Author’s response to reviews

Title: What makes gouty inflammation so variable?

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Author’s response to reviews:

I thank the reviewers for the efforts and helpful suggestions. Below are my point to point responses:

Reviewer #1 Martin Herrmann:

“In his manuscript „What makes gouty inflammation so variable?„, Robert Terkeltaub reviewed the etiopathogenesis of gout. The author describes gout as an pleomorphic clinical condition. As a known expert the review is unbiased and includes most of the features from clinical and basic science. There is only minor criticism.”

Response: These comments are appreciated.

1. “page 3/60 empty brackets.”

Response: This was corrected.

2. “page 6/45 since gout is reportedly associated with beer with and without alcohol, the role of alcohol has to be discussed a little bit more in detail.”

Response: This would be beyond the scope of this minireview.

3. “page 13/44 "Conversely, failure of clearance of circulating urate microaggregates in phagocytes was suggested to promote NETosis to toxic to the vasculature” this sentence is not clear.”

Response: This was corrected.
4. “Figure 1 NETosis should be changed into formation of aggregated NETs.”
Response: This was corrected in the Figure and also the table.

1. “The role of acetate is pro (page 6/40) and anti-inflammatory (page 11/50). What are the mechanisms? What do you think is more relevant?”
Response: Both were already discussed in the text, particularly highlighting mechanisms. I cannot speculate on what is more relevant.

2. “The role of monocyte/macrophage sodium overload after uptake of MSU crystals should be discussed.”
Response: This would be beyond the scope of this minireview, which focuses on research from the last 1-2 years on factors in variability of the inflammatory response, not longer-recognized fundamental mechanisms by which crystals turn on cells, such as osmotic swelling due to released sodium from MSU crystals.

3. “The role of the urate receptor Clec12a should be discussed.”
Response: Mention in the text (top of page 14) and table 1, and citation (new reference 65) are now provided. However, the concept (and net impact of this notion) of Clec12a as a “urate receptor”, rather than one of multiple cell surface proteins (eg, CD14) nonspecifically engaged by urate crystals, is well beyond the scope of this minireview.

4. “The word "NETosis" should be substituted by "NET formation" (to avoid the isophony and similarity to cell death pathways).”
Response: NETosis is the far more commonly used term, and is kept at a few junctures in the text, but NET formation is now mentioned frequently throughout.
Reviewer #2 Ann Rosenthal:

“This is a comprehensive and very interesting review of the current state of knowledge concerning modulation of gouty inflammation. It warrants publication. It needs some proof reading for sentence fragments, missing prepositions, tense agreement and simplification of overlong and un-necessarily complex sentences.”

Response: The paper was edited for grammar and style, as suggested.