Reviewer’s report

Title: Signal transduction mechanisms involved in S100A4-induced activation of the transcription factor NF-kappaB

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Reviewer: guenter schneider

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Grotterød et al. investigated the molecular mechanism by which S100A4 activates NFκB in the osteosarcoma cell line II-11b. They observed that the multi Ser/Thr kinase inhibitors H-7 and staurosporine prevent S100A4-dependent IκB phosphorylation. Furthermore, the authors demonstrate using chemical inhibitors or dominant negative kinases that phospholipase C, protein tyrosine kinases, protein kinase C, G-protein coupled receptors, MEKK1, NIK and PI 3-kinases are not involved in S100A4-induced NFκB activation. Also, the putative S100 protein receptor RAGE is not involved in the model investigated. In addition, the authors provide evidence, that a process occurring at the level or downstream of the IKK complex is affected by H-7 and staurosporine to prevent IκB phosphorylation. This study addresses an important topic of S100A4 protein function in cancer. However, there is no clear mechanism provided and the authors cannot exclude that a H-7/staurosporine-induced processes affects IKK function or assembly independent on the kinase-inhibitor activities. Both compounds used can induce overt apoptosis and there is clear evidence that staurosporine induced apoptosis can lead to the cleavage of NEMO and therefore to impaired IKK function. Hence, I would suggest a Journal with a scope focusing on signaling at the moment.

Further points:
1. For the phospho-specific IκB blots pan-IκB must be provided.
2. Genistein affects IκB phosphorylation; this should be discussed.
3. Statistics should be provided.
4. Is S1004A induced expression of ephrinA1 and optineurin also prevented by staurosporine?

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:
'I declare that I have no competing interests'