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

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Keywords
crystals; granuloma; inflammation; necrosis; particulate matter; thrombosis

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(Received 1 November 2019, accepted 9 December 2019)
doi:10.1111/febs.15174

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.
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.

Crystall formation and handling in human diseases

Supersaturation of solutes often results in the formation of microcrystals, which serves as a nidus for crystall 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 fibrillar 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 cosinophil 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 phagocyte 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.
| 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-/doucholithiasis                            | [1]                      |
| Nanoparticles (e.g., formed by titanium dioxide, carbon, polystyrene, metallic, nanodiamonds) | Necroinflammation, inflammation     | Kidney/Ureter: Nephro-/uroolithiasis                                      | [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-/uroolithiasis       | [80]                     |
| β-Amyloid (protein aggregates and amyloid fibrils) | NLRP3 inflammasome activation      | Dementia, hyperglycemia, polyneuropathy, cardiomyopathy                   | [12,94]                  |
| Bile pigment                                | Necroinflammation                   | Bile cast nephropathy, pancreatitis, cholecystolithias 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, fibriaryl 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) | Necroinflammation, tissue fibrosis | Nephro-/uroolithiasis, acute oxalate nephropathy, chronic oxalate nephropathy (primary hyperoxaluria) | [29,63]                  |
| Calcium oxalate monohydrate and dehydrate   | Necroinflammation                   | Pseudogout, chondrocalcinosis, hemochromatosis, hyperparathyroidism, hyperphosphatemic familial tumoral calcinosis, vascular calcification, calciphylaxis, warfarin calcification, Dent’s disease, nephrocalcinosis | [17,104,105]             |
| Calcium pyrophosphate or calcium phosphate  | Necroinflammation                   |                                                                          |                          |
| 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) | Necroinflammation, immunothrombosis | Atherosclerosis, cholesterol embolism, nonalcoholic steatohepatitis, cholesteryl ester storage disease, cholecysto-/doucholithiasis | [31,51] (C. Shi, T. Kim, S. Steiger, S. R. Mulay, B. M. Klinkhammer, T. Bäuerle, M. E. Melica, P.) |

Table 1. Guide to crystal- and microparticle-related diseases. COPD, chronic obstructive pulmonary disease.
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...
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-1\(\beta\) 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
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.
A guide to crystal biology

S. R. Mulay et al.

Crystal nephropathy

A Crystal adhesion

B Extratubulation

C Granuloma formation

Silicosis

A Silica inhalation

B Epithelial cells

C Fibrous tissue development

D Silicotic nodule

Gouty arthritis

A Crystal formation

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
the production of leukotriene B4 in an inflammatory assembly of liposomes in the cytoplasm, which leads talline silica particles inside the phagosome trigger the expression of light chain 3-II and beclin-1 and the crystals induce autophagy, as evident from increased pains. Calpains are calcium-dependent proteases within lysosomes also mobilizes calcium from calcium activator of the NLRP3 inflammasome. Acidity 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 toxicity and secondary water influx via osmotic forces. Water influx and cell swelling lower the intracellular potassium concentration, a known activator of the NLRP3 inflammasome. Prolonged silica exposure can eventually cause the formation of interstitial silicotic nodules, which contain macrophages, lymphocytes, and fibroblasts with disorganized collagen patches. These silicotic nodules cause progressive lung fibrosis and reduction of lung volume. Gouty arthritis is associated with MSU crystals inside joints, a process promoted by a local imbalance of uric acid supersaturation. 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. 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.

**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 toxicity and secondary water influx via osmotic forces. Water influx and cell swelling lower the intracellular potassium concentration, a known activator of the NLRP3 inflammasome. Acidity within lysosomes also mobilizes calcium from calcium phosphate crystals, a process activating cytosolic calpains. Calpains are calcium-dependent proteases that contribute to inflammation by cleaving pro-IL-1α into active IL-1α. 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. Crystalline silica particles inside the phagosome trigger the assembly of liposomes in the cytoplasm, which leads to the production of leukotriene B4 in an inflamma-some-independent manner.

**Numerous mechanisms minimize crystal-induced necroinflammation**

Beyond the many ways how crystals and micropar-ticles 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.

Microparticle or crystal deposits cause medical problems also in a noninflammatory or cytotoxic man-ner, especially in the draining ducts of excreto-ry 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 as the sticky nature of chromatin released by NETs. Intrinsic crystallization inhibitors such as citrate of hypocitrature interfere with further apposition or minerals and prevent stone formation in the majority of the population. 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. Vascular deposits of calcium phosphate crystals cause vascular wall or heart valve calcifications that are a central ele-ment of numerous cardiovascular complications of dia-betes and chronic kidney disease and often relate to a dysbalance of calcification inhibitors such as matrix Gla protein and fetuin-A. 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
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 comple-
ments, 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) [85]. Also, NETs partially con-
tribute 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). 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) [86]. Also, NETs partially con-
tribute 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 micropar-
ticles induce diverse tissue responses. NLRP3-driven inflam-
mation and several pathways of regulated necro-
sis contribute to acute necroinflammation, for exam-
ple, in acute gouty arthritis or acute dust exposures. Persistent particle deposits cause foreign body reac-
tions characterized by granuloma formation and tissue fibrosis. Numerous molecular mechanisms can limit persistent inflammation in this setting, but these mech-

anisms are diverse and depend on the atomic nature, shape, and size of the particle deposits. Within the bloodstream, CC embolism triggers microvascular clot-
ing 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 pathomech-
nisms should help to develop better therapies for patients with crystallopathies.

Acknowledgements

This work received support from the Department of Biotechnology, Government of India (BT/RLF/Re-en-
try/01/2017 to SRM), the Deutsche Forschungsgemeins-
schaft (STE 2437/2-1 to SS and AN372/16-2, 20-2, 24-
1, and 27-1 to HJA), the LMU excellent initiative (to SS), and the Chinese Scholarship Council (to CS).

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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