inflammatory disorders like sepsis, inflammatory bowel disease, rheumatoid arthritis, and other autoimmune diseases. At concentrations found during inflammation *in vivo* they exhibit pro-inflammatory effects *in vitro*, depending on interaction and activation of TLR-4 expressing cells of the innate immune system. However, the regulation of the activity of DAMP molecules is only poorly understood.

S100A8 and S100A9 are known to form homodimers, heterodimers as well as heterotetramers and our investigations showed that the activity of S100A8/S100A9 strongly depends on oligomer formation. Due to their pro-inflammatory properties alarmins are supposed to enhance not only innate but also adaptive immune processes via activation of dendritic cells. In contrast to this widespread view we now have evidence for a novel mechanism by which S100A8 and S100A9 dampen adaptive immunity. We observed that S100A8/S100A9 complexes inhibit maturation of bone marrow-derived DC resulting in a weaker T cell-stimulatory ability. Next we verified our findings *in vivo* in a mouse model of allergic contact dermatitis (ACD), known to be a DC-dependent T cell driven disease. We found a stronger disease outcome in S100A9 deficient mice than in wt mice. Moreover T cells from challenged S100A9 deficient mice secreted more IL-17, a cytokine known to trigger inflammatory reactions, compared to their wt counterparts. In conclusion, an enhanced Th17 response in association with more active DC accounts for the increased disease outcome of ACD in S100A9 deficient mice.

Our results link a pro-inflammatory role of a danger molecule on innate immune mechanisms to a regulatory function in adaptive immune responses.

1.08
Immobilized immune complexes stimulate release of neutrophil extracellular traps from human neutrophils via FcγRIIIb by induction of reactive oxygen species

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Background: Neutrophil activation through immune complexes (IC) plays a central role in pathogenesis of autoimmune inflammatory diseases. However, the effect of surface-bound IC on release of neutrophil extracellular traps (NETs) remains uncharacterized.
Materials and methods: Human neutrophils were incubated with plate-bound HSA/anti-HAS immune complexes and release of reactive oxygen species (ROS) and NETs was tested. The contribution of various ROS was assessed by using inhibitors of ROS-generating pathways. Roles of FcγRII and FcγRIIIb were determined by incubation with blocking antibodies. Signaling pathways engaged downstream of FcγR were investigated by western blotting and use of specific inhibitors.
Results: Treatment of neutrophils with immobilized IC significantly induced the release of NETs. The IC-induced NET formation depends on ROS-production by NADPH-oxidase and myeloperoxidase. Activation of IC-induced oxidative burst is mediated by FcγRII and in a stronger manner by FcγRIIIb, whereas NET release mainly depends on activation of FcγRIIIb. The p38-MAPK-andERK1/2 pathways link the IC-induced NETosis downstream of FcγR, as these molecules are phosphorylated upon IC-stimulation and specific inhibitors abrogated NET formation. We also observed a role of Syk, Src and PI3K in IC-induced NET formation, suggesting that FcγRIIIb, which lacks an intracellular domain, signals in association with FcγRIIa.
Conclusion: Present datashow for the first time that immobilized IC induce NET formation by human neutrophils in a ROS dependent manner via FcγRIIIb and suggest that NETs play a role in autoimmune inflammatory disorders associated with surface-bound IC.

1.09
Engineered nanoparticles (ENM) cause lung pathology by increasing lysosomal membrane permeability and activation of the NLRP3 inflammasome in macrophages

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Background: The purpose of the study was to determine the mechanism of bioactivity of ENM by linking their ability to cause lysosomal dysfunction and activation of the NLRP3 inflammasome in macrophages to lung pathology.
Materials and methods: A library (raw and modified MWCNT, metal oxides of different shapes and modifications, and silver of different sizes) of nanomaterials were prepared, characterized and tested *in vitro* using THP-1 macrophages, alveolar macrophages isolated from C57Bl/6 mice and *in vivo* using C57Bl/6 mice. Assessments were made of: uptake, lysosomal dysfunction, cathepsin B release, NLRP3 inflammasome activation, IL-1β release, lung inflammation and pathology.
Results: All ENM were effectively taken up by macrophages. However, only bioactive ENM caused phagolysosomal membrane disruption, cathepsin B release, NLRP3 inflammasome activation and IL-1β release from both macrophage models. THP-1 cells proved to be a more sensitive model than primary macrophages. Furthermore, the relative activity of ENM in THP-1 cells was a good predictor of *in vivo* NLRP3 inflammasome activation, inflammation and lung pathology. Long aspect ENM of the same material were more active than spherical and dependent on length. Carboxylation of ENM decreased bioactivity and surface area was a good predictor of bioactivity of spherical materials.
Conclusions: ENM cause lung inflammation and injury through activation of the NLRP3 inflammasome and there is now increasing knowledge linking ENM structure with bioactivity.

1.10
Annexin A1 turns off inflammation

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To avoid self-inflicted damage to the host, an appropriate inflammatory response against xenobiotic and internal (e.g. ischaemia) insults must be proportionate in its intensity, duration and location. This goal is achieved by an articulate cascade of pro-inflammatory and pro-resolving mediators, engaging specific receptors (by and large GPCRs) to modulate several distinct processes spanning from leukocyte trafficking to cell apoptosis, from efferocytosis to cell egress via the lymph vessels. Annexin A1 (AnxA1) is a pro-resolving and homeostatic mediator that promotes quite a few of these cellular responses mainly by