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A GUIDE TO...

A guide to crystal-related and nano- or microparticle-related tissue responses

Shrikant R. Mulay[1], Stefanie Steiger[2], Chongxu Shi[2] and Hans-Joachim Anders[2]

1 Pharmacology Division, CSIR-Central Drug Research Institute, Lucknow, India
2 Renal Division, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, LMU Munich, Germany

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Correspondence
H. –J. Anders, Nephrologisches Zentrum, Medizinische Klinik und Poliklinik IV, Klinikum der Universität München, Ziemssenstr. 1, D-80336 München, Germany
Tel: +49-89-4400-53583
E-mail: hjanders@med.uni-muenchen.de

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Crystals and nano- and microparticles form inside the human body from intrinsic proteins, minerals, or metabolites or enter the body as particulate matter from occupational and environmental sources. Associated tissue injuries and diseases mostly develop from cellular responses to such crystal deposits and include inflammation, cell necrosis, granuloma formation, tissue fibrosis, and stone-related obstruction of excretory organs. But how do crystals and nano- and microparticles trigger these biological processes? Which pathomechanisms are identical across different particle types, sizes, and shapes? In addition, which mechanisms are specific to the atomic or molecular structure of crystals or to specific sizes or shapes? Do specific cellular or molecular mechanisms qualify as target for therapeutic interventions? Here, we provide a guide to approach this diverse and multidisciplinary research domain. We give an overview about the clinical spectrum of crystallopathies, about shared and specific pathomechanisms as a conceptual overview before digging deeper into the specialty field of interest.

Introduction

Atoms or ions aggregating in a periodic manner endorse a spontaneous self-perpetuating growth of regular-shaped crystals. Organisms also catalyze the aggregation of atoms and ions into amorphous crystals and use these to create endo- or exoskeletal structures such as corals, shells, bones, or teeth [1]. In the wrong place, the same process can be injurious, for example, extraskeletal calcifications of vascular walls or tendons. Single crystals glued together can grow up to polycrystalline masses such as calculi or stones. Indeed, numerous diseases are caused by or at least associated with deposition of crystals, misfolded proteins, or airborne particulate matter at nano-, micro-, or macroparticle size [1] (Table 1). Similar to infectious organism, it is often not the agent itself causing health problems but rather the body's own responses originating from life-saving ancient danger response programs [2,3]. Such responses include necroinflammation [4], immunothrombosis [5], granuloma formation, and tissue fibrosis [6]. Other diseases relate to stone formation and ductal obstructions [7–9]. The discovery of the NACHT, LRR, and PYD domains-containing protein 3 (NLRP3) inflammasome as a universal signaling platform that converts the uptake of very diverse microparticles into secretion of interleukin (IL)-1β/IL-18 and the subsequent inflammation has raised broad attention across different research domains [10,11]. This landmark insight posed a number of important research questions such as: Do other shared pathomechanisms across different crystallopathies exist or are

Abbreviations
CC, cholesterol crystals; Clec, C-type lectin; COPD, chronic obstructive pulmonary disease; CYPD, cyclophilin D; IL, interleukin; MARCO, macrophage receptor with collagenous structure; MLKL, mixed lineage kinase domain-like; MOMP, mitochondrial outer membrane potential; MSU, monosodium urate crystals; NETs, neutrophil extracellular traps; NLRP3, NACHT, LRR, and PYD domains-containing protein 3; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species; SR, scavenger receptor.

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there also unique pathomechanisms specific to single molecular crystal entities, crystal shapes, or sizes [2]? Here, we provide a guide into general concepts of this research domain, highlight some of the recent research activities, and provide key references for further reading.

Crystal formation and handling in human diseases

Supersaturation of solutes often results in the formation of microcrystals, which serves as a nidus for crystal growth *in vitro*. Inside the human body, the excretory organs are especially prone to crystallization upon supersaturation since they concentrate ions from body fluids to facilitate excretion, for example, via the urinary and biliary tract. Certain pathological conditions involve formation of crystals inside the human body such as vascular calcification and atherosclerosis. Furthermore, misfolded proteins are known to form self-aggregates leading to the formation of fibrillary proteins, for example, α-synuclein in Parkinson's disease or tau and amyloid-beta in Alzheimer's disease. Interestingly, a recent study reported that under certain conditions, protein fibrils form protein crystals—the most stable form of proteins consuming less energy than fibrils on the energy landscape of protein folding [12]. Indeed, the deposition of amyloid crystals, and not amyloid fibrils, might be the main pathomechanisms of progressive neurodegenerative diseases and warrants further exploration. Moreover, certain drugs also tend to crystallize in the human body, for example, acyclovir, indinavir, amoxicillin, and methotrexate (MTX) [13,14]. In addition, dying cells form crystals of uric acid, as well as eosinophil granule releases form Charcot–Leyden crystals (CLCs) that serve as danger-associated molecular patterns (DAMPs) and trigger inflammation [15,16]. Another route of exposure to crystals and crystalline particles is environmental exposures where particulates enter the human body from the outside. For example, airborne occupational, environmental particulate matter enters the lungs via inhalation and eyes via direct exposure. Cosmetics, metallic, plastic or silicone implants, dental materials [17,18], as well as nanoparticles used as drug carriers, represent extrinsic sources of crystalline particles.

Of note, the human body has evolved mechanisms to minimize exposures to crystalline particles. For example, eyelashes and nasal hair protect eyes and lungs from airborne occupational and environmental particulate matter exposures. Tears and mucus facilitate rapid clearance of particulate matter from external and internal surfaces. On the corneal surface of the eyes, the first-line defender cells of the innate immune system—the neutrophils—trap airborne particulates by forming neutrophil extracellular traps (NETs), and aggregated clots containing crystals and NETs are cleared as eye rheum [19]. Acids and enzymes in the intestinal tract degrade ingested particles. Conversely, the physiological response of our body to intrinsic crystals is quite different and involves multiple mechanisms determined by particle size. Neutrophils, macrophages, and other phagocytes usually phagocytose particles within the nano- to micrometer size range [20]. Lytic proteases try to degrade engulfed particles in phagolysosomes, failure of which can result in lysosome destabilization, leakage of lysosomal content into the cytosol, cell stress, autophagy or necrosis, and inflammation. When the particle cargo is significant, macrophages appear as foam cell. Alternatively, macrophages fuse together to form giant cells enabling engulfment of larger particles [21,22]. Inability to handle larger particles leads to frustrated phagocytosis, resulting in necrosis and inflammation [20]. Crystal exposures ending in frustrated phagocytosis by neutrophils license the release of NETs [23,24]. Furthermore, polycrystalline particles that aggregate and grow to the size of calculi and stone can fill body cavities and ducts up to mechanical obstruction and organ failure, for example, in diseases such as biliary colic, unilateral or bilateral renal colic, nephrocalcinosis, acute pancreatitis, and sialolithiasis [13,25,26]. Several mechanisms promote crystal growth *in vivo*—for example, crystal adhesion molecules such as CD-44, annexin II, osteopontin, pentraxin-3, or uromodulin/Tamm–Horsfall protein-1 in the urinary tract [27,28]. Tumor necrosis factor receptor signaling induces the expression of these molecules on the tubular lumen as a starting point for nephrocalcinosis [29]. In addition, NETs contribute to the formation and growth of gallstones [30].

The crystal masses also cause vascular obstructions—for example, cholesterol crystal (CC) dislocating from ruptured atherosclerotic plaques of larger vessels can enter the bloodstream [31]. Such CC showers end in smaller peripheral arteries of the skin, intestinal tract, or kidneys and cause obstruction, tissue infarction, and organ failure, that is, CC embolism [21,32]. In addition, vascular calcifications in the medial layer of arteries cause calciphylaxis [33]. Together, crystals may form inside the human body via various physiological processes as well as enter the human body from various extrinsic sources like air pollution, and occupational, environmental dust and induce colic, inflammation, and tissue necrosis, and occasionally might lead to organ failure.

Table 1. Guide to crystal- and microparticle-related diseases. COPD, chronic obstructive pulmonary disease.

Crystalline material	Pathomechanisms	Disorder and disease manifestation	References
Amorphous and mineral-based solids			
Air pollutants, volcano ashes	Necroinflammation, tissue fibrosis	Smog-related asthma, pneumonitis, COPD	[87,88]
Calcium carbonate	Inflammation, NETs, and aggNETs formation	Gall ducts/bladder: Cholecysto-/docholithiasis	[1]
Nanoparticles (e.g., formed by titanium dioxide, carbon, polystyrene, metallic, nanodiamonds)	Necroinflammation, inflammation	Kidney/Ureter: Nephro-/urolithiasis Tissue injury, mesothelioma, asthma, cardiovascular disease, malignancy	[89–91]
Tobacco smoke particulates	NLRP3 inflammasome ?	Smoking-related COPD, emphysema	[92,93]
Protein- and purine-derived crystals			
Adenine	Tissue fibrosis	Adenine phosphoribosyltransferase deficiency, nephro-/urolithiasis	[80]
β-Amyloid (protein aggregates and amyloid fibrils)	NLRP3 inflammasome activation	Dementia, hyperglycemia, polyneuropathy, cardiomyopathy	[12,94]
Bile pigment	Necroinflammation	Bile cast nephropathy, pancreatitis, cholecystolithiasis or docholithiasis	[95]
Charcot–Leyden crystals	NLRP3 inflammasome activation	Eosinophilia, infection with helminths, hematologic malignancies	[16,96]
Hemozoin	NLRP3 inflammasome activation	Malaria	[81,82]
Light chains	NLRP3 inflammasome activation	Light-chain Fanconi syndrome, myeloma cast nephropathy, crystalloglobulinemia, fibrillary glomerulonephritis, cast nephropathy	[26,97,98]
Myoglobin or heme	NLRP3 inflammasome activation	Myoglobin cast nephropathy	[99,100]
Uromodulin glycoprotein	Inflammasome activation		[71]
Fibrous material			
Asbestos	Lung fibrosis, NLRP3 inflammasome activation, fibrosis	Asbestosis, asbestos-mediated mesothelioma	[101,102]
Cotton, silk	Inflammation, fibrosis	Cotton dust lung disease	[103]
Crystalline solids			
Small or short microparticles (1–10 µm in size)			
Calcium oxalate monohydrate and dehydrate	Necroinflammation, tissue fibrosis	Nephro-/urolithiasis, acute oxalate nephropathy, chronic oxalate nephropathy (primary hyperoxaluria)	[29,63]
Calcium pyrophosphate or calcium phosphate	Necroinflammation	Pseudogout, chondrocalcinosis, hemochromatosis, hyperparathyroidism, hyperphosphatemic familial tumoral calcinosis, vascular calcification, calciphylaxis, warfarin calcification, Dent's disease, nephrocalcinosis	[17,104,105]
Cystine	Inflammation, NLRP3 inflammasome activation, fibrosis	Cystinosis	[106,107]
Silica	Chronic inflammation, granuloma, lung fibrosis	Silicosis	[108,109]
Large/long microparticles (10–100 µm in size)			
Cholesterol	Necroinflammation, immunothrombosis	Atherosclerosis, cholesterol embolism, nonalcoholic steatohepatitis, cholesteryl ester storage disease, cholecysto-/docholithiasis	[31,51] (C. Shi, T. Kim, S. Steiger, S. R. Mulay, B. M. Klinkhammer, T. Bäuerle, M. E. Melica, P.

Table 1. (Continued).

Crystalline material	Pathomechanisms	Disorder and disease manifestation	References
			Romagnani, L. Yang, D. Möckel, M. Baues, E. Mammadova-Bach, B. Sanne, J. W. M. Heemskerk, A. Braun, T. Lammers, P. Boor, H. J. Anders, unpublished observation)
Drugs: Acyclovir, indinavir, amoxicillin, MTX	Necroinflammation, tissue fibrosis	Drug-related kidney injury	[13,14,110,111]
Monosodium urate	Necroinflammation	Acute or tophaceous gout, acute urate nephropathy	[11,75,112]
Polycrystalline solids			
Large microcrystals (100 μm–1 cm in size)			
Calculi or stones of multiple crystalline materials and proteins	Tissue fibrosis, granuloma formation	Biliary colic, nephrocalcinosis, sialoliths, acute pancreatitis, unilateral or bilateral renal colic, gallstones	[8,30]
Cholesterol	Immunothrombosis	Thrombosis and foreign body reaction	[5] (C. Shi, T. Kim, S. Steiger, S. R. Mulay, B. M. Klinkhammer, T. Bäuerle, M. E. Melica, P. Romagnani, L. Yang, D. Möckel, M. Baues, E. Mammadova-Bach, B. Sanne, J. W. M. Heemskerk, A. Braun, T. Lammers, P. Boor, H. J. Anders, unpublished observation)
Monosodium urate	Aggregated NETs, tissue fibrosis, granuloma formation	Tophi, chronic urate nephropathy, nephrolithiasis	[76,113,114]
Implants (plastic or silicone)	Tissue fibrosis, granuloma formation	Aseptic osteolysis, foreign body reactions	[115,116]

How do crystals activate cells from the outside and enter into intracellular compartments?

Exogenous crystals such as silica and titanium can interact with a number of different surface receptors on macrophages and other cells (Fig. 1) [34]. For example, the transmembrane scavenger receptors (SR) SR-A1, SR-B1, CD36, and macrophage receptor with collagenous structure (MARCO) [35,36] can contribute to lung injury and fibrosis in animals exposed to occupational dust particulate such as silica or asbestos fibers [37,38]. CD36 is another member of this family that facilitates the phagocytic uptake of crystalline particles and fibers [39]. Outside-in signaling or phagocytosis via such SRs can engage with the NLRP3 inflammasome in resident and infiltrating macrophages [35,39,40]. The physiological role of these receptors rather relates to host defense, phagocytic clearance of dead cells, or cellular uptake of lipid particles including high-density lipoprotein particles that have a key role on cholesterol transport [41–43].

Other surface receptors are involved in the outside-in signaling of endogenous crystals and microparticles [34]. C-type lectin (Clec)-12a is a surface receptor expressed by dendritic cells and macrophages that has been described to respond to uric acid microcrystals released by dying cells [15]. Interestingly, Clec-12a signaling inhibits the pro-inflammatory signaling pathways related to the tyrosine kinase Syk, while eliciting pro-inflammatory effects by augmenting type I interferon signaling [15,44]. CD16/FcγRIII and complement factors potentiate the response to monosodium urate crystals (MSU) [45,46]. As another mechanism, uric acid crystals can

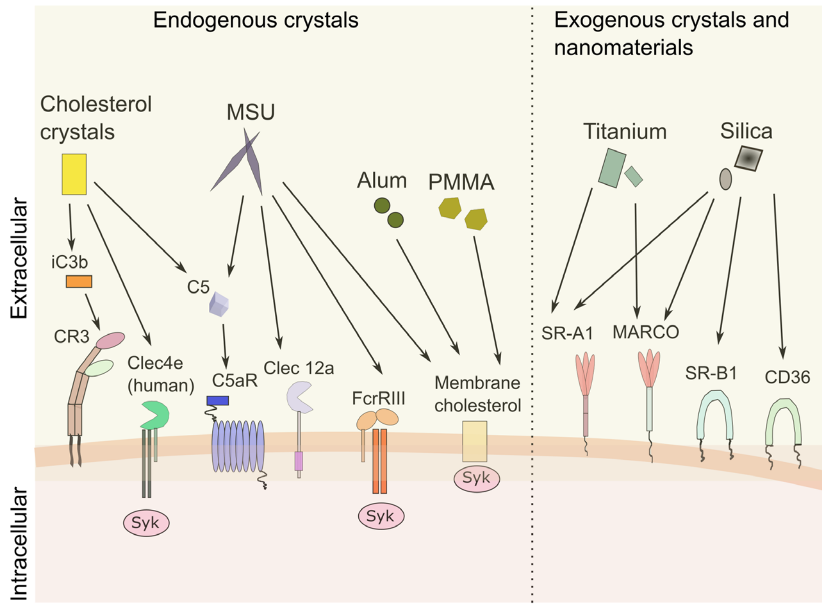

Fig. 1. Crystal-related outside-in signaling. Crystals and microparticles induce outside-in signaling in various ways. A series of different scavenger receptors such as MARCO, SR-A1, SR-B1, and CD36 contributes to intracellular uptake of crystals by phagocytosis. Crystalline endogenous metabolites, proteins, or microparticles can also interact with other elements of the outer plasma membrane. For example, the lipid nature of CCs allows direct interaction with cholesterol components inside certain membrane domains. Surface receptors of the C lectin-type link crystal binding to Syk kinase signaling leading to the activation of either pro- or anti-inflammatory signaling pathways. Certain crystals also activate complement components on cell surfaces, which can contribute to cell injury. CD, cluster of differentiation; Clec, C-type lectin; CR, complement receptor; MARCO, macrophage receptor with collagenous structure; MSU, monosodium urate; SR, scavenger receptor.

also directly interact with lipid structures of the outer plasma membrane of dendritic cells and induce Syk kinase signaling potentially by spatial rearrangements of signaling elements in cholesterol-rich lipid rafts [47].

Cholesterol crystals seem to activate cells also via activation of the alternative complement pathway and tumor necrosis factor [48–50]. CC-mediated cell death is unrelated to mixed lineage kinase domain-like (MLKL) kinase-dependent (necroptosis), gasdermin D (inflammasome-dependent pyroptosis), caspase 8 (apoptosis), Ca^{2+} influx, K^{+} efflux, and SYK but involves direct plasma membrane destabilization as CC plates extract cholesterol from the plasma membrane [51]. These effects relate to the lipid nature of CCs and are different from those of most other crystals and nano- and microparticles that enter cells via phagocytosis.

How do crystals activate cells from the inside to induce necroinflammation?

Mechanisms shared by crystals of different chemical nature, size, and shape

Necroinflammation describes the tight link between inflammation and regulated necrosis, two processes that can be activated within the same cell, for example, during the release of extracellular traps from neutrophils [52], or in separate cells. For example, cytokines released from one cell can trigger regulated necrosis in another, vice versa danger-associated molecular patterns released from a dying cell trigger innate immune activation in others [4,53]. Crystals and nano- and microparticles are potent triggers of necroinflammation. As mentioned earlier, macrophages and other phagocytes engulf these crystals or crystalline particles. The phagosomes then fuse with the lysosomes to form phagolysosomes, where lytic proteases attempt to digest the cargo. Crystalline particles often resist digestion, which can destabilize lysosomes resulting in lysosomal leakage of lysosomal content into the cytosol. One of these proteases is cathepsin B that affects the mitochondrial outer membrane potential (MOMP) leading to the generation of reactive oxygen species (ROS) [54]. Cathepsin B and ROS activate the NLRP3 inflammasome to yield mature forms of IL-1β and IL-18 that set up an inflammatory response (Fig. 2) [55]. Cytosolic cathepsin B also changes the conformation of receptor-interacting protein kinase (RIPK)-1 and turns inhibition into activation of necroptosis [56,57]. Degradation of RIPK1 induces oligomerization and phosphorylation of RIPK3, which

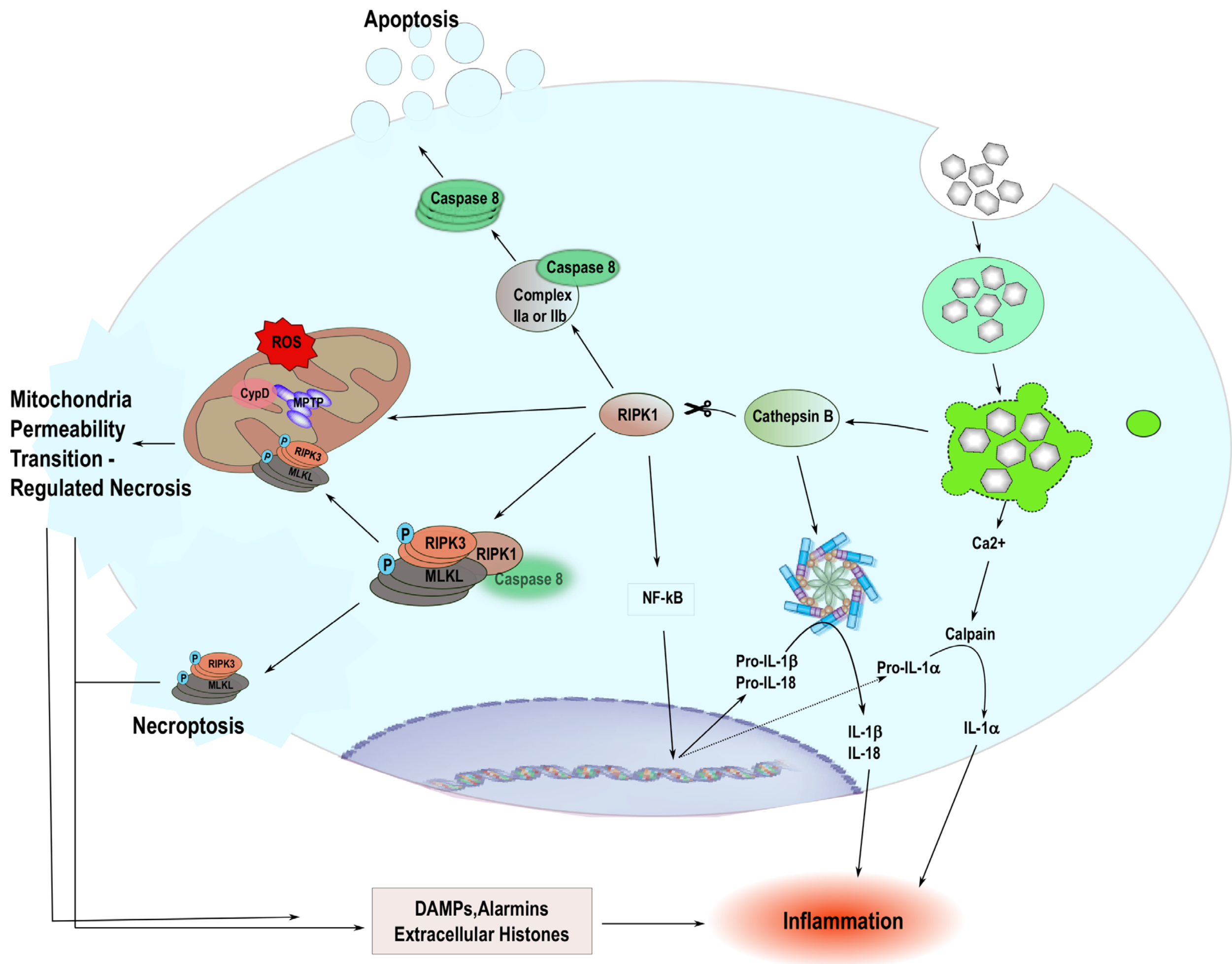

Fig. 2. Molecular mechanisms of crystal-induced necroinflammation. The crystal-induced necroinflammation involves the activation of multiple pathways of necroinflammation. Upon exposure, the cells internalize crystals or crystalline particles into phagosomes. Then, phagosomes fuse with lysosomes to form phagolysosomes, where several lytic enzymes try to degrade the crystals or crystalline particles. Failure of degradation induces phagolysosome destabilization leading to the release of several lytic enzymes, for example, cathepsin B in the cytosol. Cathepsin B cleaves the endogenous inhibitor of necroptosis, RIPK1, and thereby promotes the formation of RIPK3-MLKL necrosome complex, in the absence of caspase 8. The activated MLKL oligomers then translocate to the plasma membranes where they induce pore formation leading to necroptosis. These MLKL oligomers also translocate to mitochondria membrane where they induce ROS formation by opening MPTP in a CypD-dependent manner and lead to mitochondrial permeability transition-related necrosis (MPT-RN). Both necroptosis and MPT-RN lead to release of DAMPs, alarmins, and histones in the extracellular compartment where they contribute to inflammation. In addition, RIPK1 also contributes to inflammation via activation of the NFkB via IKK complex. However, in the absence of caspase 8, RIPK1 activation leads to apoptosis, devoid of inflammation. Cathepsin B also activates the NLRP3 inflammasome that cleaves pro-IL-1β and pro-IL-18 into mature IL-1β and IL-18, and contribute to inflammation. Moreover, calcium ions released from the phagolysosomes activate calpains that cleave pro-IL-1α into mature IL-1α and contribute to inflammation. Ca2+, calcium ions; CypD, cyclophilin D; DAMPs, danger-associated molecular patterns; IL, interleukin; MLKL, mixed lineage kinase domain-like; MPTP, mitochondrial permeability transition pore; RIPK, receptor-interacting protein kinase; ROS, reactive oxygen species.

in turn phosphorylate, and MLKL [58]. Activated MLKL undergoes oligomerization and translocation to nuclear and plasma membranes where it forms pores, which can induce necroptosis [58,59]. Crystal-induced loss of the MOMP also leads to cyclophilin D (CYPD)-dependent mitochondrial permeability transition-related regulated necrosis [60]. A broad range of environmental and metabolic crystals, for example, calcium oxalate, MSU, calcium phosphate, cysteine, cholesterol, asbestos, silica, and titanium dioxide, have been demonstrated to induce cathepsin B and ROS-mediated NLRP3 inflammasome activation

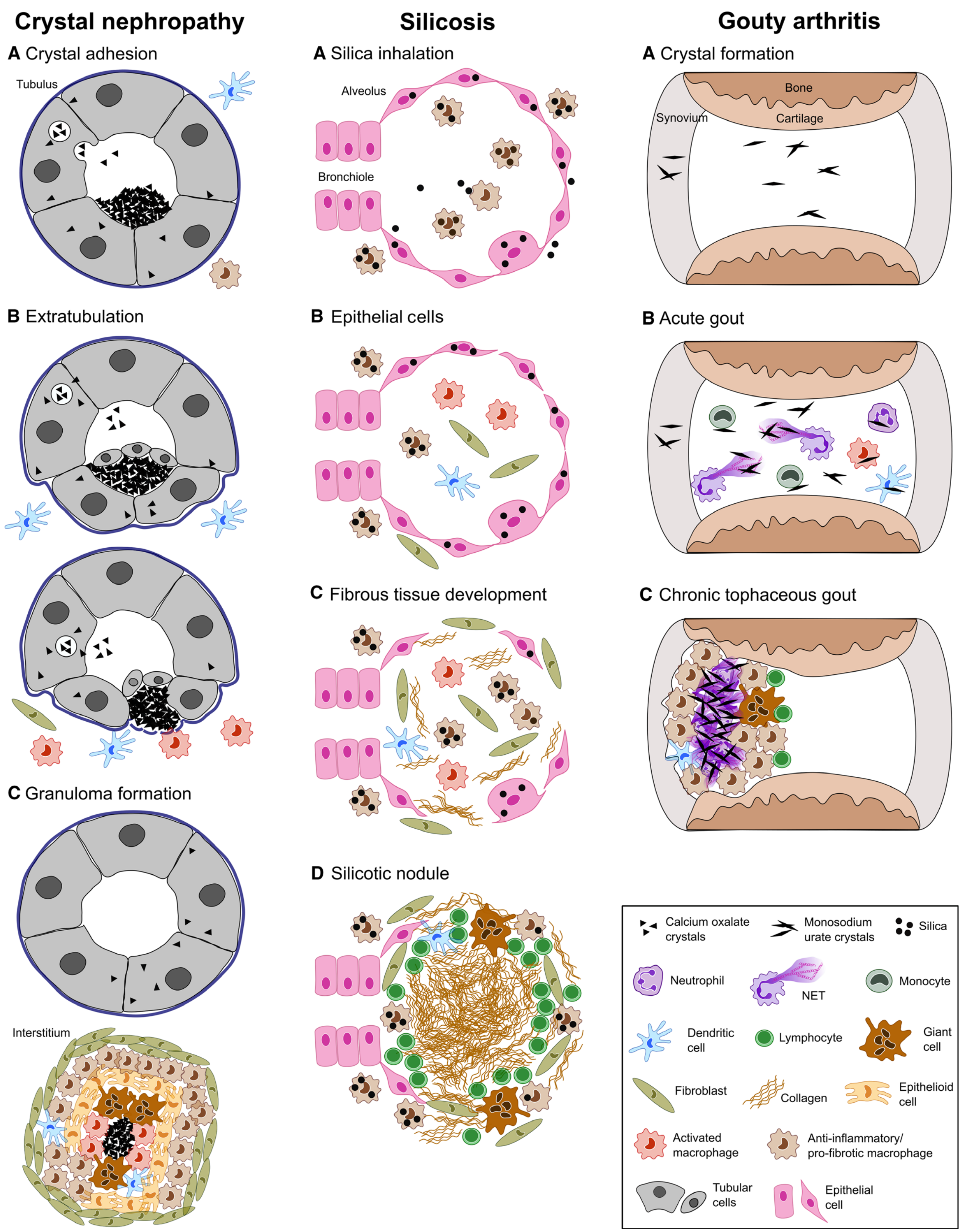
Crystal nephropathy
A Crystal adhesion
Tubulus
B Extratubulation
C Granuloma formation
Interstitium
Silicosis
A Silica inhalation
Alveolus
Bronchiole
B Epithelial cells
C Fibrous tissue development
D Silicotic nodule
Gouty arthritis
A Crystal formation
Bone
Synovium
Cartilage
B Acute gout
C Chronic tophaceous gout
Calcium oxalate crystals
Monosodium urate crystals
Silica
Neutrophil
NET
Monocyte
Dendritic cell
Lymphocyte
Giant cell
Fibroblast
Collagen
Epithelioid cell
Activated macrophage
Anti-inflammatory/ pro-fibrotic macrophage
Tubular cells
Epithelial cell

Fig. 3. Mechanisms of crystal granuloma/tophus formation in kidney, lung, and joint. During crystal nephropathy, (A) supersaturation of calcium oxalate (CaOx) in the urine leads to the formation of CaOx crystals. Crystals adhere on the surface of tubular cells and create a nidus for crystal growth, which leads to crystal plug formation in the tubular lumen and obstruction of the tubule. (B) Tubular cells dedifferentiate and grow on the surface of the crystal plug, eventually leading to translocation of the crystal plug into the interstitial compartment. (C) In the interstitial compartment, frustrated phagocytosis of large crystal plugs triggers the formation of giant cells, subsequently leading to a granuloma, which isolates the crystal plug from the renal parenchyma. Silicosis is one of the chronic fibrotic pulmonary diseases caused by inhalation of inorganic occupational dusts like silica particles, which are ingested by alveolar macrophages (A). Silica crystals cause cytotoxicity to the endothelial cells (B) and the secretion of inflammatory and fibrotic mediators by macrophages leading to lung remodeling through collagen and elastin deposition (C). Prolonged silica exposure can eventually cause the formation of interstitial silicotic nodules, which contain macrophages, lymphocytes, and fibroblasts with disorganized collagen patches (D). These silicotic nodules cause progressive lung fibrosis and reduction of lung volume. Gouty arthritis is associated with MSU crystals inside joints (A), a process promoted by a local imbalance of uric acid supersaturation. (B) MSU crystals cause an acute inflammatory response characterized by immune cell infiltration, NET formation, necroptosis, activation, and differentiation of macrophages and dendritic cells. This immune response will spontaneously resolve after a few days. (C) In contrast to acute gout, chronic tophaceous gout involves persistent MSU crystal masses (tophi) that cause a smoldering local or systemic inflammation via granuloma-like foreign body reaction. These granulomatous lesions are comprised of central MSU crystal-NET masses surrounded by mono- and multinucleated phagocytes (giant cells), lymphocytes, and fibroblast, which leads to cartilage and bone damage.

and IL-1β and IL-18 release, as well as RIPK3-MLKL-mediated necroptosis of epithelial cells and neutrophils [2,60–64].

Crystal-specific mechanisms

Beyond such shared mechanisms, intracellular uptake of MSU crystals elicits also a specific effect. The acidity inside phagolysosomes releases sodium ions from MSU crystals into the cytosol, where they increase intracellular tonicity and secondary water influx via osmotic forces. Water influx and cell swelling lower the intracellular potassium concentration, a known activator of the NLRP3 inflammasome [65]. Acidity within lysosomes also mobilizes calcium from calcium phosphate crystals, a process activating cytosolic calpains [66]. Calpains are calcium-dependent proteases that contribute to inflammation by cleaving pro-IL-1α into active IL-1α [66]. In addition, calcium oxalate crystals induce autophagy, as evident from increased expression of light chain 3-II and beclin-1 and the presence of autophagy-related vacuoles [67]. Crystalline silica particles inside the phagosome trigger the assembly of liposomes in the cytoplasm, which leads to the production of leukotriene B4 in an inflammasome-independent manner [68].

Numerous mechanisms minimize crystal-induced necroinflammation

Beyond the many ways how crystals and microparticles can trigger inflammation, they can also directly interact on the cell surface to attenuate pro-inflammatory signal pathways. For example, MSU crystals specifically bind to the myeloid inhibitory Clec-like receptor Clec-12a on macrophages, dendritic cells, and neutrophils [15,69].

Microparticle or crystal deposits cause medical problems also in a noninflammatory or cytotoxic manner, especially in the draining ducts of excretory organs such as liver and kidney, where calculi can grow to stones persisting in gall bladder or renal pelvis that occasionally cause symptomatic obstruction. Stone growth involves a gradual apposition of mineral and organic material that may involve some of the aforementioned molecular mechanisms such as the sticky nature of chromatin released by NETs [30]. Intrinsic crystallization inhibitors such as citrate of hypocitrate interfere with further apposition or minerals and prevent stone formation in the majority of the population [70]. As another example, uromodulin, a sticky glycoprotein selectively secreted by epithelial cells of the kidney‘s loop of Henle, covers crystals and calculi in the draining system. Within the urinary tract, uromodulin is immunologically inert and masks the pro-inflammatory and cytotoxic potential of crystals, although once picked up by phagocytes, uromodulin itself can activate the NLRP3 inflammasome, for example, when tubular epithelial cell damage exposes uromodulin particles to resident or infiltrating mononuclear phagocytes in the kidney [71]. Vascular deposits of calcium phosphate crystals cause vascular wall or heart valve calcifications that are a central element of numerous cardiovascular complications of diabetes and chronic kidney disease [72] and often relate to a dysbalance of calcification inhibitors such as matrix Gla protein and fetuin-A [73,74]. These calcium phosphate deposits are usually devoid of any inflammatory response and rather mimic the process of ossification. Such sclerotic vessels not only lose their compliance but occasionally develop vascular obstructions followed by tissue necrosis, for example, in calciphylaxis [33].

Another unexpected molecular mechanism that suppresses crystal-induced inflammation relates to conditions where masses of neutrophils form NETs around crystals, for example, in gouty arthritis. Indeed, gouty arthritis is a biphasic MSU crystal-related disease as the crescendo of pain and swelling is followed by spontaneous resolution of these signs of inflammation usually after 3–7 days [75]. The massive influx of neutrophils results in the formation of so-called aggregated NETs that are also found in gouty tophi devoid of intense inflammation in patients with chronic gout. Aggregated NETs release of large amounts of proteases that digest all locally secreted cytokines and chemokines, and thereby induce resolution of inflammation and some form of immune anergy [76].

Microparticles entering interstitial compartments of lungs, skin, or kidney can form crystal granulomas as a common foreign body reaction (Fig. 3). Indeed, granuloma formation is a form of microparticle compartmentalization. Silica particles or asbestos fibers cannot be cleared by phagocytes from the lung and hence trigger granuloma formation. Such granulomas have a core of activated phagocytes and an outer aspect of anti-inflammatory and profibrotic immune cells, which promote remodeling and fibrosis of the surrounding healthy tissue [77]. In the kidney, crystal plugs within tubules may cause fibrosis also of the surrounding as a secondary response to nephron loss [78] but interstitial granuloma formation upon 'exotubulosis' of intratubular crystal plugs into the interstitial compartment has also been reported [79]. This interesting process starts from tubular epithelial cells that migrate to the crystal plug and form a neo-basement membrane between cells and plug surface (Fig. 3) [79,80]. At the same time, interstitial macrophages degrade the original basement membrane below the crystal plug, a coordinated process ending in a shift of the crystal plug from the tubule into the interstitial compartment [80], where it forms a granuloma [28,79,80].

Thus, crystals can persist in the human body without causing permanent necroinflammation but it depends on the type of particle, the tissue compartment, and the presence of various immune cells in this compartment whether crystals form stones, granuloma, anergic tophi, or bone-like calcifications. However, crystals remain an irritating factor frequently causing chronic tissue remodeling, sclerosis, and scaring.

How do crystals trigger thrombosis?

Certain crystals occur in the bloodstream. For example, hemozoin crystals are released from erythrocytes during febrile episodes of malaria and the NLRP3 and absent in melanoma 2 inflammasomes as well as IL-33 are thought to contribute to systemic inflammation [81,82]. As another example, spontaneous mechanic ruptures of atherosclerotic plaques can dislocate CCs from inside plaques into the bloodstream, where they flush into peripheral arteria and arterioles. The clinical presentation of the cholesterol embolism syndrome is dominated by ischemic tissue injury, and histopathological examination demonstrates how CCs impact the vascular wall [83]. However, not the crystals

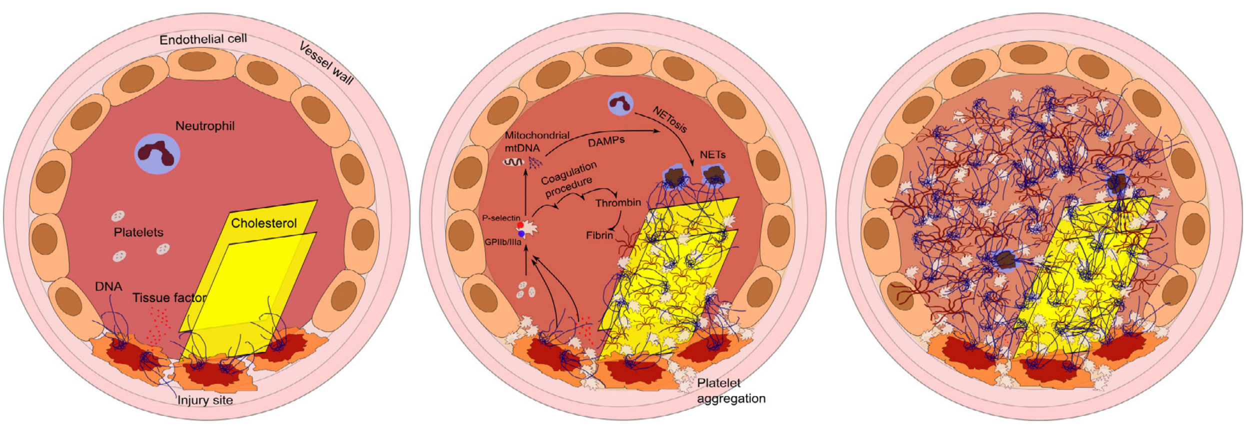

Fig. 4. CC embolism triggers endovascular clot formation. CC embolism is a complication of advanced atherosclerosis when atheromatous plaques in larger arterial vessels rupture and release crystalline cholesterol into the bloodstream. Crystals induce injury to endothelial cells of smaller arteries or arterioles. Injured endothelial cells release nuclear and mitochondrial DNA and tissue factors, which contribute to platelet activation, plasmatic clotting, release of extracellular traps from NETs, and clot formation. Whenever such crystal clots cause obstruction of terminal arteries, tissue ischemia and necrosis occur.

themselves but crystal-related clots obstruct the vascular lumen and are the cause of tissue ischemia (Fig. 4) [84]. CCs do not activate platelets directly or induce clotting of full blood [50] (C. Shi, T. Kim, S. Steiger, S. R. Mulay, B. M. Klinkhammer, T. Bäuerle, M. E. Melica, P. Romagnani, L. Yang, D. Möckel, M. Baues, E. Mammadova-Bach, B. Sanne, J. W. M. Heemskerk, A. Braun, T. Lammers, P. Boor, H. J. Anders, unpublished observation) but trigger mechanical injury to endothelial cells and activate complements, which leads to the release of tissue factor and nuclear DNA both initiating the clotting process [50] (C. Shi, T. Kim, S. Steiger, S. R. Mulay, B. M. Klinkhammer, T. Bäuerle, M. E. Melica, P. Romagnani, L. Yang, D. Möckel, M. Baues, E. Mammadova-Bach, B. Sanne, J. W. M. Heemskerk, A. Braun, T. Lammers, P. Boor, H. J. Anders, unpublished observation). The indirect activation of platelets increases the amount of prothrombotic extracellular DNA as activated platelets release mitochondrial DNA (C. Shi, T. Kim, S. Steiger, S. R. Mulay, B. M. Klinkhammer, T. Bäuerle, M. E. Melica, P. Romagnani, L. Yang, D. Möckel, M. Baues, E. Mammadova-Bach, B. Sanne, J. W. M. Heemskerk, A. Braun, T. Lammers, P. Boor, H. J. Anders, unpublished observation) [85]. Also, NETs partially contribute to this process [62] (C. Shi, T. Kim, S. Steiger, S. R. Mulay, B. M. Klinkhammer, T. Bäuerle, M. E. Melica, P. Romagnani, L. Yang, D. Möckel, M. Baues, E. Mammadova-Bach, B. Sanne, J. W. M. Heemskerk, A. Braun, T. Lammers, P. Boor, H. J. Anders, unpublished observation). In contrast, small amounts of CCs that do not cause endothelial cell injury remain inside the vasculature without triggering crystal clots [86].

Conclusions

Intrinsic or extrinsic crystals and nano- and microparticles induce diverse tissue responses. NLRP3-driven inflammation and several pathways of regulated necrosis contribute to acute necroinflammation, for example, in acute gouty arthritis or acute dust exposures. Persistent particle deposits cause foreign body reactions characterized by granuloma formation and tissue fibrosis. Numerous molecular mechanisms can limit persistent inflammation in this setting, but these mechanisms are diverse and depend on the atomic nature, shape, and size of the particle deposits. Within the bloodstream, CC embolism triggers microvascular clotting followed by ischemic tissue infarction and organ failure. Clearance of microparticles is essential for body surfaces and excretory organs, and several mechanisms prevent calculi and stone formation there. However, a significant proportion of the population suffers from kidney and gallstones that can cause obstruction, colic, and other disabling clinical complications. Studying the shared and specific pathomechanisms should help to develop better therapies for patients with crystallopathies.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

HJA conceived the idea. SRM, SS, CS, and HJA wrote the manuscript and prepared the figures. All authors approved the final version.

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