Reviewer's report

Title: A synergistic interaction between transcription factors nuclear factor-kappaB and signal transducers and activators of transcription 3 promotes gastric cancer cell migration and invasion

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Reviewer: sergei I. grivennikov

Reviewer's report:

This is a review for the paper by B.L. Lee and co-authors. This is a well planned and done study with enough novelty and mechanistic insight to be considered by BMC Gastroenterology magazine. Most of the points raised by this referee can be address without further experimental work, although some of the points would require additional experiments. Specific suggestions/critique is below:

1) Background, page 4. When literature about NF-kB activation in gastric cancer is mentioned, it is important to say whether it happens in cancer cells, infiltrating cells or probably both. Also 1 sentence before, not only cytokines etc can activate the pathway, but also TLR signaling and many other pathways of microbial recognition, relevant for gastrointestinal tumorigenesis.

2) Page 5. NF-kB deletion is not often used, it is likely IKKb deletion which results in defective NF-kB activation

3) Methods, page 6. Slides after deparaffinization are likely to be rehydrated, not dehydrated

4) When authors discuss simultaneous activation of NF-kB and STAT3 (Fig1 and elsewhere) it would be nice to see double color (IF) co-staining for both in the same cell/nucleus.

5) Table 1 data presentation looks a little bit not clear to me. How the data is organized. Table should be explained better. For example, how to find/deduce from the table that NF-KB is activated in 16% of tumors?

6) Page 11. More references about EMT should be provided with 1-2 specific to the cases of gastric cancer, because not in all types of cancer the existence and importance of EMT has yet been demonstrated.

7) Fig5A would look better and more convincing if fractionated nuclear extracts would be blotted.

8) Page 12. These data suggest that STAT3 –induced............. I would suggest to correct wording here: NF-kB in this system is induced not only through Stat3, but through something else. It is known that Stat3 pathway can be induced by many NF-kB independent pathways including some cytokines and Tyr-kinases.

9) This study would benefit from at least the most simplistic in vivo metastatic/dissemination assay of injecting Stat3 silenced, NF-kB inactivated cells into
mouse and scoring metastasis to prove the role in vivo

10) It seems to be important to mention a paper from Hua Yu group Cancer Cell. 2009 Apr 7;15(4):283-9 about the ability of activated Stat3 to maintain NF-kB activation and retention in the nucleus.

11) It is not clear whether indeed MMP9 expression really correlates with NF-KB and Stat3 activation in a biological sense- Table 1 data suggest that there are way more MMP9+ cells than cells with an activated NF-kB and Stat3, therefore MMP9 only sometimes correlates with NF-kB or Stat3, in many other cases it does not look dependent on Nf-kB and Stat3, is it correct?

**Level of interest:** An article of importance in its field

**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'