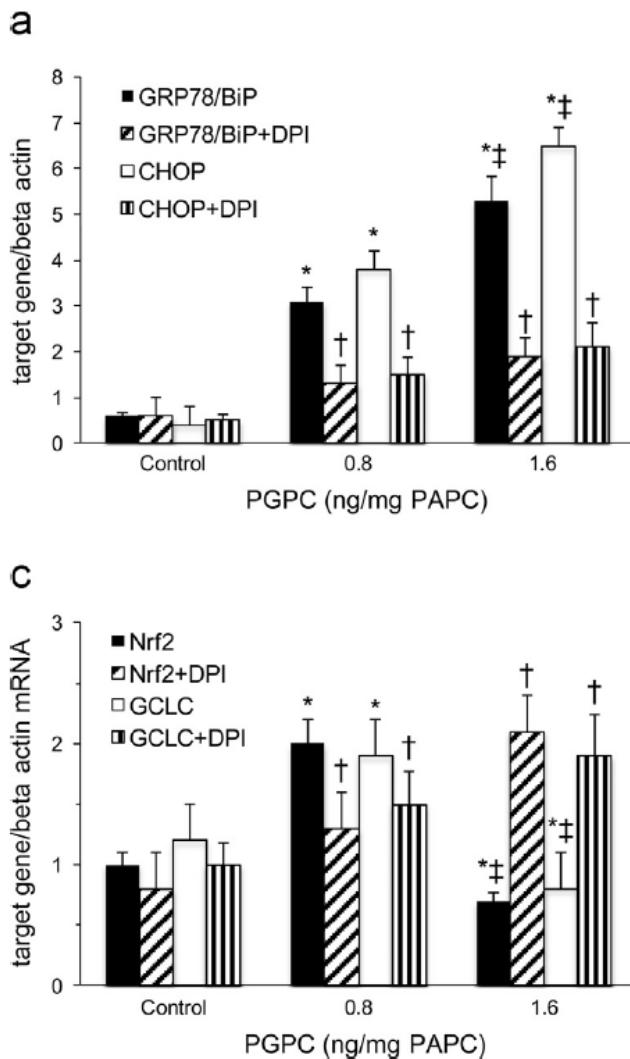
- ✓ SYNERGISTIC EFFECT OF ER AND OXIDATIVE STRESS ON MACROPHAGE APOPTOSIS IN VULNERABLE PLAQUE

DEFECTIVE EFEROCYTOSIS OF APOPTOTIC MACROPHAGES IN VULNERABLE PLAQUE

ER GENES EXPRESSION (a,b) AND VALUES OF OX-PAPC IN SERUM (c) AND IN PBMC (d) OF CONTROLS (C) AND STABLE CORONARY ARTERY DISEASE (CAD) PATIENTS



EFFECT OF DPI ON ER-STRESS GENE EXPRESSION IN THP-1 CELLS



VULNERABLE ATHEROSCLEROTIC PLAQUE

MACROPHAGE APOPTOSIS IN EVOLVING ATHEROSCLEROTIC PLAQUE

MECHANISMS OF MACROPHAGE APOPTOSIS IN ADVANCED ATHEROSCLEROTIC PLAQUE

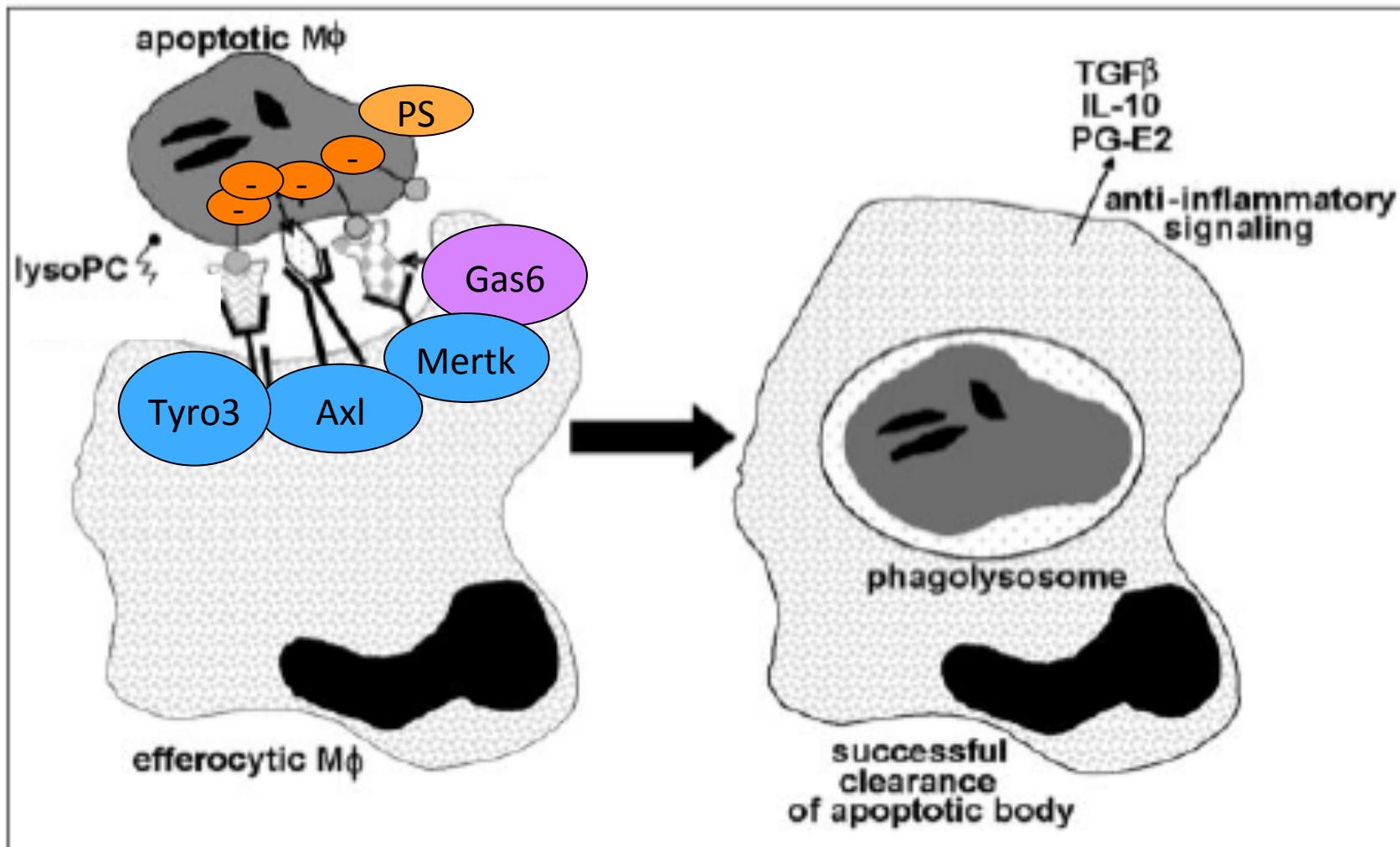
ENDOPLASMIC RETICULUM STRESS

ENDOPLASMIC RETICULUM STRESS AND MACROPHAGE APOPTOSIS IN THE VULNERABLE PLAQUE

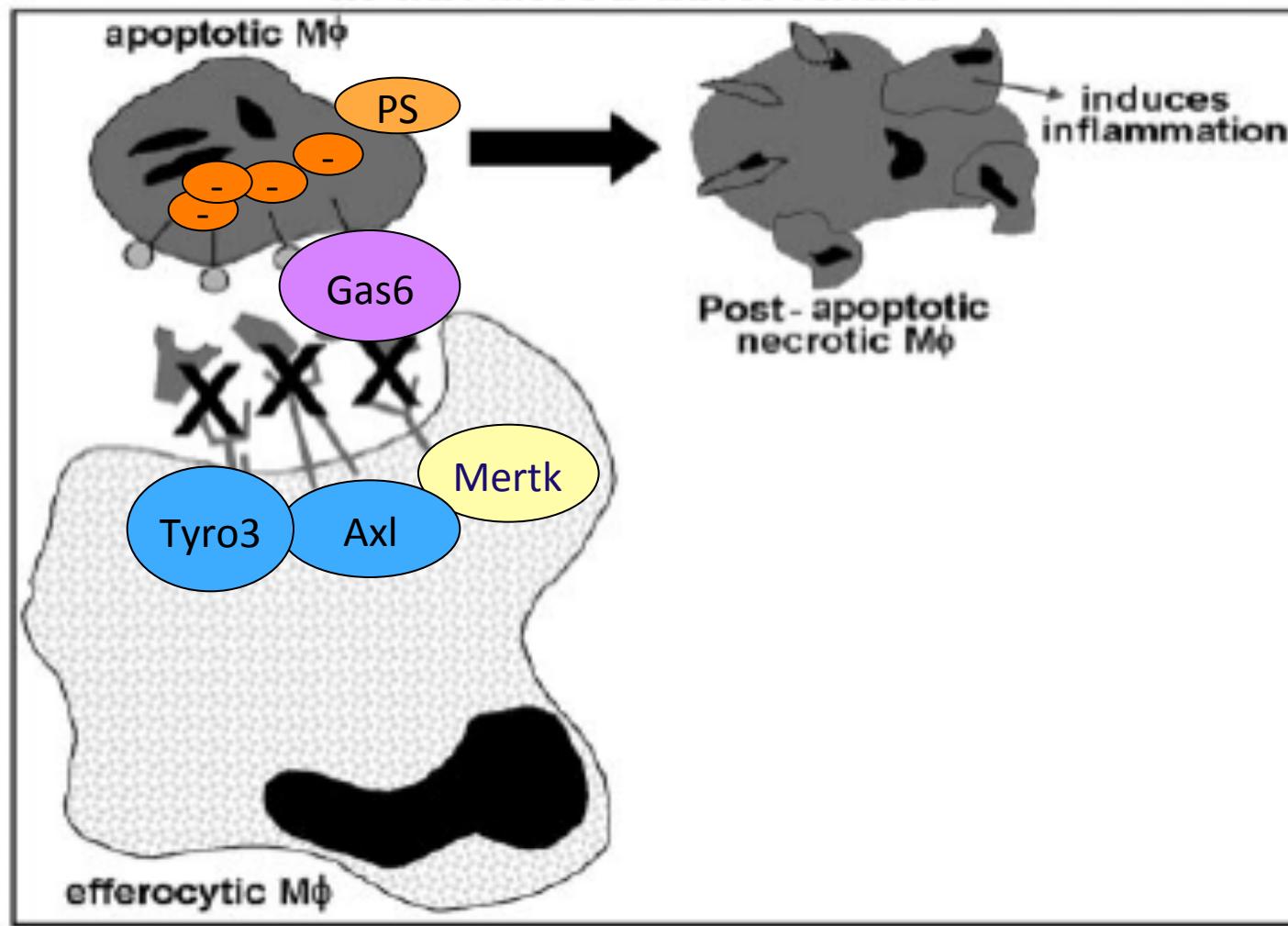
SYNERGISTIC EFFECT OF ER AND OXIDATIVE STRESS ON MACROPHAGE APOPTOSIS IN VULNERABLE PLAQUE

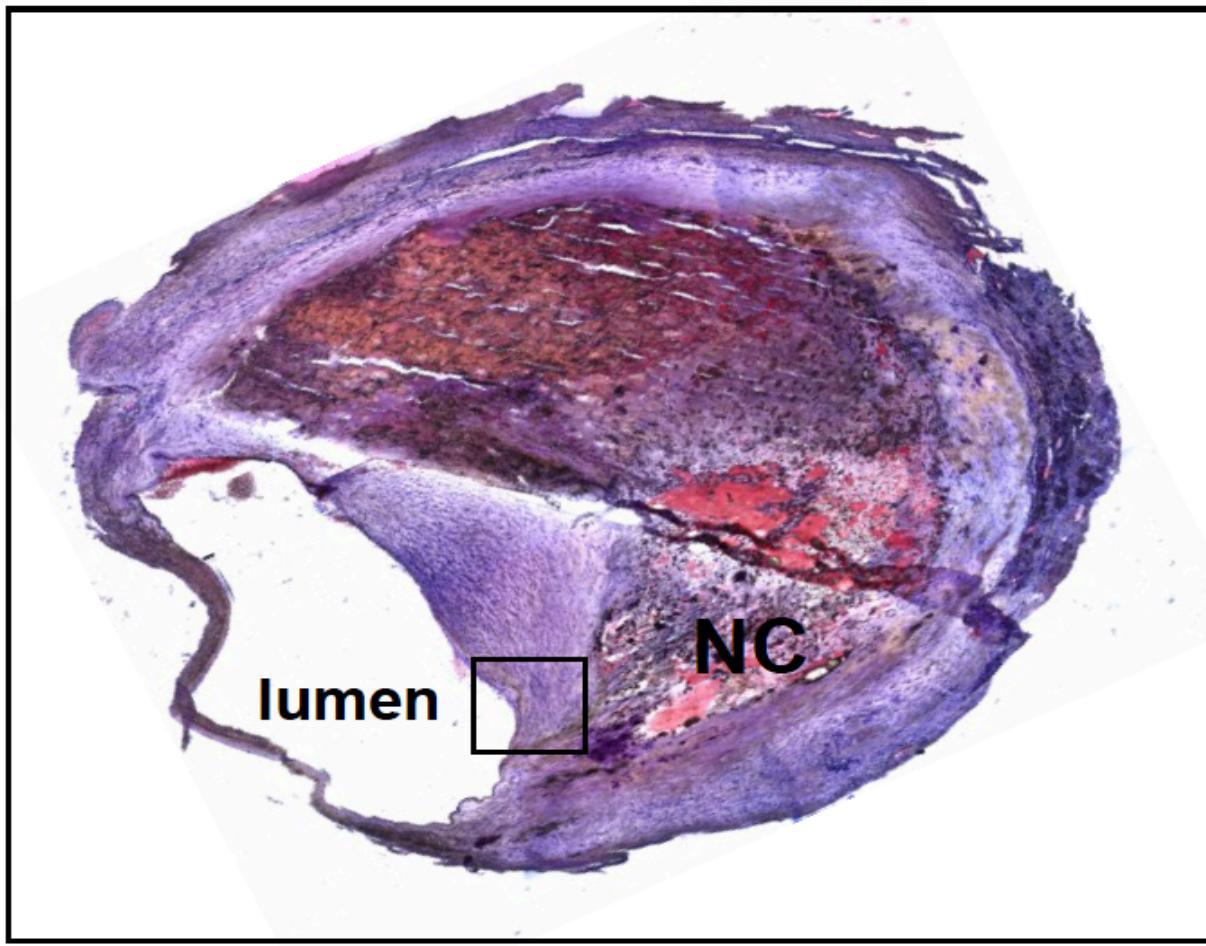
- ✓ DEFECTIVE EFEROCTOSIS OF APOPTOTIC MACROPHAGES IN VULNERABLE PLAQUE

Physiologic efferocytosis



Pathologically defective efferocytosis in advanced atheromata

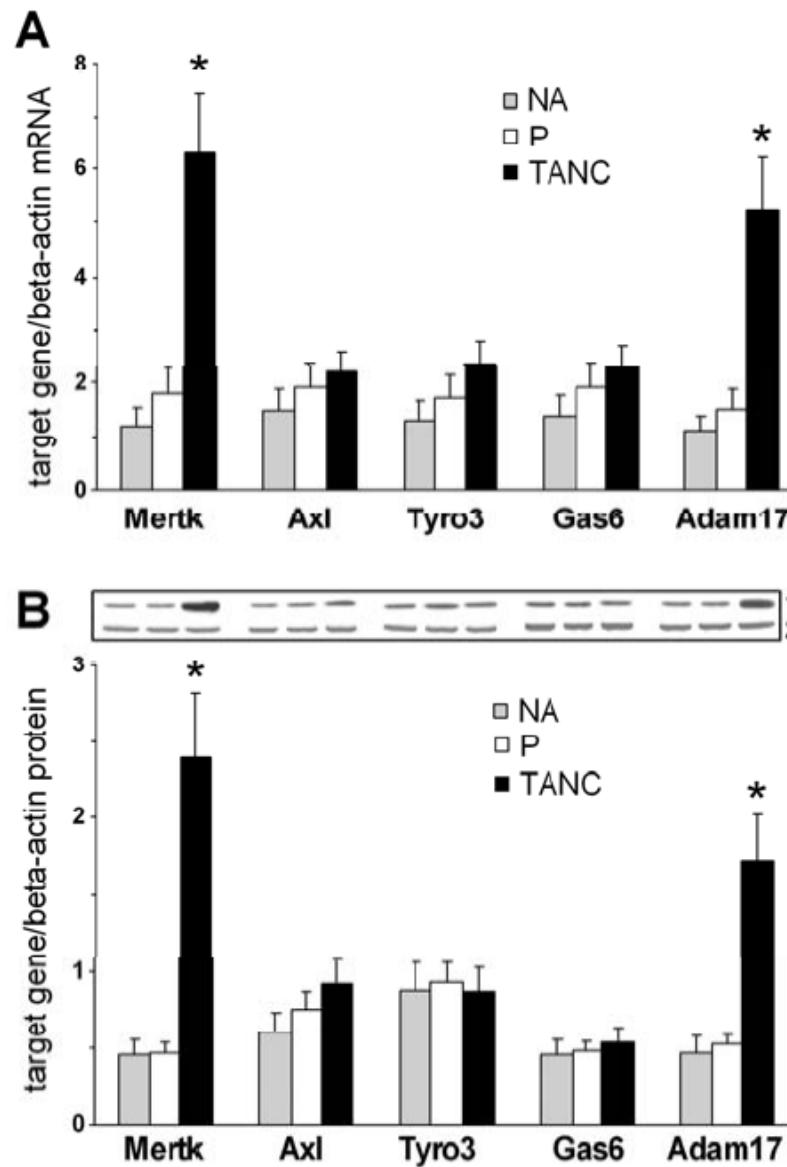




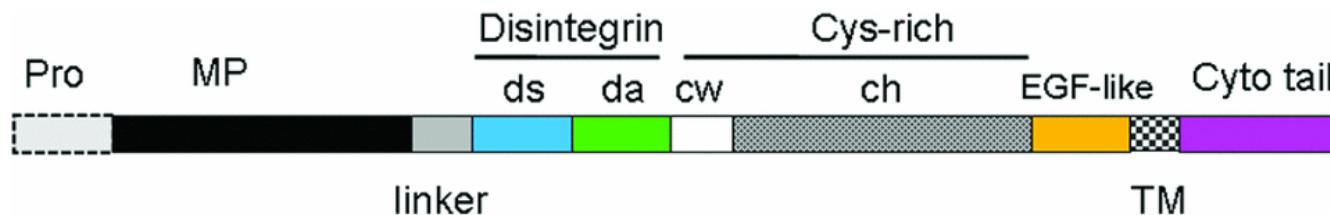
Garbin et al, Card res 2012

TAM RECEPTOR EXPRESSION IN TANC AND P OF HUMAN CAROTID PLAQUES

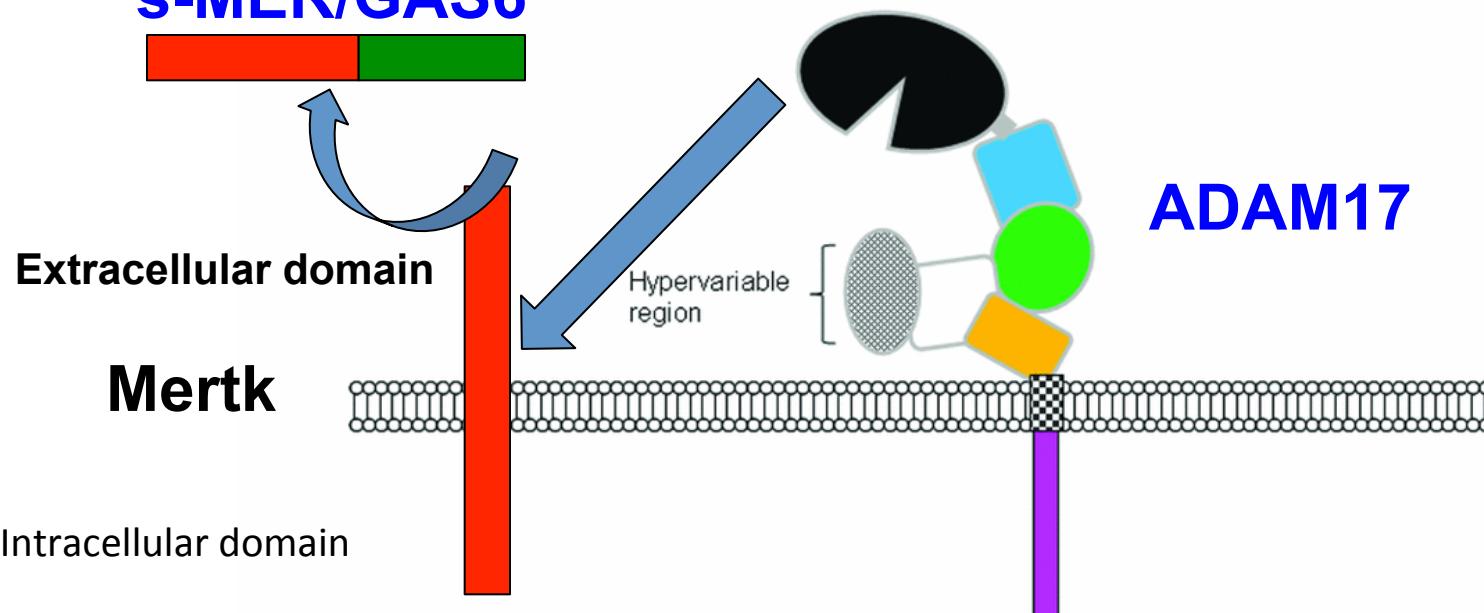
TANC=tissue around necrotic core
P=periphery
NA=normal artery



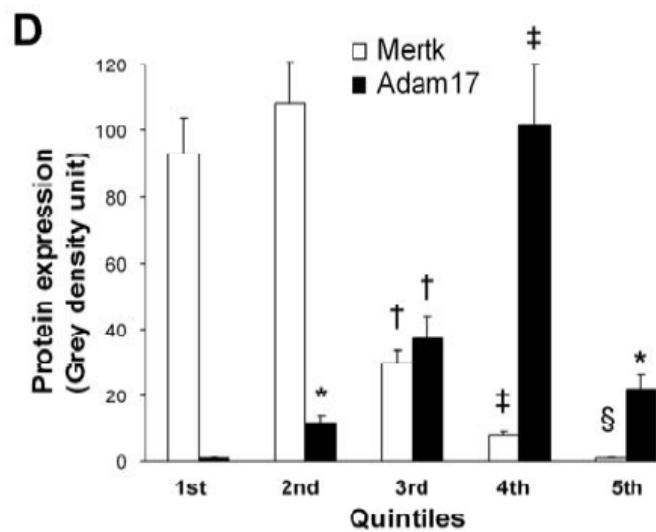
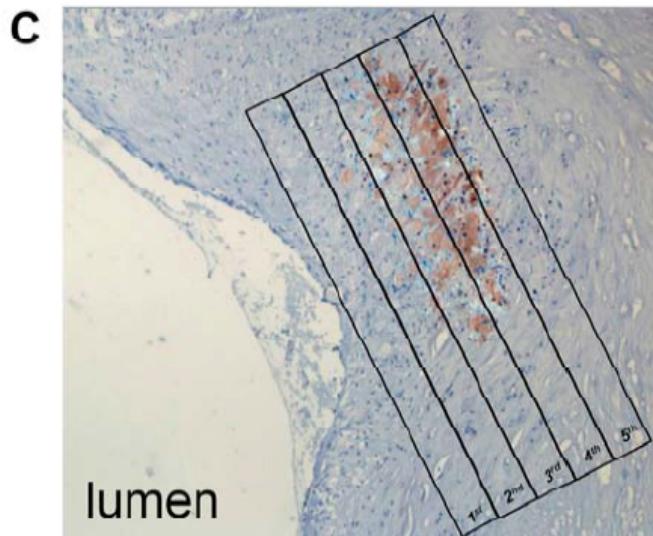
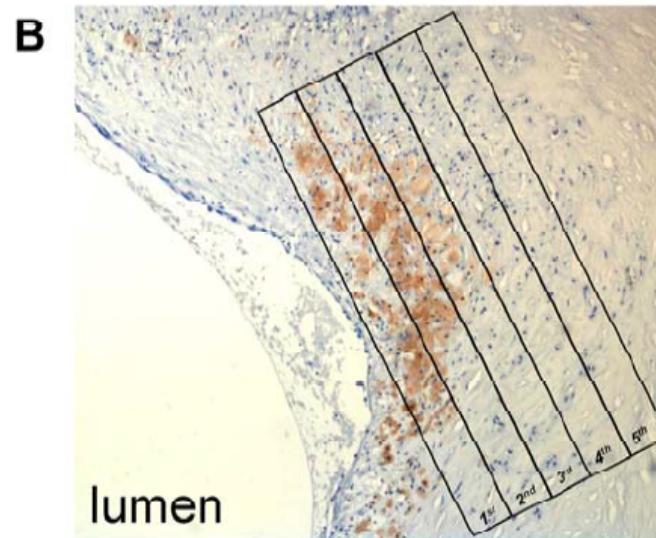
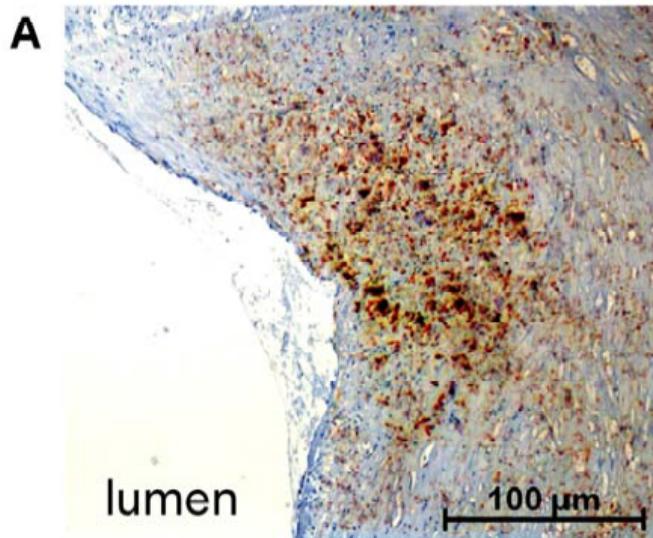
SHAPED STRUCTURE OF FULL-LENGTH ADAMS



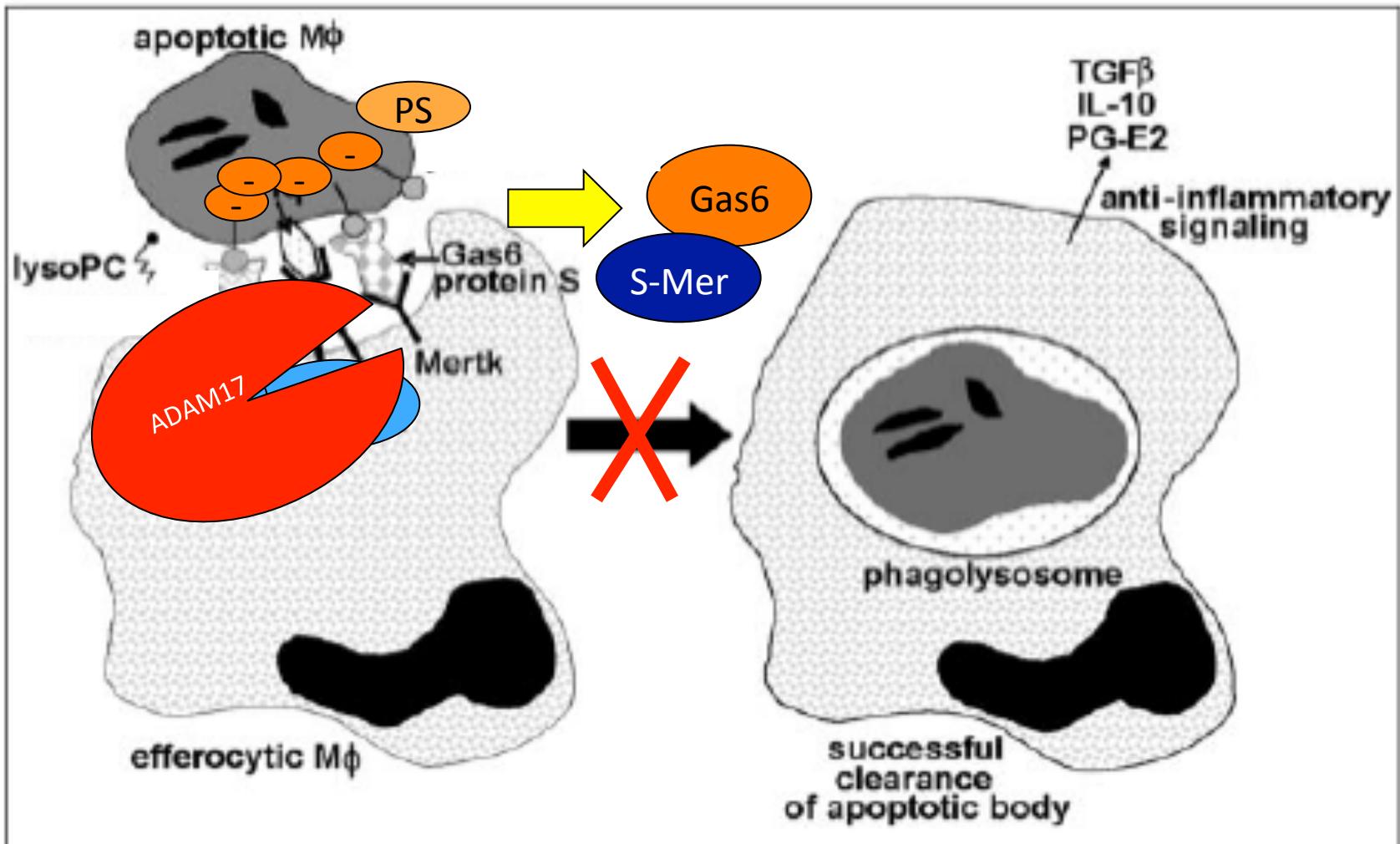
s-MER/GAS6



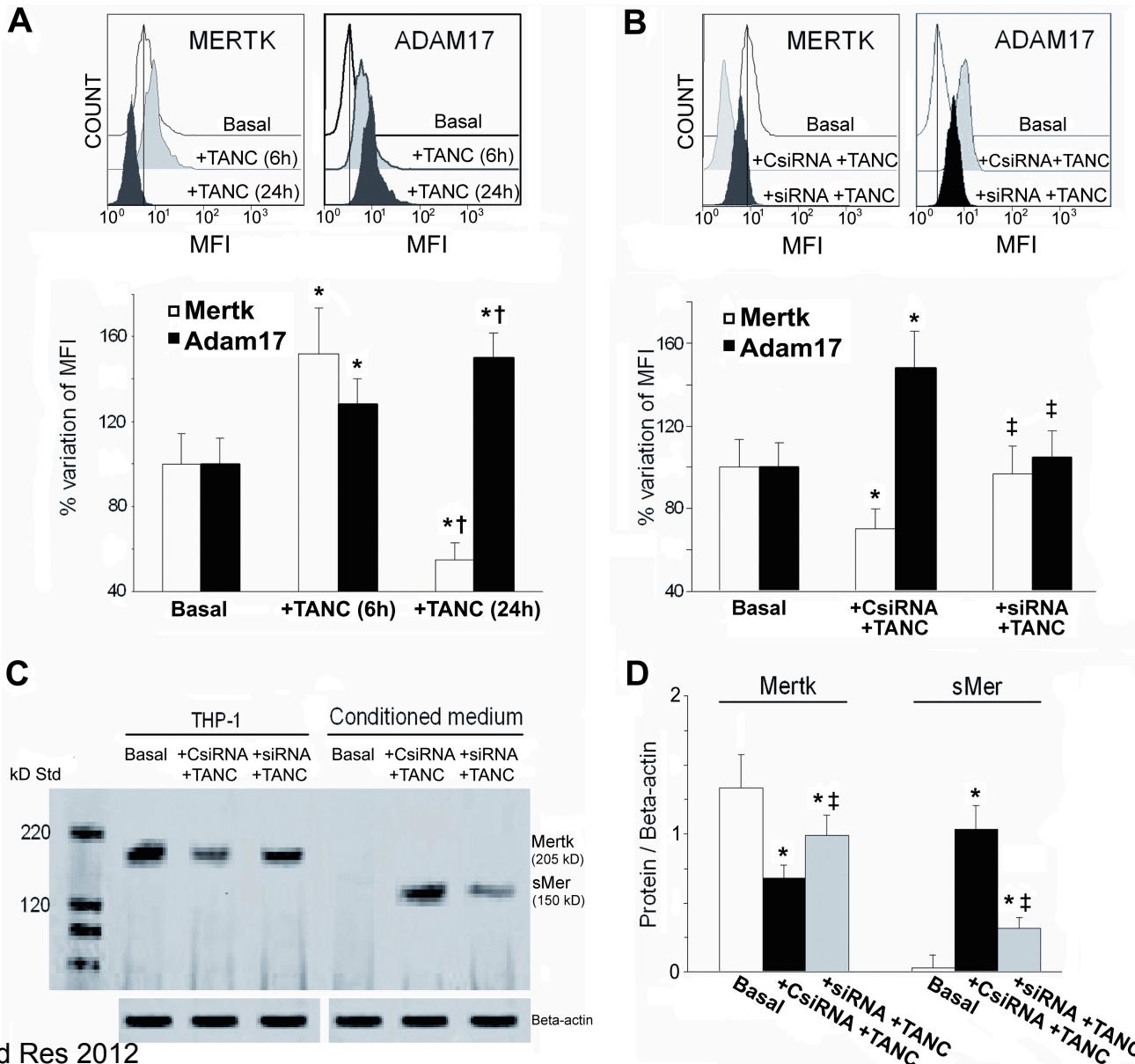
IMMUNOHISTOCHEMISTRY OF ADAM17 AND MERTK IN THE TISSUE AROUND THE LIPID CORE (TANC) OF HUMAN CAROTID PLAQUES.



Defective efferocytosis



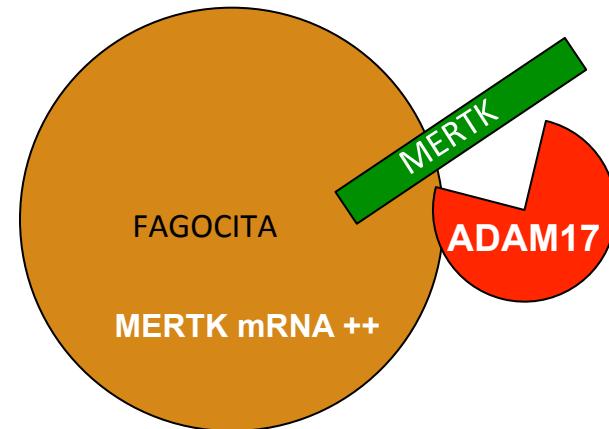
TIME-DEPENDENT EFFECT OF TANC EXTRACT ON MERTK AND ADAM 17 PROTEIN EXPRESSION AMD ON GENERATION OF S-MER



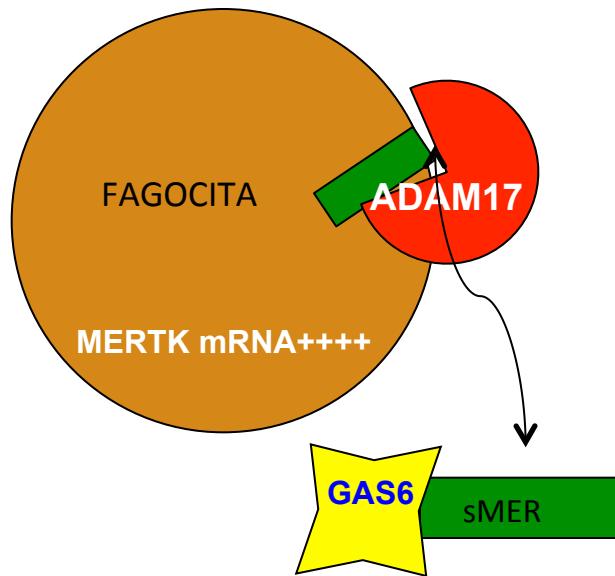
+TANC 0



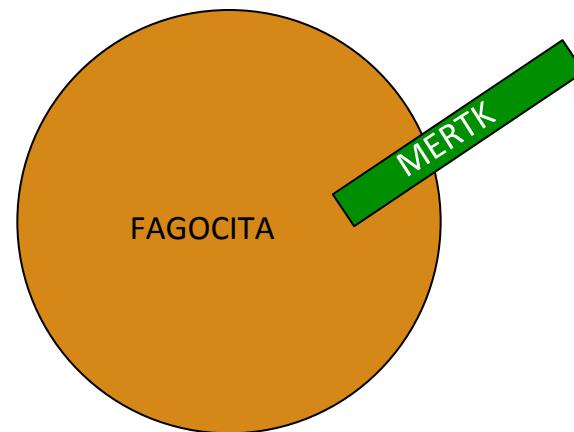
+TANC 6 h



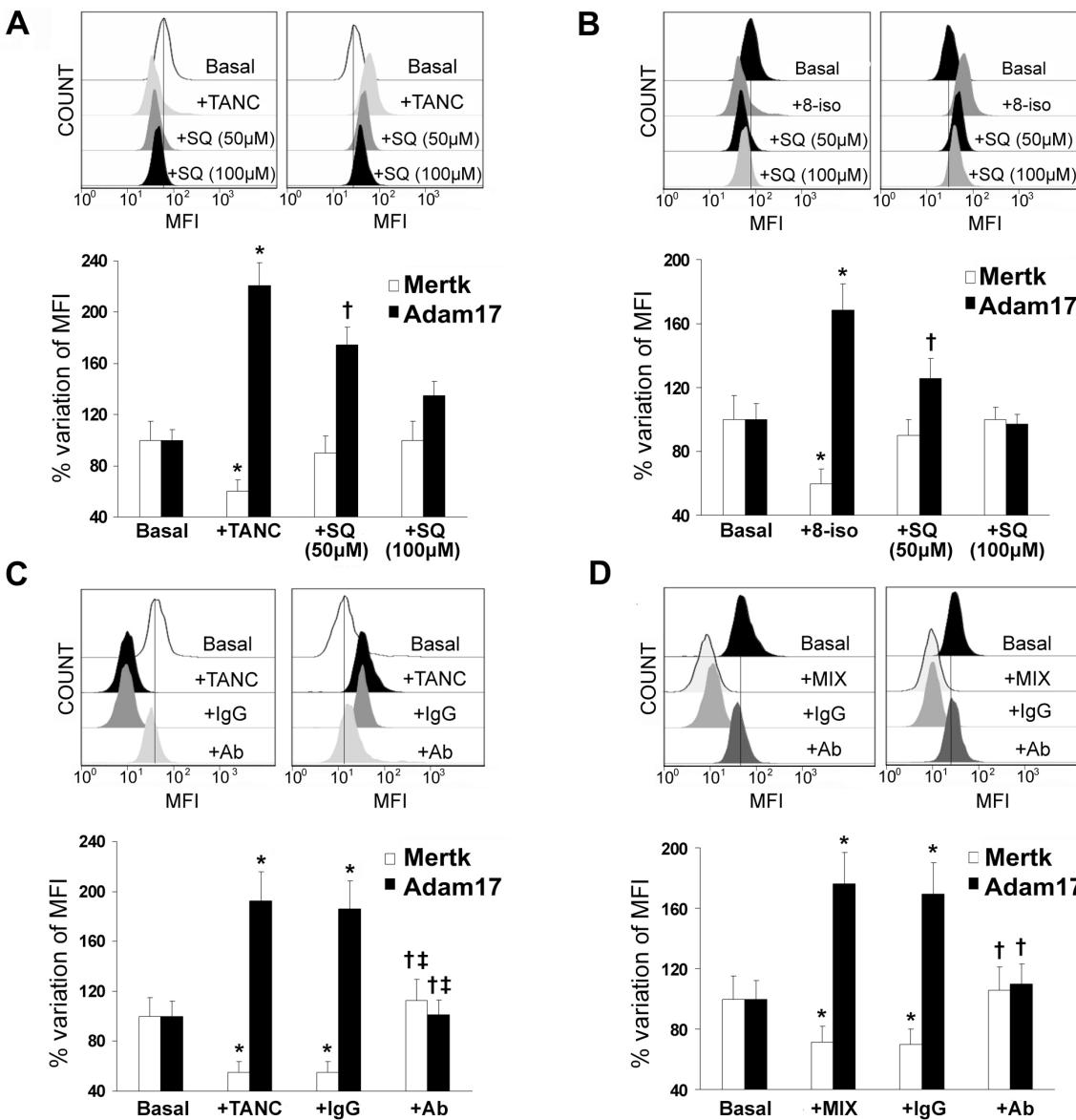
+TANC 24 h



+siRNA



Effect of SQ29512 and of G2A specific antibody on Adam17 and on the extracellular domain of Mertk induced by TANC extract, 8-isoPGF2 alpha and by HETEs and HODEs in THP-1 cells.



KEY POINTS

- Atherosclerotic plaque rupture is responsible for two-thirds of all acute events
- Although plaques vulnerable to rupture are characteristically large and contain big necrotic cores, they may not necessarily impinge on the coronary lumen because of expansive vascular remodeling
- Unstable plaques are called 'thin-cap fibroatheromas'; thin fibrous caps are severely inflamed
- Defective efferocytosis and secondary necrosis of apoptotic macrophages contribute to necrotic core enlargement
- Oxidative derivatives of PUFAs favour macrophage apoptosis
- Oxidative derivatives of PUFAs favour Adam17 expression and activity with Mertk receptor inactivation
- Oxidative derivatives of PUFAs may be markers of vulnerable plaque
- TP- and G2A- receptors may be future therapeutic targets