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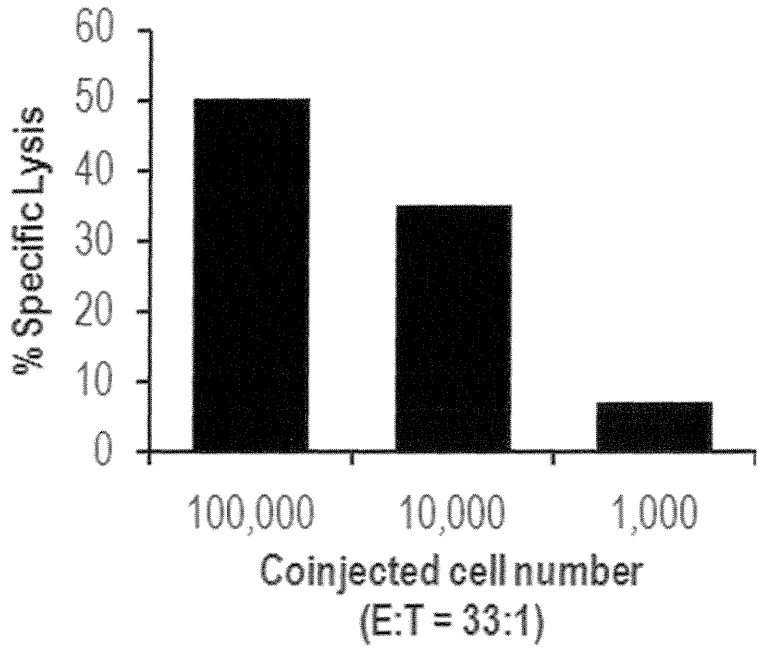

Fig. 1. Cells contain an endogenous adjuvant activity that augments the priming of $CD8^+$ T-cell responses

A limiting amount of antigen (5 μg ovalbumin-conjugated beads) was co-injected into mice together with either 10^5, 10^4, or10^3 mitomycin C-treated syngeneic GL261 cells. Seven days later, splenocytes were harvested and stimulated with ovalbumin-transfected EG7 cells. CTL activity was measured against EG7 cells 5 days later in a ^{51}Cr release assay. E:T ratio= 33:1. The data show that the GL261 cells, which lack antigen, contain an activity that markedly augments the priming of $CD8^+$ T-cell responses to the co-injected antigen.

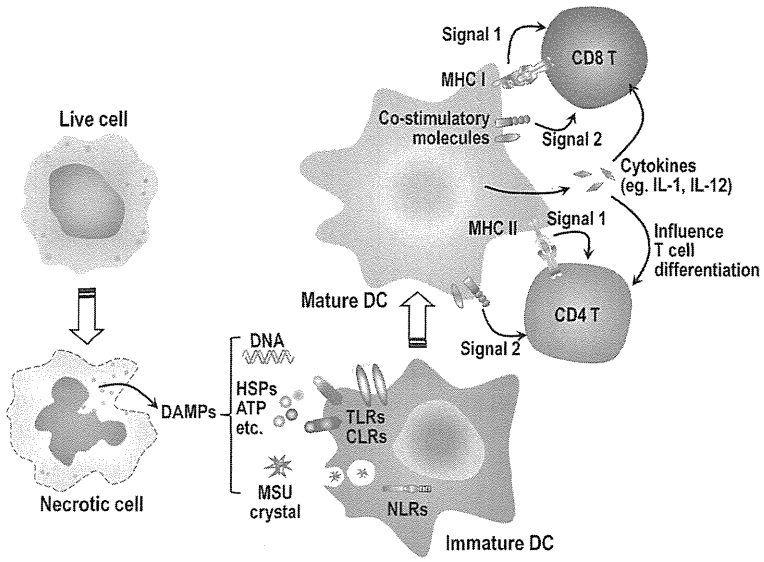

Fig. 2. Adjuvant effect of DAMPs in stimulating dendritic cells

When cells undergo necrosis intracellular DAMPs (such as DNA, HSPs, MSU, etc.) are released into the extracellular milieu. Some of these DAMPs can act as adjuvants to stimulate dendritic cells (DCs), through pattern recognition receptors, such as TLRs, CLRs, or NLRs, or other receptors to increase the expression of MHC molecules, co-stimulatory ligands, and cytokines. These mature DC can then optimally activate T cells and direct their differentiation. HSPs, heat-shock proteins; MSU, monosodium urate crystal; TLRs, Toll-like receptors; CLRs, C-type lectin receptors; NLRs, NOD-like receptors.

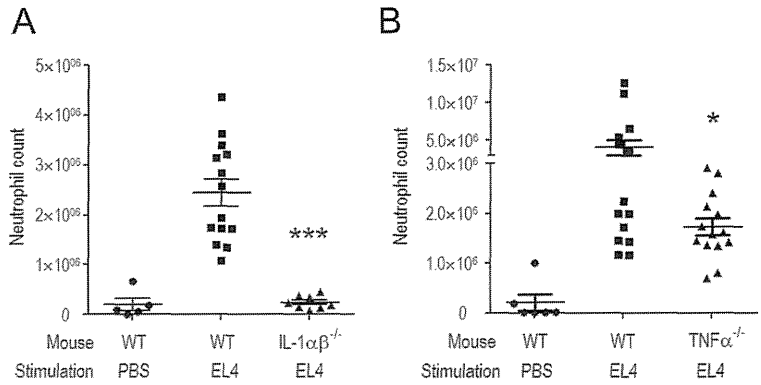

Fig. 3. Role of IL-1 and TNFα in cell death-induced inflammatory responses

Wildtype (WT) C57BL/6 and (A) IL-1αβ double-deficient or (B) TNFα-deficient mice were injected intraperitoneally with 30 million heat-shocked necrotic EL4 cells. Total neutrophil number in the peritoneal cavity was determined 14 h after stimulation. The data are combined results of three experiments with values from individual mice displayed along with means ± SEM. *$p<0.05$, ***$p<0.0001$ versus WT group. The data shown that TNFα can make some contribution to the cell death-induced inflammatory responses; notably this contribution is less than from IL-1.

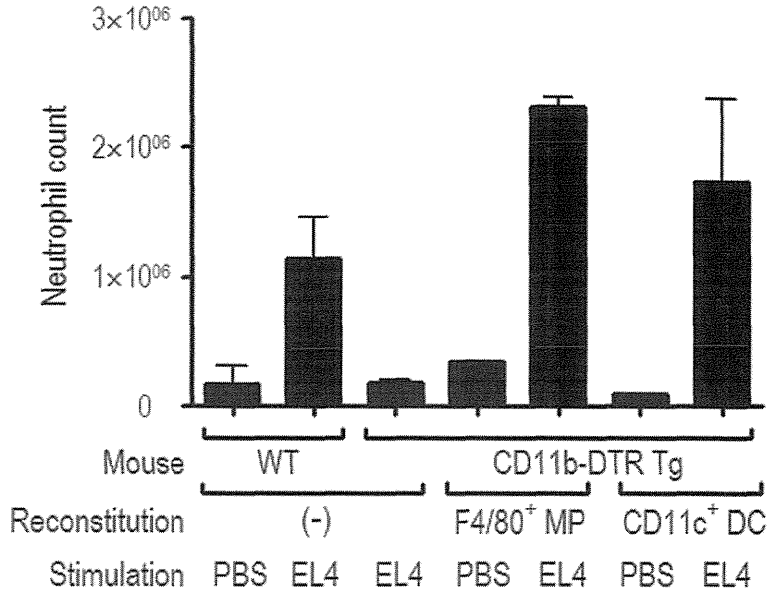

Fig. 4. Analysis of the cells required for the generation of cell death-induced inflammation

Wildtype (WT, FVB/N) or CD11b-DTR-Tg mice were injected intravenously with 500 ng of diphtheria toxin (500 ng); this procedure depletes macrophages in the transgenic mice. The treated animals were then reconstituted with F4/80$^+$ macrophages (MPs) from thioglycollate-elicited peritoneal cells or CD11c$^+$ dendritic cells (DCs) from spleens of Flt3L-treated mice (C57BL/6 mice injected with Flt3L-transduced cells). Neutrophil number in the peritoneum was determined 14 h after intraperitoneal injection of heat-shocked necrotic EL4 cells or PBS and displayed as the mean ± SEM. The data show that loss of CD11b$^+$ cells in the host markedly inhibits inflammation to dead cells and that these responses can be reconstituted by the adoptive transfer of MPs or DCs.

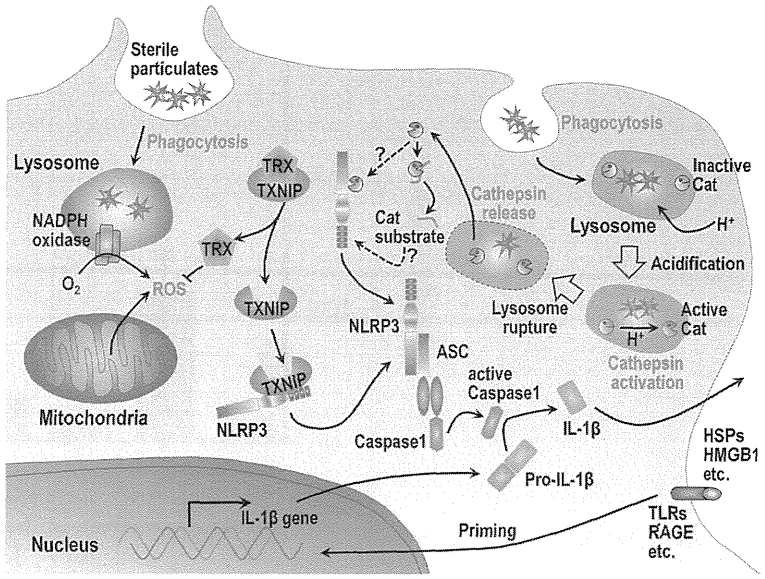

Fig. 5. Mechanisms of NLRP3 inflammasome activation by sterile stimuli

There are two distinct mechanisms proposed as to how NLRP3 inflammasomes are activated by sterile particles. The first model suggests that after phagocytosis, the particles stimulate ROS from NADPH oxidase and/or mitochondria. The increased level of ROS in the cytosol is then sensed by thioredoxin (TRX) and causes its dissociation from thioredoxin-binding protein (TXNIP). The released TXNIP then binds and activates NLRP3 through interaction with LRR and NATCH domains of NLRP3. The second model also requires phagocytosis of the sterile particles. In this pathway phagosomes acidify and the drop in pH causes Cathepsin (Cat) activation. Through some unknown mechanism, some of the particulate-containing phagosomes rupture and release their contents into the cytosol. This vacuolar rupture is somehow sensed by NLRP3, possibly by binding a cleavage product of activated cathepsins or by the cathepsins cleaving NLRP3 in a way that activates it. NLRP3 associates with ASC and pro-Caspase 1 to form the inflammasome and cleaves the Caspase 1 zymogen into its active form. Active Caspase 1 then cleaves pro-IL-1β into active IL-1β. In most cases, the synthesis of pro-IL-1β is induced by "priming", which requires the stimulation of pattern recognition receptors or cytokines to stimulate transcription of pro-IL-1β.