

Phosphatidylserine-dependent ingestion of apoptotic cells promotes TGF- β 1 secretion and the resolution of inflammation

Huynh, Fadok, Henson

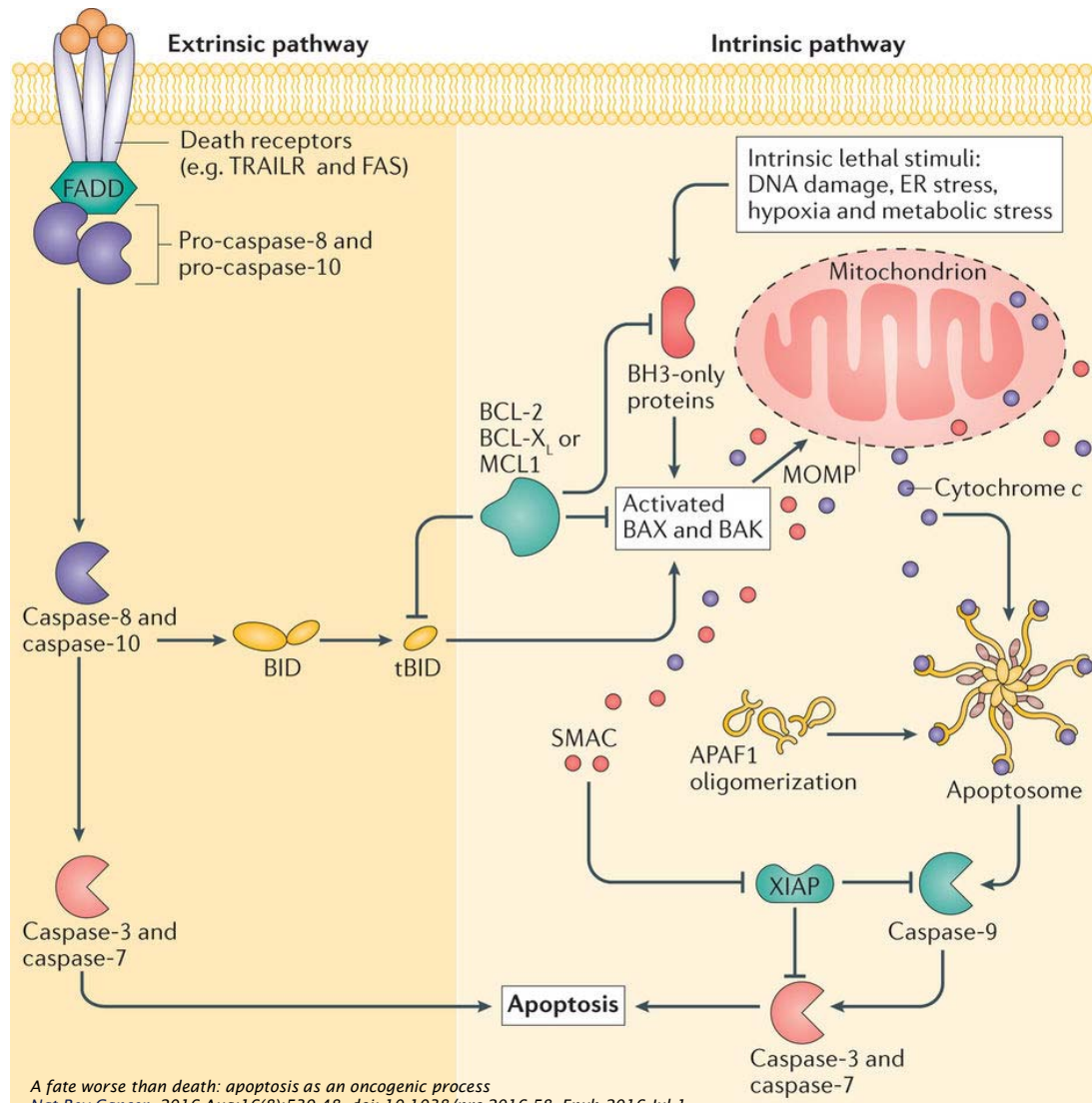
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background

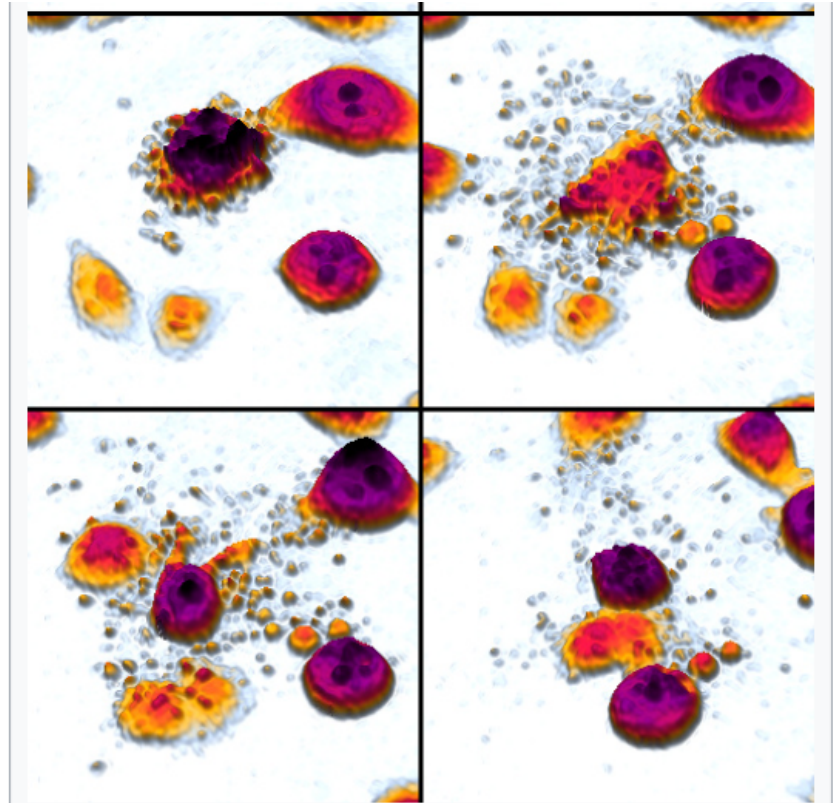
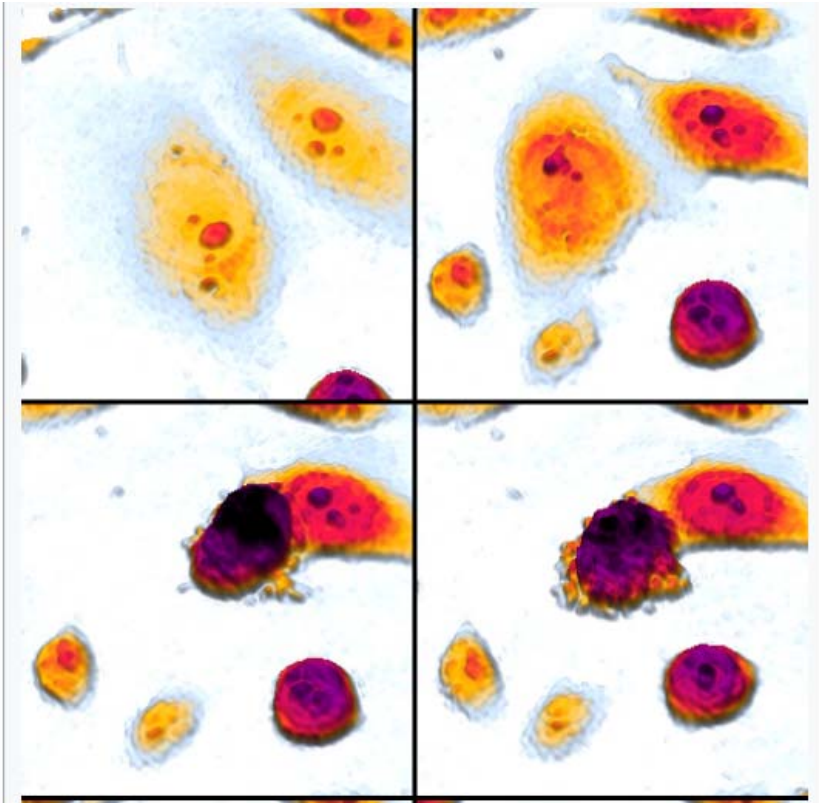
apoptosis
ancient Greek
'falling off'

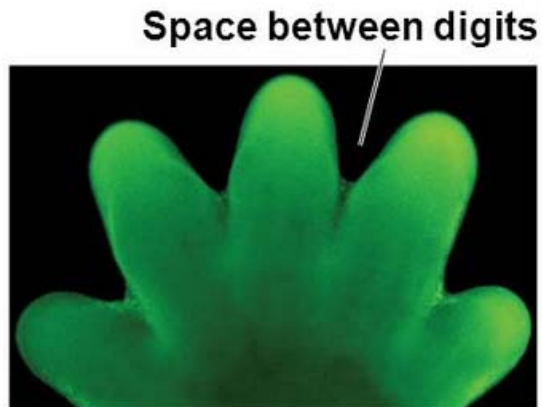
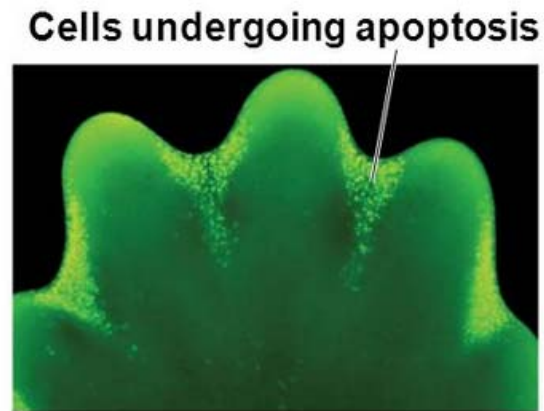
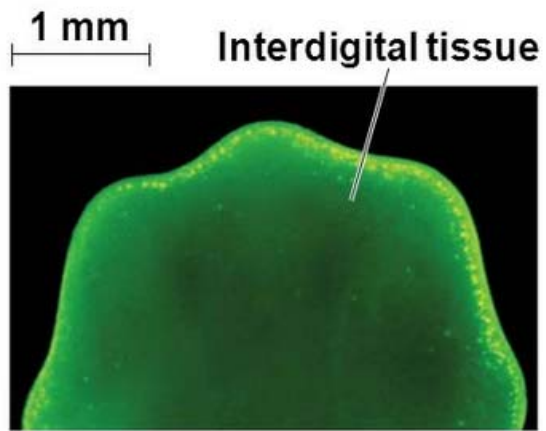


A fate worse than death: apoptosis as an oncogenic process
Nat Rev Cancer. 2016 Aug;16(8):539-48. doi: 10.1038/nrc.2016.58. Epub 2016 Jul 1.
Ichim G, Tait SW



•loss of PL asymmetry





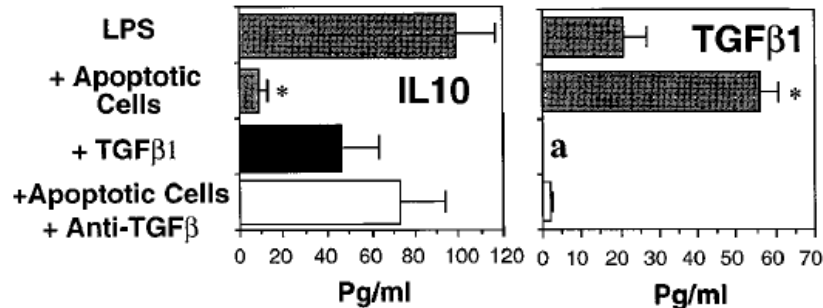
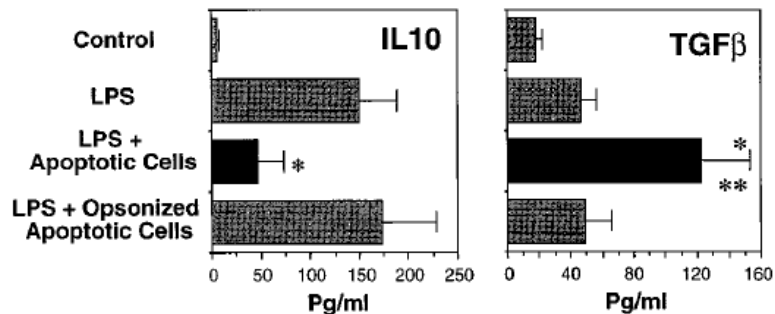
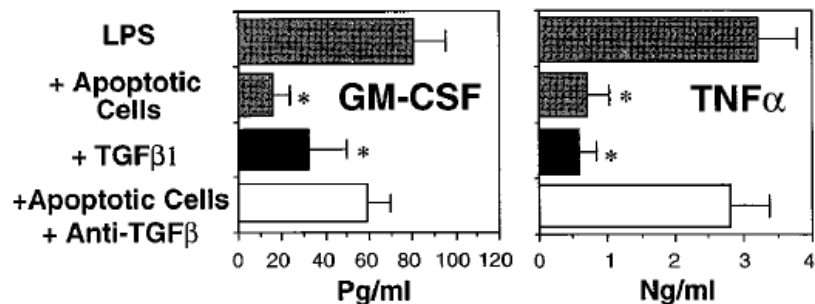
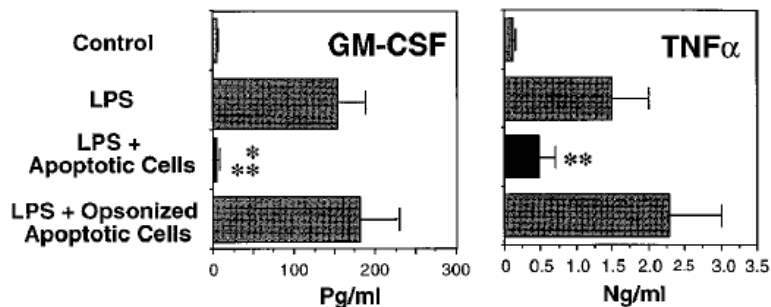
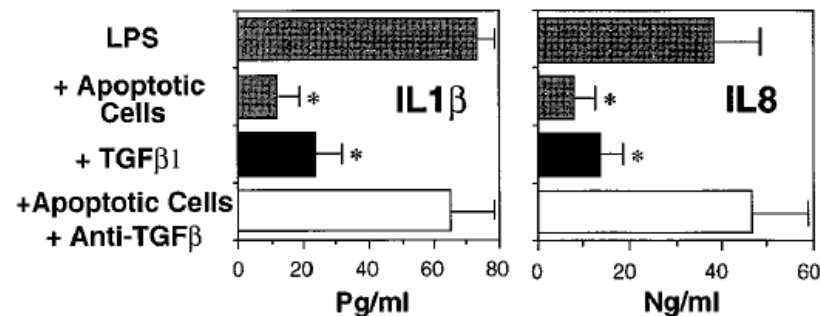
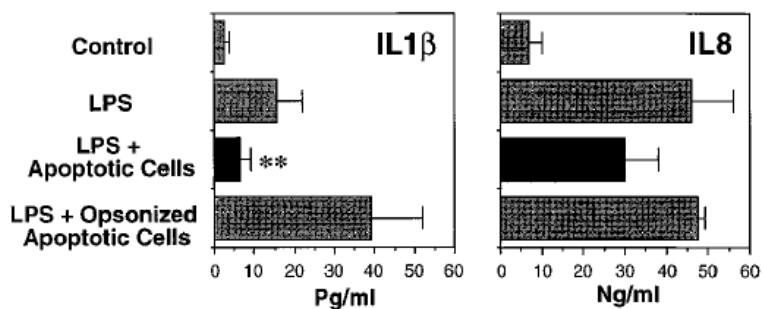
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- embryogenesis & adult: maintain tissue f(x) & structure
- engulfed by (non-)professional phagocytes
- | release of potentially toxic / immunogenic content
- clinical implication



mφ that have ingested apoptotic cells in vitro inhibit proinflammatory cytokine production through autocrine/paracrine mechanisms involving TGF- β , PGE₂, & PAF

Fadok, et al., 1998, *J Clin Invest*



purpose of this study

TGF- β 1 & R expressed by almost all cells

-| growth & dx/dt

regulates immune & infl responses

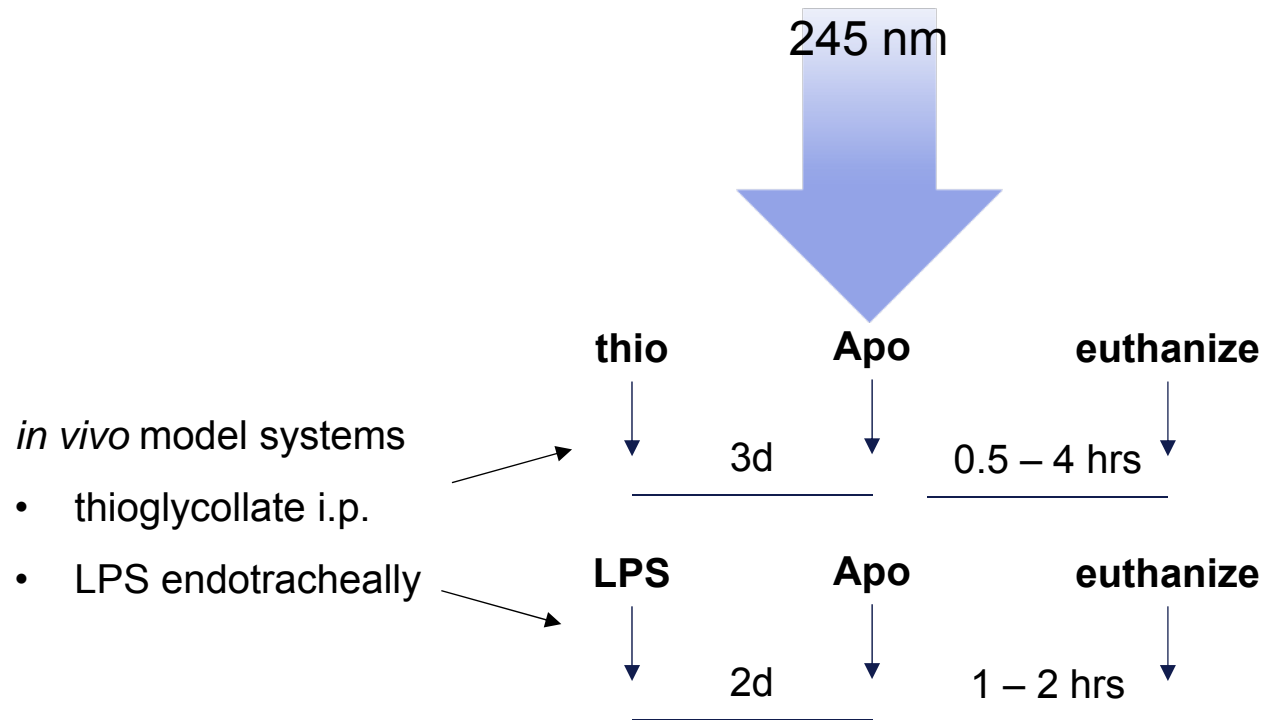
modulates wound healing, ECM composition, adhesion & migration

apoptotic cell recognition systems: PSR, vitronectin R, CD14, collectin R

- determine the role of TGF- β 1 in clearance of apop cells
- elucidate a potential role of PS for TGF- β 1 production following ingestion of apop cells

m&m's

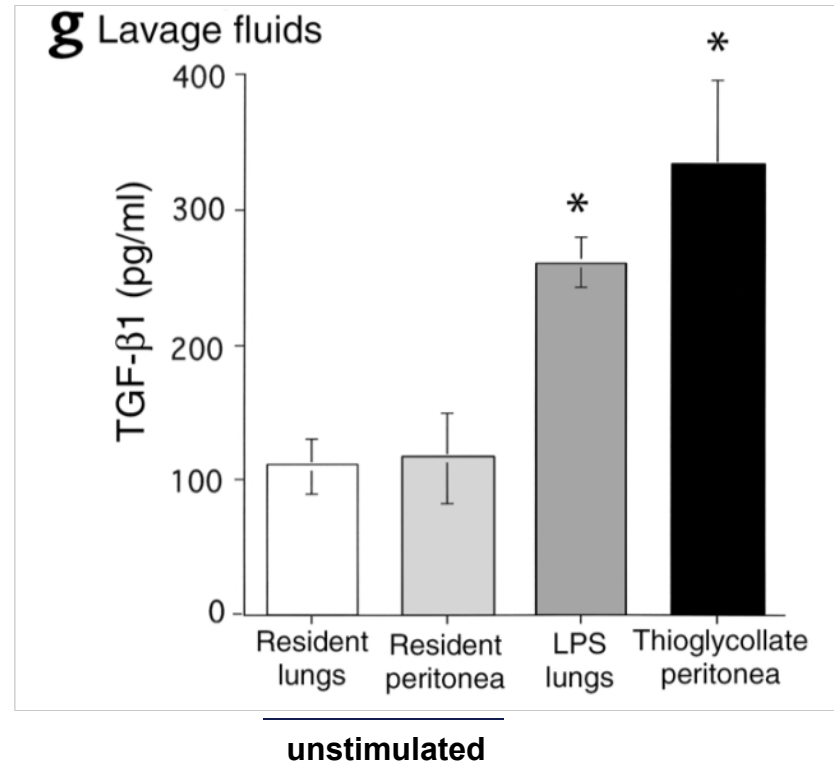
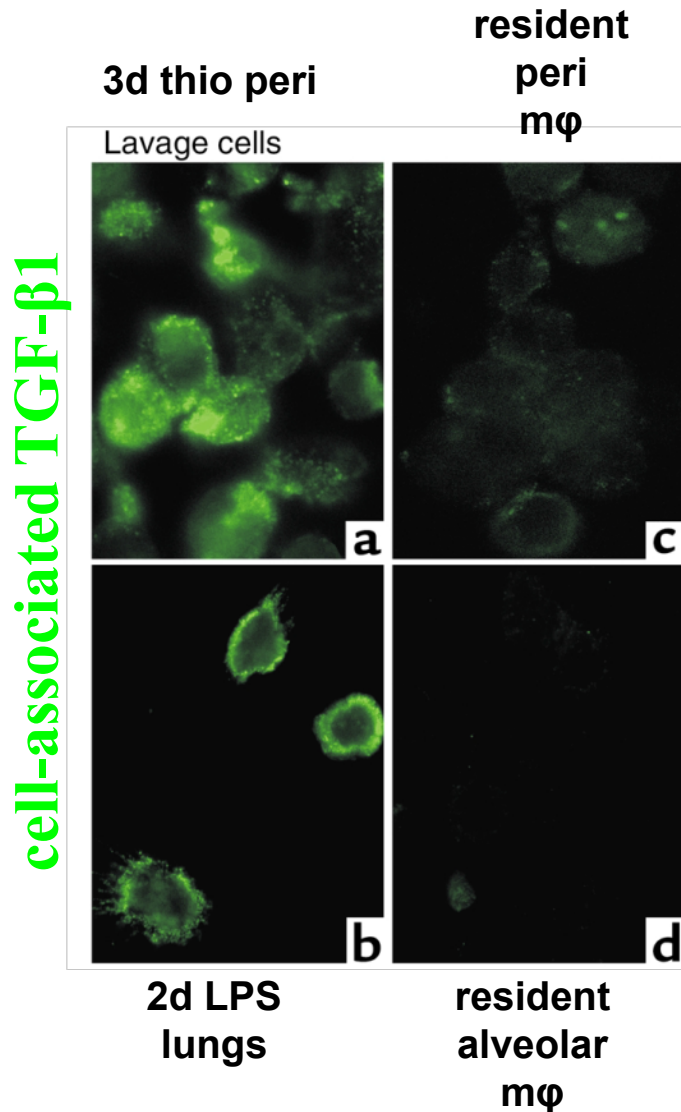
- human T lymphocyte Jurkat cell line
- human monomyelocyte PLB-985



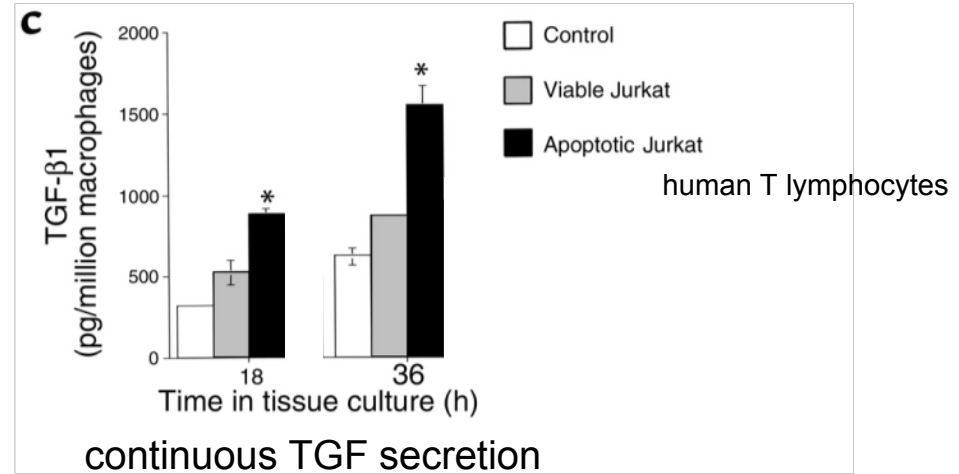
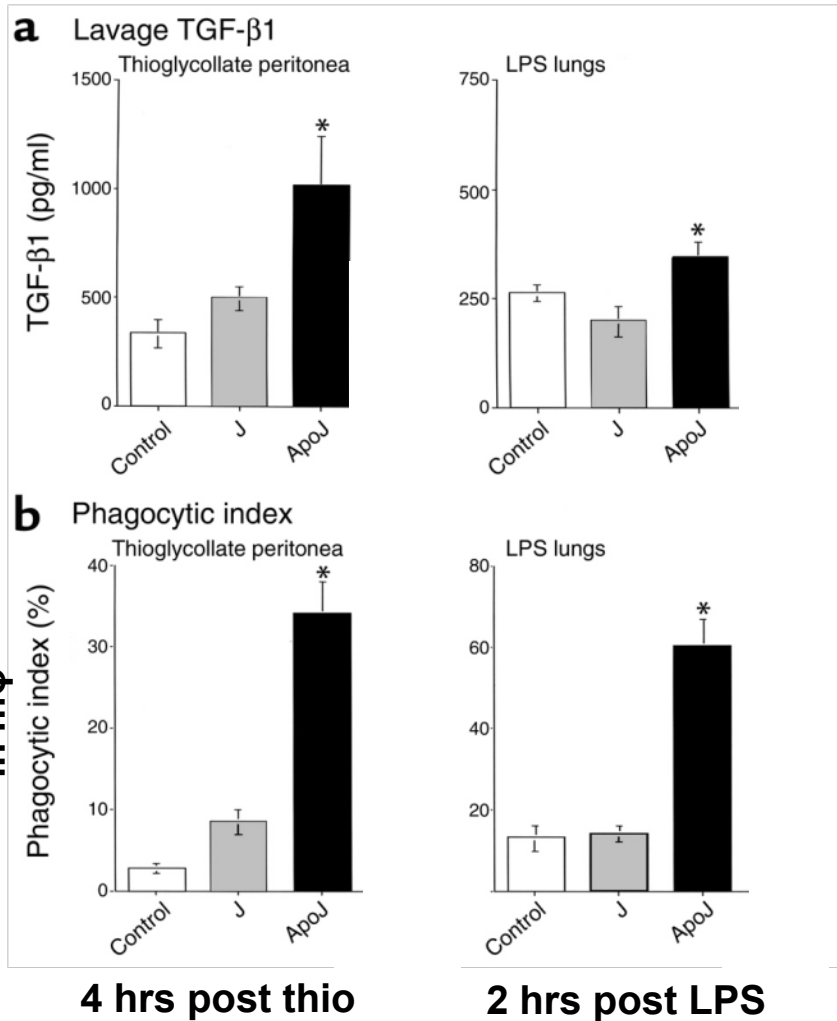
results



TGF- β 1 production of inflamed sites-derived m ϕ

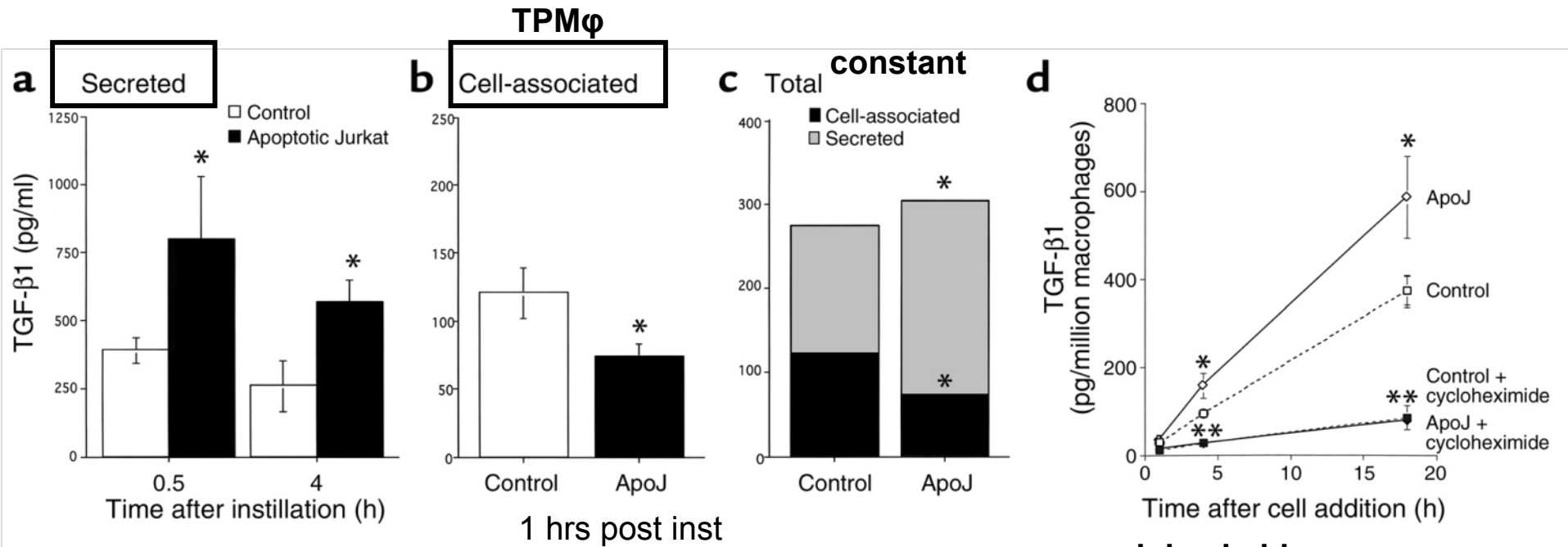


ApoJ-induced TGF- β 1 secretion correlates w/ ϕ cytic uptake



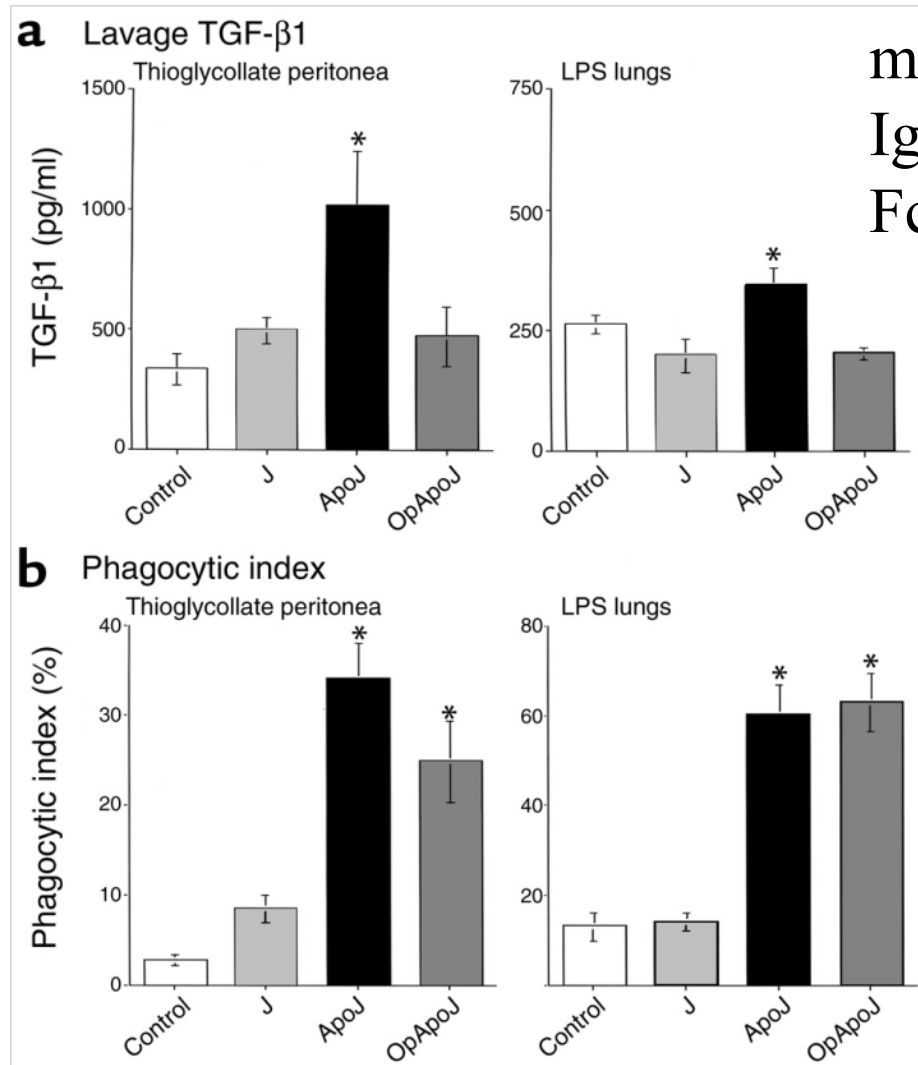
ApoJ in non-inflamed tissues failed to induce TGF secretion

TGF- β 1 secretion results from increased release & *de novo* synthesized TGF- β 1



cycloheximide
added 1 hr prior to addition of ApoJ
abolished TGF release

apoptotic cell recognition is specific for TGF- β 1 induction

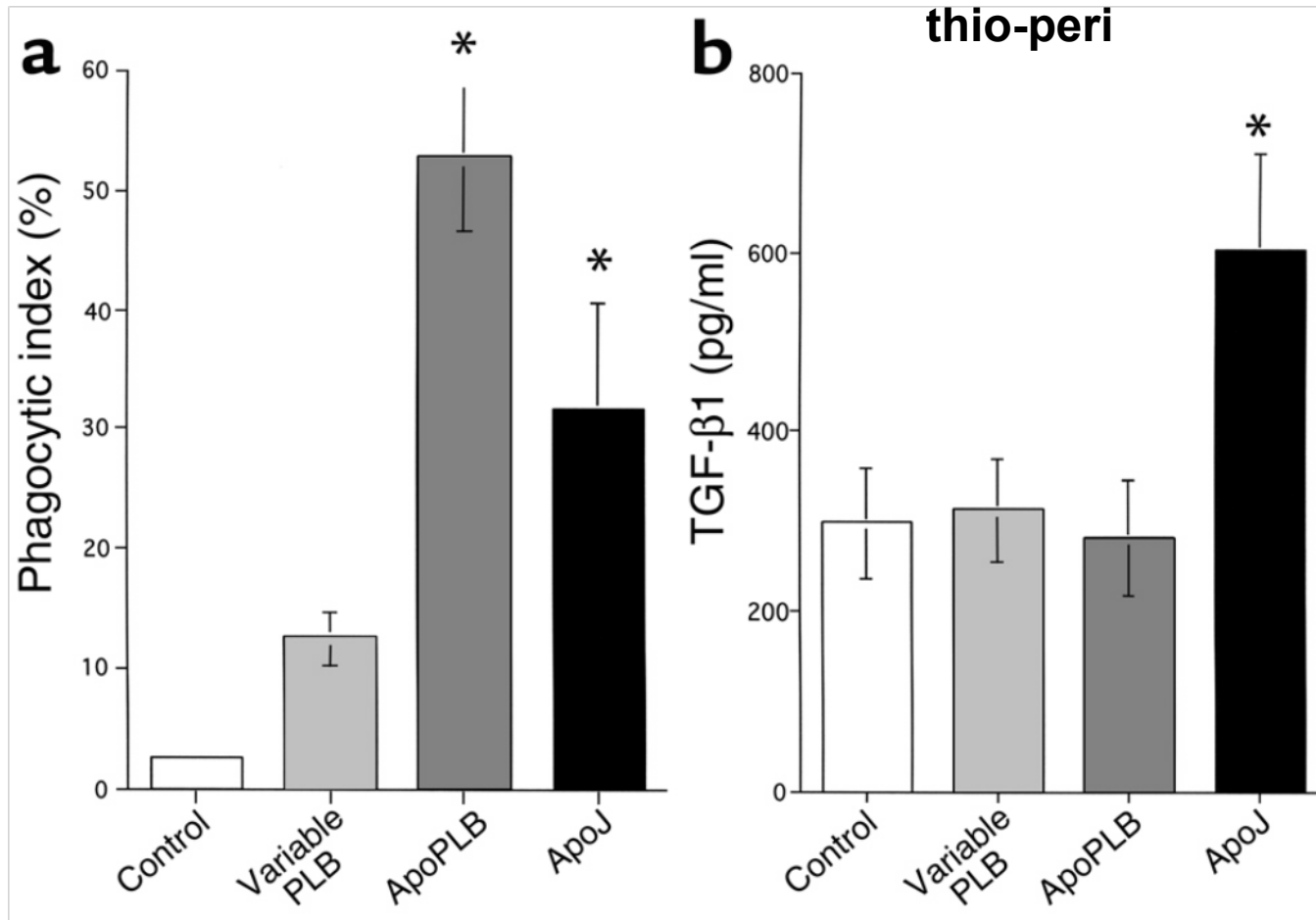


ms- α h CD45 (LCA)
IgG opsonization
Fc γ

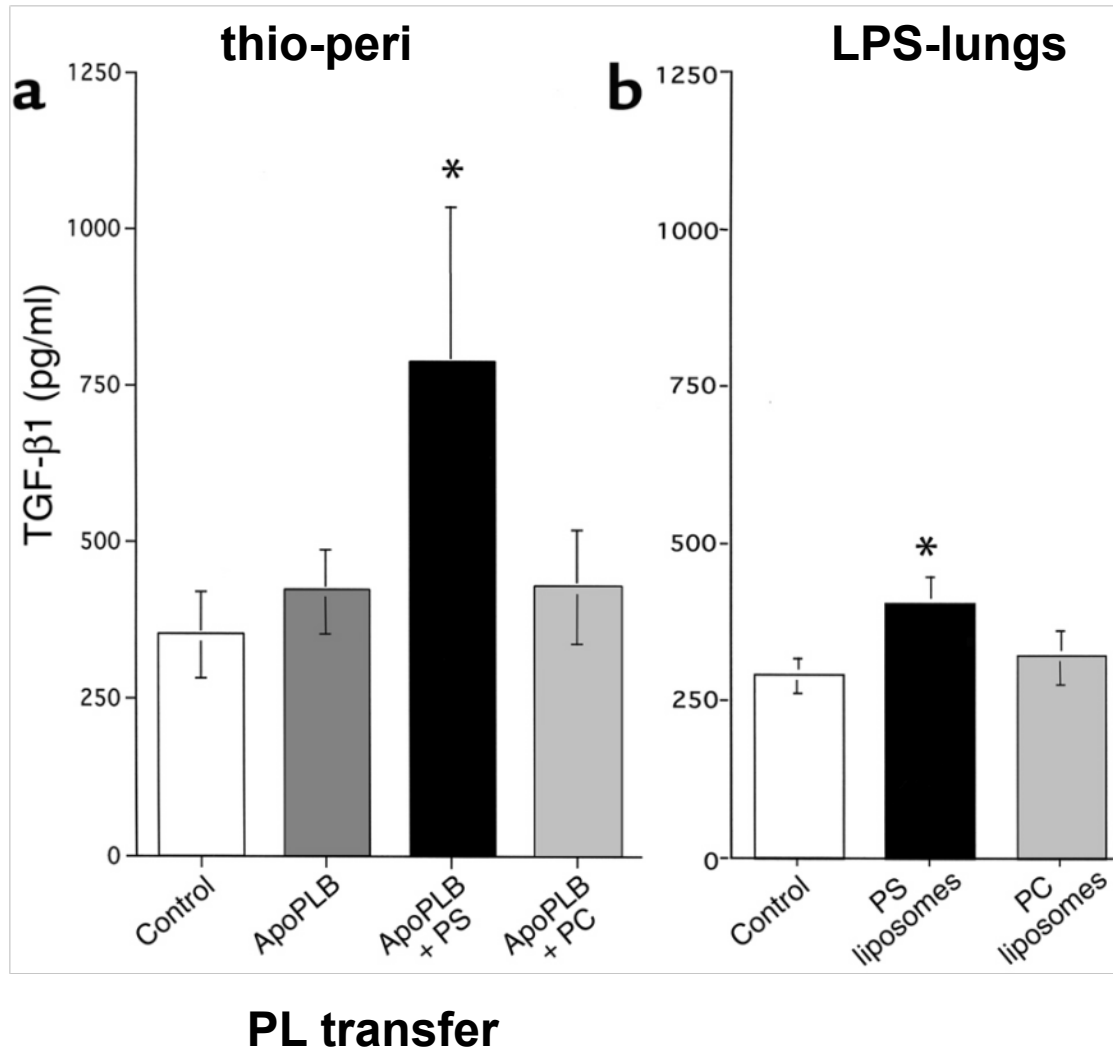
4 hrs post thio

2 hrs post LPS

Requirement of surface PS in apoptotic cell recognition for TGF- β 1 induction



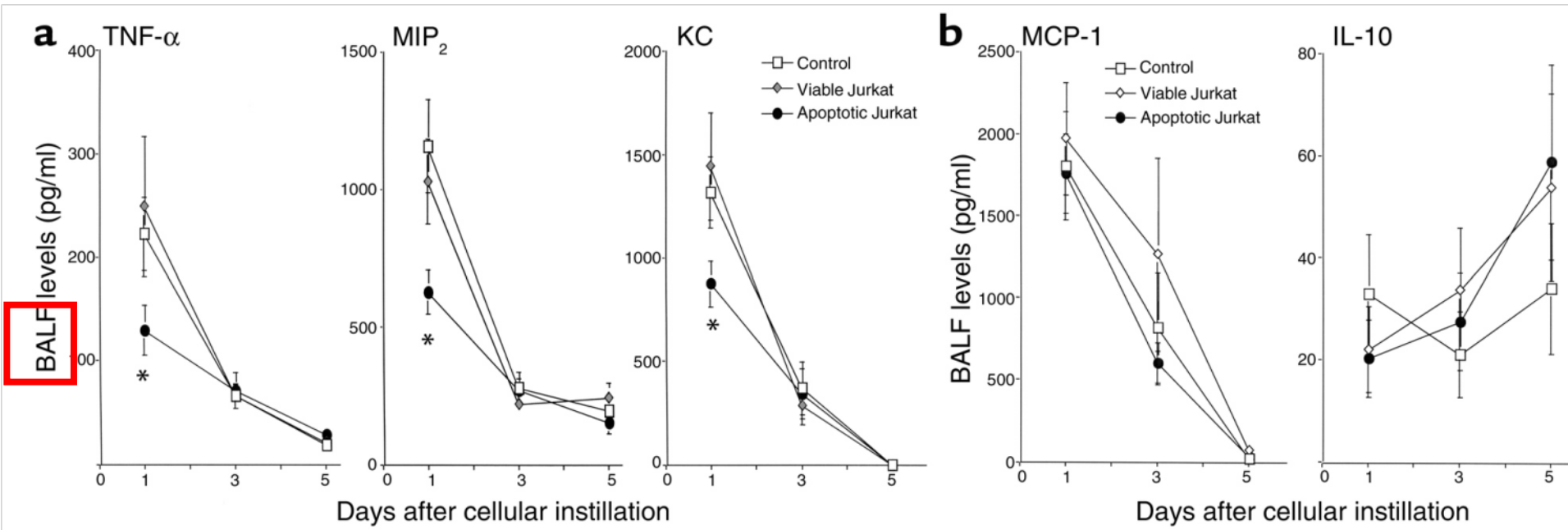
Requirement of surface PS in apoptotic cell recognition for TGF- β 1 induction, c'd



ApoJ-induced reduction of pro-inflammatory mediators

Δ 1d post cell instillation

no Δ

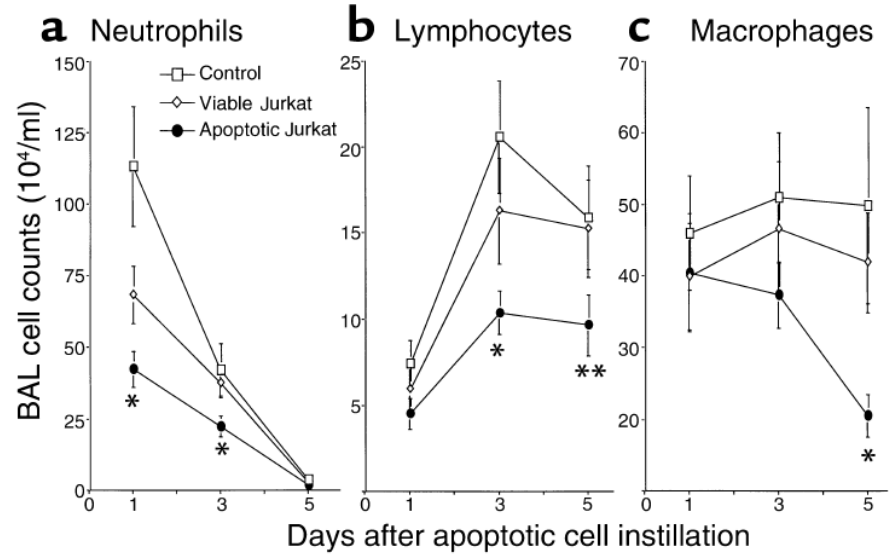
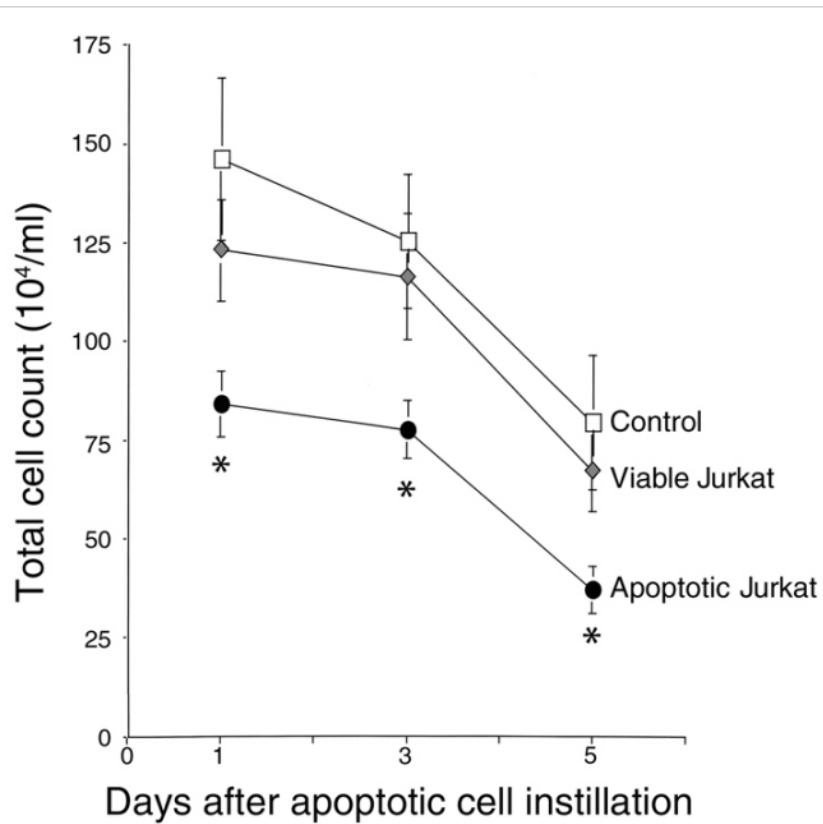


mp inflammatory protein2
 CXCL2
 chemokine 4 leukocytes

cytokine-induced
 neutrophil chemoattractant

monocyte chemoattractant
 protein 1
 CCL2
 monocytes, memTcells, DC

ApoJ resultet in reduction of infiltrated BALF mφ on d5

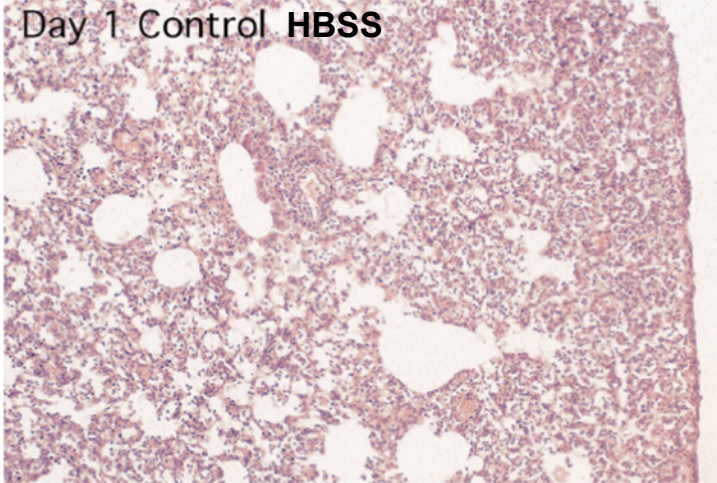


ApoJ resultet in reduction of infiltrated BALF mφ

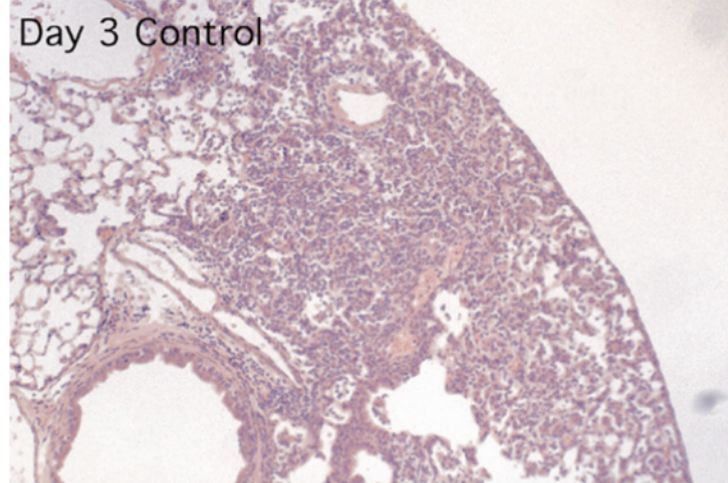
significant reduction in parenchymal infiltrates and intra-alveolar cells

LPS

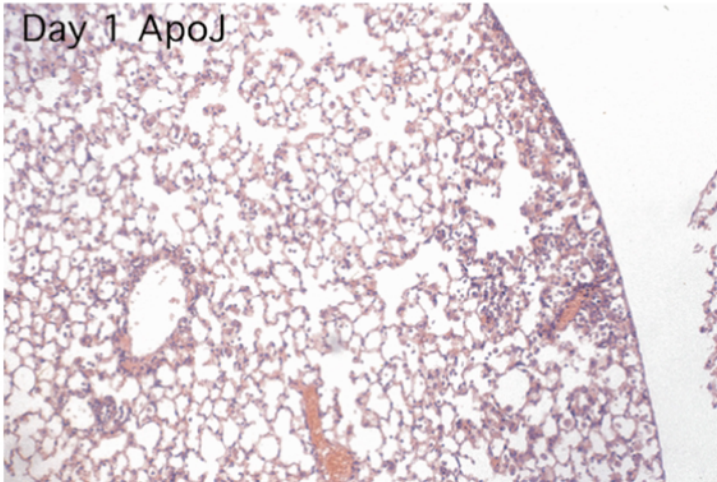
a Day 1 Control HBSS



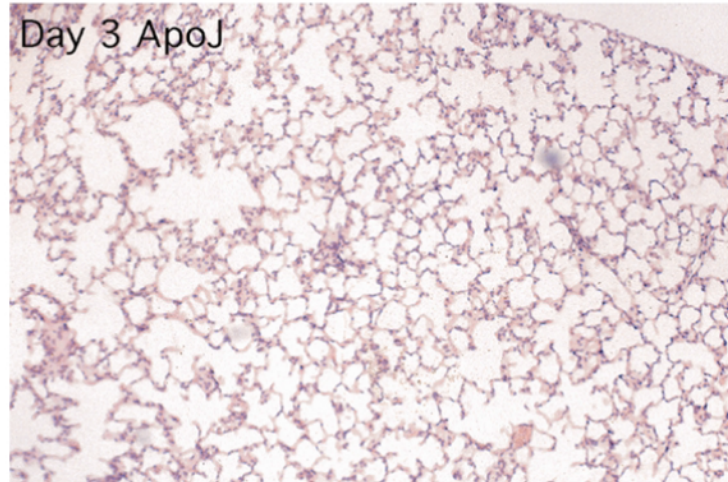
b Day 3 Control



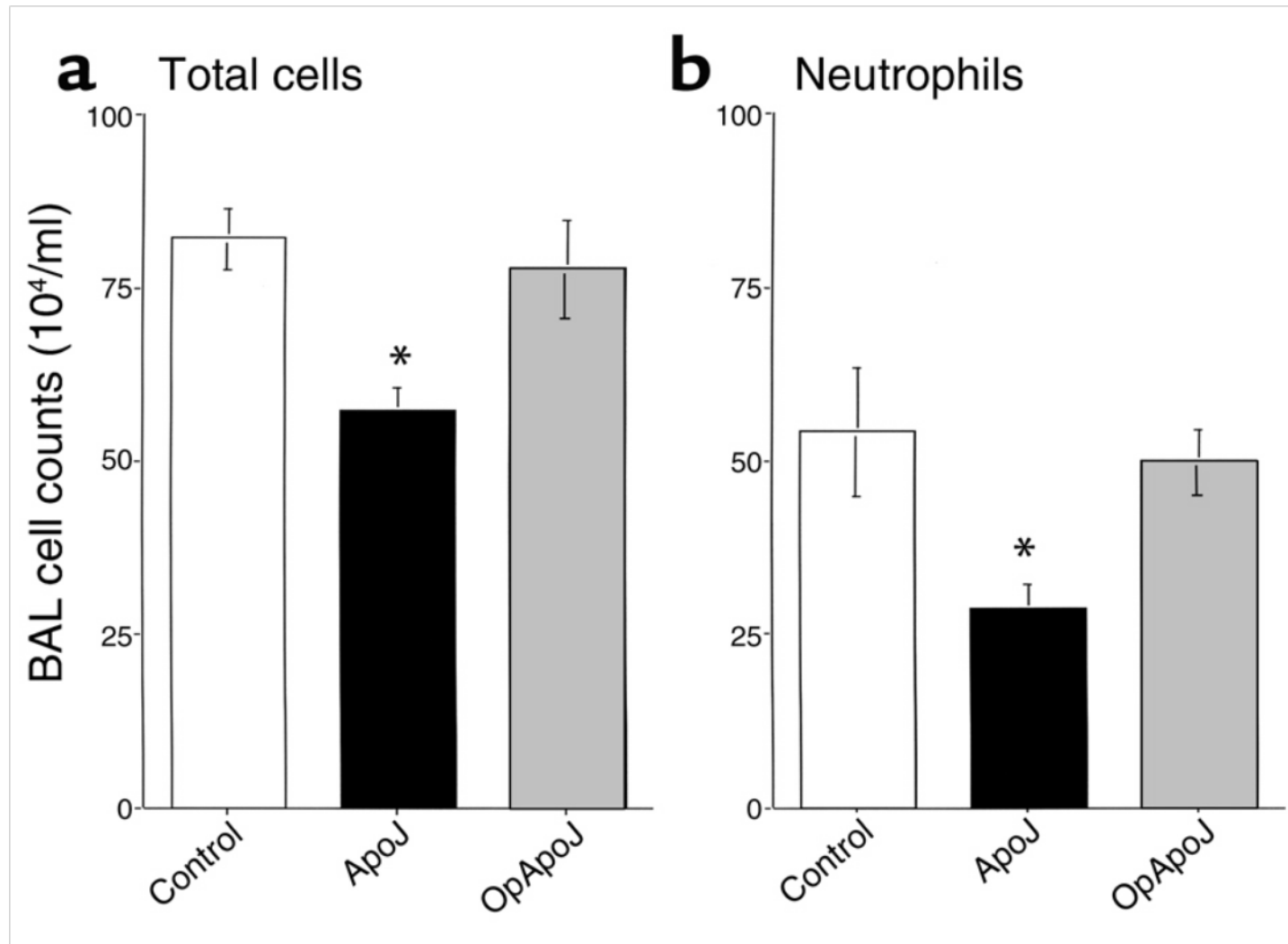
Day 1 ApoJ



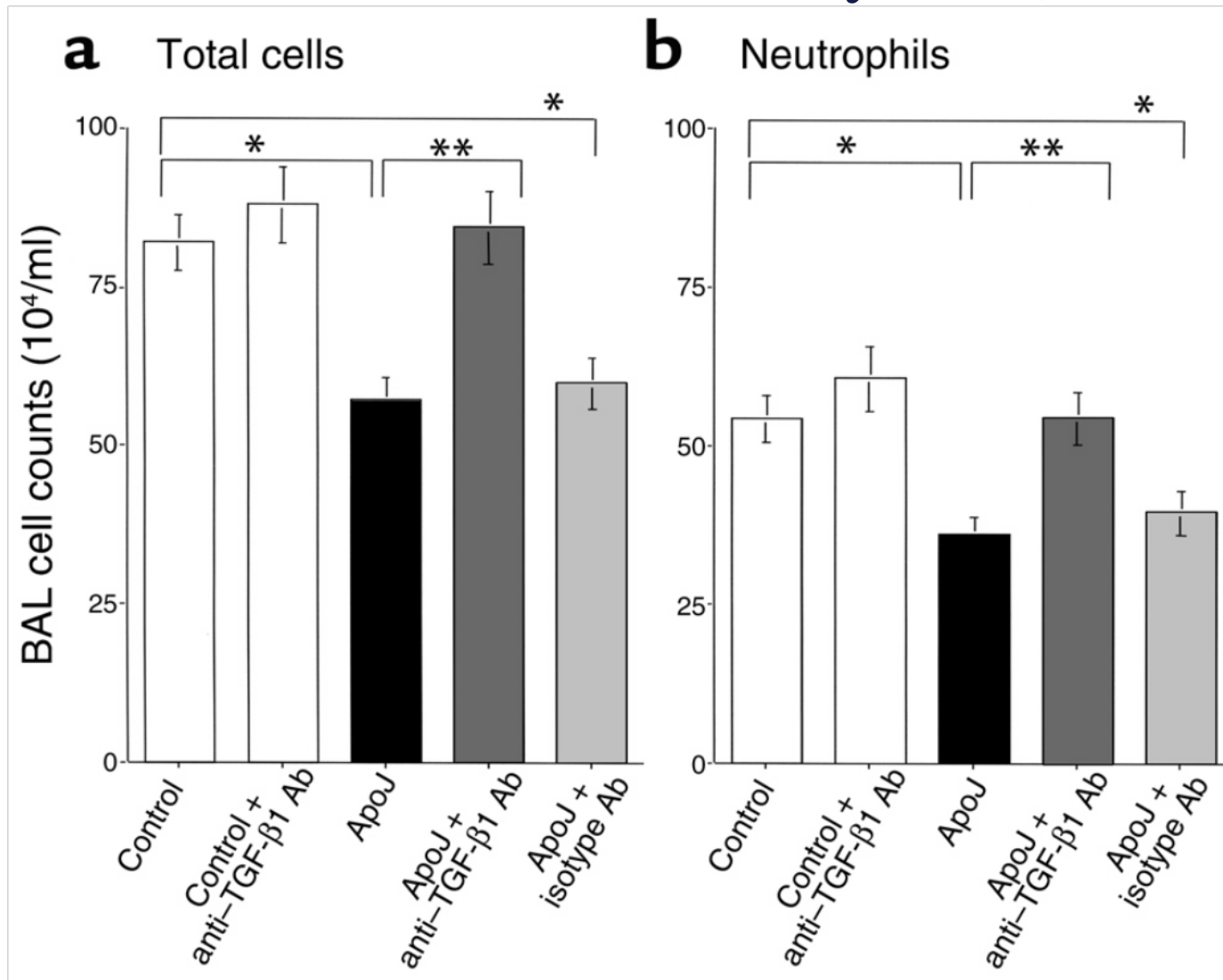
Day 3 ApoJ



Resolution of inflammation is specific for apoptotic cell clearance and is mediated by TGF



Resolution of inflammation is specific for apoptotic cell clearance and is mediated by TGF, c'd



concluding remarks

- instillation of apoptotic cells promotes TGF- β 1 production in inflamed tissues
- m ϕ -derived TGF- β 1 is preformed & *de novo* synthesized
- apoptotic cell recognition, but not Fc γ phagocytic system induces TGF secretion
- PS on apoptotic cell surface is crucial for TGF secretion
- reduction of pro-inflammatory mediators & infl cell infiltrates by instillation of apop cells
- **resolution of inflammation is specific for apoptotic cell clearance & mediated by TGF- β 1 & dependent on surface PS**

thank you

