Basic calcium phosphate crystals induce NLRP3 inflammasome activation: The in vitro and in vivo face to face

We read with interest the recent article published by Jin et al. (1) showing that hydroxyapatite (HA) crystal-induced IL-1 β secretion was NLRP3-inflammasome dependent both in vitro and in vivo. HA belongs to the family of basic calcium phosphate (BCP) crystals, which also encompasses carbonated-apatite, octacalcium phosphate (OCP), and tricalcium phosphate. Their findings confirmed our in vitro results with HA crystals and other BCP crystals (ref. 1 and references therein). However, their results contained some discrepancies that need to be highlighted.

Jin et al. (1) observed that WT macrophages did not induce TNF- α production when stimulated by HA, a result significantly different from previous published findings (refs. 1 and 2 and references therein).

By contrast to Jin et al. (1), we have recently shown that OCP crystals injected into peritoneal cavity in mice induced IL-1 β secretion through an inflammasome independent pathway (ref. 1 and references therein). Such a discrepancy between in vivo studies can have at least two explanations. First, OCP and HA are different crystals, because they have different physicochemical and biological properties. Even in HA crystals, different samples displayed different biological effects as shown in this paper (1). Indeed, we have previously shown that BCP crystal inflammatory properties were correlated with their specific surface and their Ca/P ratio. Second, the air pouch model was definitively different from the peritonitis model, which was already observed in ref. 1 and references therein and Chen et al. (3). Hence, monosodium urate (MSU) crystal-induced IL-1 β production was TLR-2- and -4-dependent in the air pouch model, whereas zero of nine TLRs were involved in the peritonitis model (refs. 1 and 3 and references therein).

It is interesting to note that Jin et al. (1) observed a crucial role for NLRP3 inflammasome in HA-induced IL-1 β secretion in vitro

(almost total inhibition of its secretion in NLRP3 inflammasome-deficient macrophages) but a limited role in vivo (about 25% reduction of the pathological severity score of HA-associated murine arthropathy in NLRP3-deficient mice). This finding is reminiscent with the effect of MSU crystal-induced IL-1 β secretion, with once again, NLRP3 inflammasome playing a crucial role in vitro but a moderate or almost no role in vivo (reviewed in ref. 4). Altogether, these results show that, in vivo, mechanisms of BCP crystal-induced inflammation deserve additional studies to highlight the exact role and activation mechanisms of IL-1 β .

Last, we want to point out that the role of IL-1 β in osteoarthritis (OA) pathogenesis is currently unclear. Moreover, blocking IL-1 β does not seem a good therapeutic target in OA, which was evidenced by three negative independent randomized clinical trials (reviewed in ref. 5). These results suggest that, first, in vivo, the role of IL-1 β in cartilage homeostasis is more complex and second, other known (and unknown) cytokines are involved in OA pathogenesis.

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