Reviewer’s report

Title: IL-6 signaling by STAT3 participates in the change from hyperplasia to neoplasia in NRP-152 and NRP-154 rat prostatic epithelial cells

Authors:

Beverly E. Barton (bartonbe@umdnj.edu)
Thomas F. Murphy (Murphytf@umdnj.edu)
Patricia Adem (Adempa@umedj.edu)
Richard A. Watson (Watsonra@umdnj.edu)
Robert J. Inwin (Irwinri@umdnj.edu)
Hosea F. Huang (huanghf@umdnj.edu)

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Reviewer: Dr Konrad Huppi

Level of interest: A paper whose findings are important to those with closely related research interests

Advice on publication: Accept after revision, which I do not need to see

Summary-
The paper of Barton et al., compares the rat prostate epithelial lines NRP-152 and NRP-154 at several points along the JAK/STAT pathway including phosphorylation of STAT3, production of IL-6, expression of IL-6 receptor and inhibition of JAK2. Besides tumorigenicity, the NRP-152 and NRP-154 cell lines appear to differ with respect to the fact that STAT3 is constitutively phosphorylated in NRP-154 cells. The NRP-154 cells appear to be a heterogeneous population based on expression of IL-6 and IL-6 receptor. Dexamethasone treatment also appears to enhance rather than inhibit IL-6 production in NRP-154 cells. Finally, inhibition of JAK2 induced apoptosis in NRP-152 cells but not in the NRP-154 cells. As the observations have been purely descriptive, the basis for these observed differences remains to be elucidated.

Major Critique-
1. There are several critical findings presented in the paper beginning with the fact that STAT3 is found to be constitutively phosphorylated in NRP-154 but not NRP-152 cells. Unfortunately, the NRP-154 cells also appear to be a heterogeneous population based on expression of IL-6 and IL-6 receptor, and this leads to some loss of confidence in the experiments that follow, principally the effect of dexamethasone treatment and JAK2 induced apoptosis on NRP-154 cells. In figure 5, it is hard to understand how a simple interpretation of increased expression of IL-6 can be made with two (or more) populations of cells. Similarly, the effect of the JAK2 inhibitor, AG490, on NRP-154 cells could be compromised by the presence of a heterogeneous population in comparison to NRP-152 cells. The impact of the paper could be increased considerably if subclones of IL-6+ (9) and IL-6- (7) were used for the studies of dexamethasone and AG490 treatment.

Additional Comments-
1. Page 11- Discussion
Data is not shown that phosphorylation of STAT3 in NRP-154 cells is unaltered following treatment with
testosterone. Similarly, data is not shown that STAT3 remains unphosphorylated following testosterone treatment. In both cases, Figure 1 should not be referenced.

2. Page 14- second paragraph
No formal demonstration that NRP-154 cells treated with testosterone over-express the gene for Stat 3 has been made.

3. Page 14- second paragraph
The term cSTAT3 (for constitutively expressed??) has not been defined as yet.

4. Page 14- second paragraph
The sentence that begins with "Finally, we demonstrated that while both cell lines......" is awkward and should be rewritten.

5. Figure 4-
B "red line" and "red peak" are actually purple.

**Competing interests:**

None declared.