Peer Review File

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Reviewer A

In line 88: You speak about expression but do not specify whether the data is nominalized and in what way.

Reply: Thanks for your insightful comment. We calculate the TPM expression of each genes, where we normalize based on gene length and sequencing depth. We have added it in the method section and highlighted them in red.

Changes in the text: In line 364-365: We then calculate the TPM expression of each genes, where we normalize based on gene length and sequencing depth.

In line 269, 271, 173, eccecc: All tools are only mentioned. It is good practice to insert the version used and insert not the download link but the reference!!!

Reply: Thanks for your insightful comment. We have added the references for tools in the method section and mark them in red.

Changes in the text: In line 358 – 364: We next align reads to the human genome (Version: hg19) by using STAR (https://github.com/alexdobin/STAR) (Dobin et al., 2013) and perform the quality control by using multiqc (https://multiqc.info/) (Ewels et al., 2016). We quantify the gene reads by using FeatureCounts (Liao et al., 2014) (http://subread.sourceforge.net/). We use Deseq2 (Love et al., 2014) to perform the differential gene expression analysis (https://bioconductor.org/packages/release/bioc/html/DESeq2.html).

In line 367-381: We next align reads to the human genome (Version: hg19) by using Bowtie2 (Langmead and Salzberg, 2012) (http://bowtie-bio.sourceforge.net/bowtie2/index.shtml). We use Samtools (Li et al., 2009) (http://samtools.sourceforge.net/) to convert files in to sam and use bedtools (Quinlan and Hall, 2010) (https://bedtools.readthedocs.io/en/latest/) to convert files in to bed file type.

In line 388-394: We next align reads to the human genome (Version: hg19) by using Bowtie2 (Langmead and Salzberg, 2012) (http://bowtie-bio.sourceforge.net/bowtie2/index.shtml). We conduct the peak calling by using macs14 (Feng et al., 2012) (http://liulab.dfci.harvard.edu/MACS/00README.html). We next rank enhancers and identify super-enhancers by using ROSE (Whyte et al.) (http://younglab.wi.mit.edu/super_enhancer_code.html).

In line 285: it doesn't seem elegant to always repeat "we download the raw....by aspera". Resume in only one if possible.

Reply: Thanks for your insightful comment. We modified the statements and marker as red in revised method section.

In figure 1: You speak about raw data, but if true is not directly comparable without normalization. even if the acronyms of cancers are present on TCGA, it is perhaps better to put them in full in a legend.

Reply: Thanks. We normalized the raw data based on gene length and sequencing depth. The TCGA cancer codes were provided in figure legends.

Reviewer B

It is widely accepted that inflammatory cytokine IL-6 is not only elevated in cancer but is also important in carcinogenesis. However, the induction of IL-6 production in the tumor microenvironment has not been fully addressed. In the manuscript "Super-enhancers modulate Interleukin-6 expression and function in cancer", the authors investigated the role of super-enhancers in the induction of IL-6 in cancer cells.

(1) "uM" in Figure 2 is not correct.

Reply 2: Thanks. We revised in Figure 2.

Changes in the text: Revised in Figure 2.

(2) In Figure 2, (F) is missing. (A-H) are shown in Figure 2, but only (A-F) are mentioned in the Figure 2 legend.

Reply 2: Thanks. We revised in Figure 2 and the Figure legends were also revised accordingly.

Changes in the text: Figure Legends for Figure 2 (D-G): (D) Total RNA-seq signal on all enhancers. In order to remove noice, we remove the reads overlapping known transcripts and retain the reads overlapping with enhancer regions by using *intersect* in bedtools (Methods). (E) PolyA RNA-seq signal on all enhancers. (F) Heatmap of total RNA-seq signal of all enhancers. (G) Heatmap of PolyA RNA-seq signal of all enhancers. In order to remove noice, we remove the reads overlapping known transcripts and retain the reads overlapping with enhancer regions by using *intersect* in bedtools (Methods).

(3) A scale bar needs to be added to Figure 4F. Providing the big field graph of the colony formation would make the paper more convincing.

Reply 2: Thanks. The scale bar was added in Figure 4F. We also provide full field graph in revised Figure 4G.

(4) Why were Hela cells and SUM-19 cells chosen? The introduction mainly discussed pancreatic cancer.

Reply 2: Thanks. We tried to delete IL6-SE in several cell lines including pancreatic cancer cells. Although we tried several times, the stable IL6-SE knockout cell lines are hard to be established in pancreatic cancer cell lines in our hands.

(5) Analysis of the results and possible mechanism should be included in the discussion.

Reply 2: Thanks, we added four sentences to discuss the results and potential mechanism.