Reviewer's report

Title: Is the inflammasome a potential therapeutic target in renal disease?

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Reviewer: Felix Knauf

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The authors present a review on the current knowledge of the inflammasome and its relevance to renal disease, in particular acute kidney injury and chronic kidney disease. In addition, a detailed background is provided on the molecular mechanisms of NLRP3 activation and downstream cytokine release. This is followed by a comprehensive update on drugs that target the inflammasome. The review is timely and of great importance. It covers recent advancements in the understanding of the inflammasome in detail. The review is concise and easy to follow. I have only minor suggestions to further enhance the quality of the article.

1) Page 13: "Recombinant human IL-1ra (Anakinra)… has been successfully used in RA [73] and autoinflammatory syndromes [74]." Since the review focuses on the inflammasome as a potential therapeutic target in renal disease, it should involve a discussion of the drugs targeting the inflammasome that have already been studied in animal models of renal disease. Data on IL-1 receptor blockade with Anakinra in ischemia-reperfusion injury for example has been conflicting describing protective (Rusai K. et al.; Transpl Int 2008; Iyer, S. et al. PNAS ) and no effects on renal injury responses (Shigeoka et al. The journal of immunology). In particular, Shigeoka et al. have described that there is an inflammasome independent role for NLRP3 in renal injury. Hence, the conception that NLRP3 necessarily leads to caspase-1 activation and IL-1beta release may be a too simplified view. Hence, pharmacological inhibition of downstream targets may be less effective. I think it would be valuable to discuss this in more detail.

2) On page 14 it is stated: “Apart from two studies of CKD of various aetiologies [95, 108] most of the disorders studied have been acute inflammatory diseases.” In this context it may be worth adding that a recent publication did demonstrate that NLRP3-mediated inflammation is the principal cause of progressive renal failure in oxalate nephropathy (KI 2013; PMID: 23739234).

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.