Dear Editors:

On behalf of the co-authors, I am pleased to submit the manuscript entitled “The NF-kB p65 and p50 Homodimers Cooperate with pSTAT1 to Synergistically Activate iNOS Transcription” for consideration by BMC Cancer. No part of this manuscript has been published, and this manuscript is not being considered by other journals. All authors have approved the contents of this manuscript.

iNOS is a key player of the proinflammatory response in the tumor microenvironment, and exhibits both tumor-promotion and suppression functions. The mechanisms underlying this contrasting function of iNOS is not clear. Therefore, elucidating the molecular mechanisms underlying iNOS expression regulation may provide insight into the contrasting role of iNOS.

We demonstrated here that tumor cells and myeloid cells, the two major components of the tumor microenvironment, both express iNOS. We further demonstrated that IFN# and NF-kB synergistically induce iNOS expression in tumor cells and myeloid cells. IFN# up-regulates IRF8 expression to enhance NF-kB-mediated iNOS expression, whereas, NF-kB directly binds to the iNOS gene promoter to regulate iNOS transcription. Moreover, we demonstrated, for the first time, that the NF-#B p65/p65 and p50/p50 homodimers, not the canonical p65/p50 heterodimer, regulate iNOS transcription.

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Thank you for your consideration

Sincerely

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