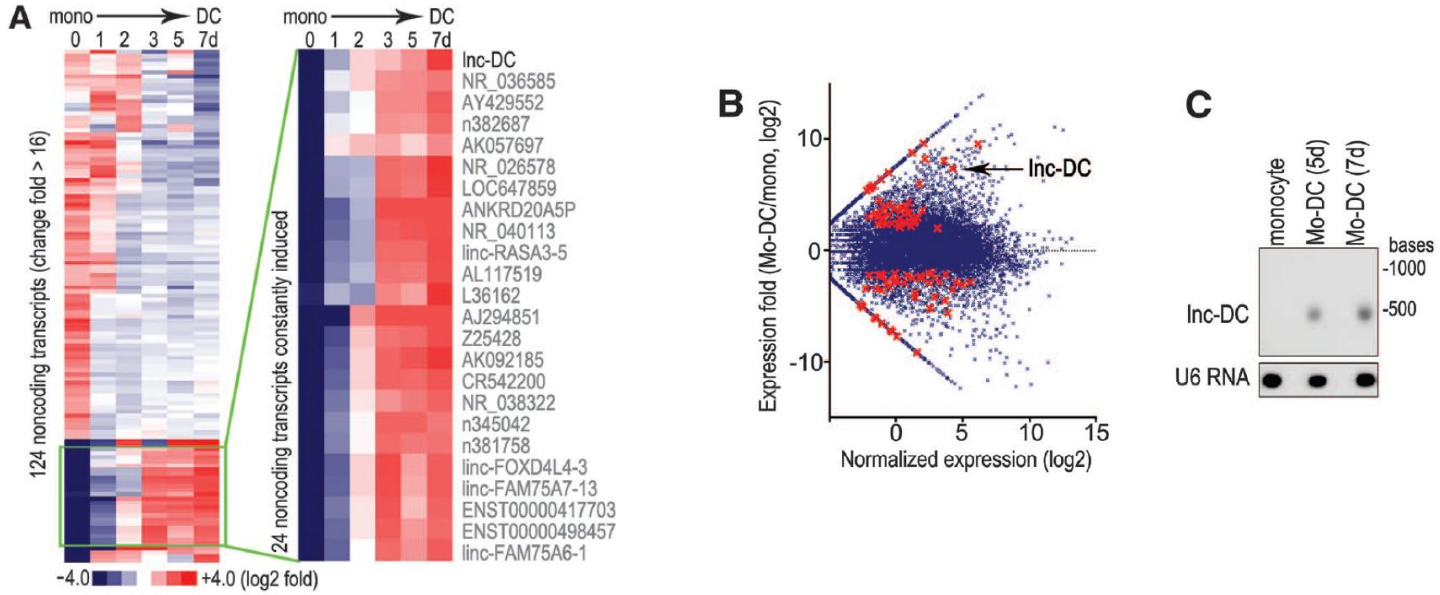
Science
AAAS

The STAT3-Binding Long Noncoding RNA lnc-DC Controls Human Dendritic Cell Differentiation

Pin Wang,[1,2] Yiquan Xue,[1] Yanmei Han,[1] Li Lin,[2] Cong Wu,[3] Sheng Xu,[1] Zhengping Jiang,[1] Junfang Xu,[3] Qiuyan Liu,[1] Xuetao Cao[1,2,3]*

Long noncoding RNAs (lncRNAs) play important roles in diverse biological processes; however, few have been identified that regulate immune cell differentiation and function. Here, we identified lnc-DC, which was exclusively expressed in human conventional dendritic cells (DCs). Knockdown of lnc-DC impaired DC differentiation from human monocytes in vitro and from mouse bone marrow cells in vivo and reduced capacity of DCs to stimulate T cell activation. lnc-DC mediated these effects by activating the transcription factor STAT3 (signal transducer and activator of transcription 3). lnc-DC bound directly to STAT3 in the cytoplasm, which promoted STAT3 phosphorylation on tyrosine-705 by preventing STAT3 binding to and dephosphorylation by SHP1. Our work identifies a lncRNA that regulates DC differentiation and also broadens the known mechanisms of lncRNA action.

Figure 1. lnc-DC is highly expressed in human cDC subsets



(**A**) The cluster heat map shows lncRNAs with expression change fold >16 from microarray data ($P < 0.05$). (**B**) Ratio of gene expression in Mo- DC to monocytes (vertical axis) and average expression of genes in Mo-DC versus that in monocytes (horizontal axis) (RNA-seq analysis). Highlighted in red are 99 lncRNAs with significant changes in expression (fold > 4, false discovery rate < 0.05). (**C**) Northern blotting of lnc-DC in monocytes and Mo-DC.

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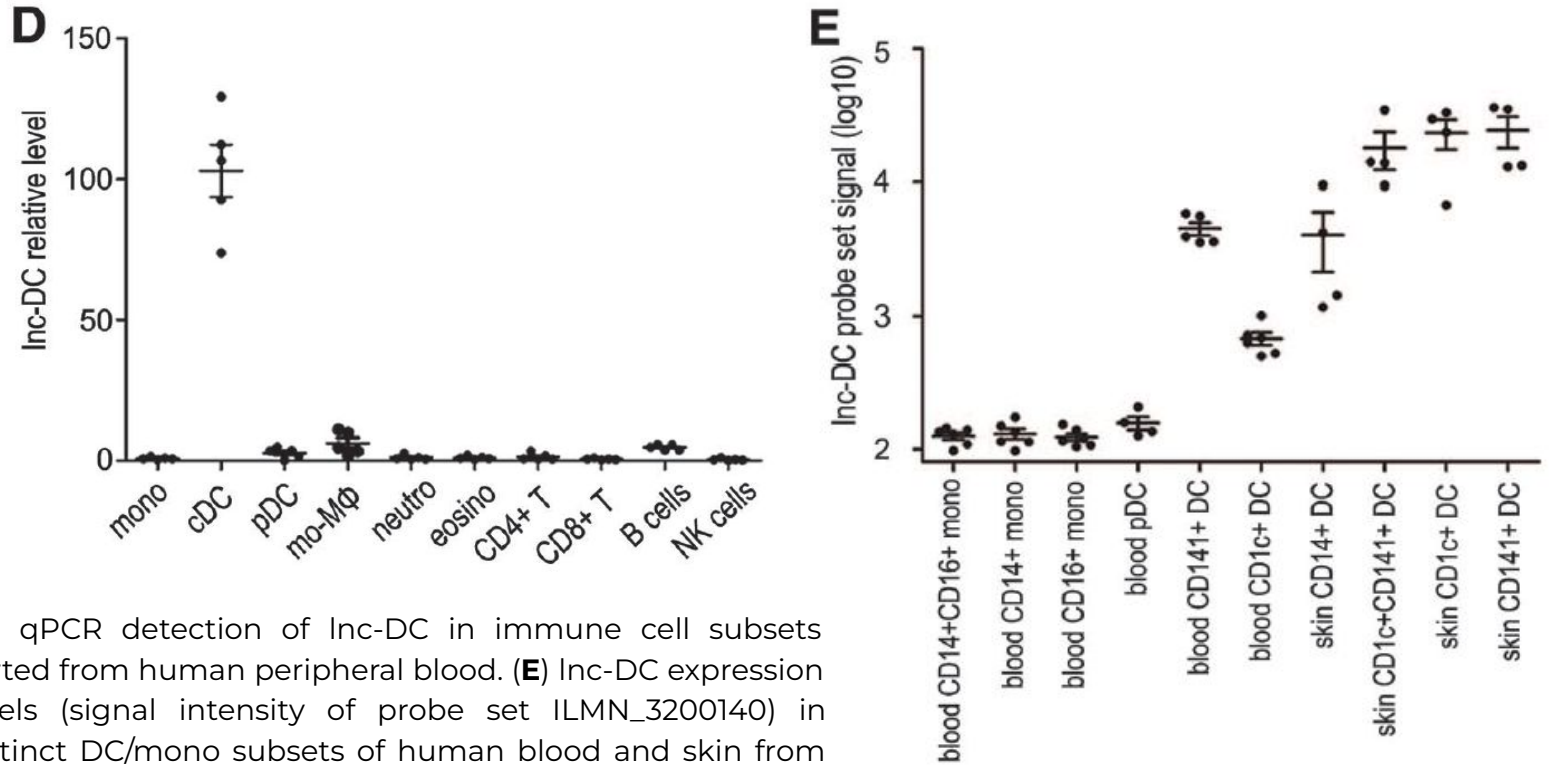


(**D**) qPCR detection of lnc-DC in immune cell subsets sorted from human peripheral blood. (**E**) lnc-DC expression levels (signal intensity of probe set ILMN_3200140) in distinct DC/mono subsets of human blood and skin from GSE35457 data.

Figure 2. The exclusive expression of lnc-DC in DC is attributed to acquired active histone modifications, accessible chromatin structures, and PU.1 binding at the promoter region.

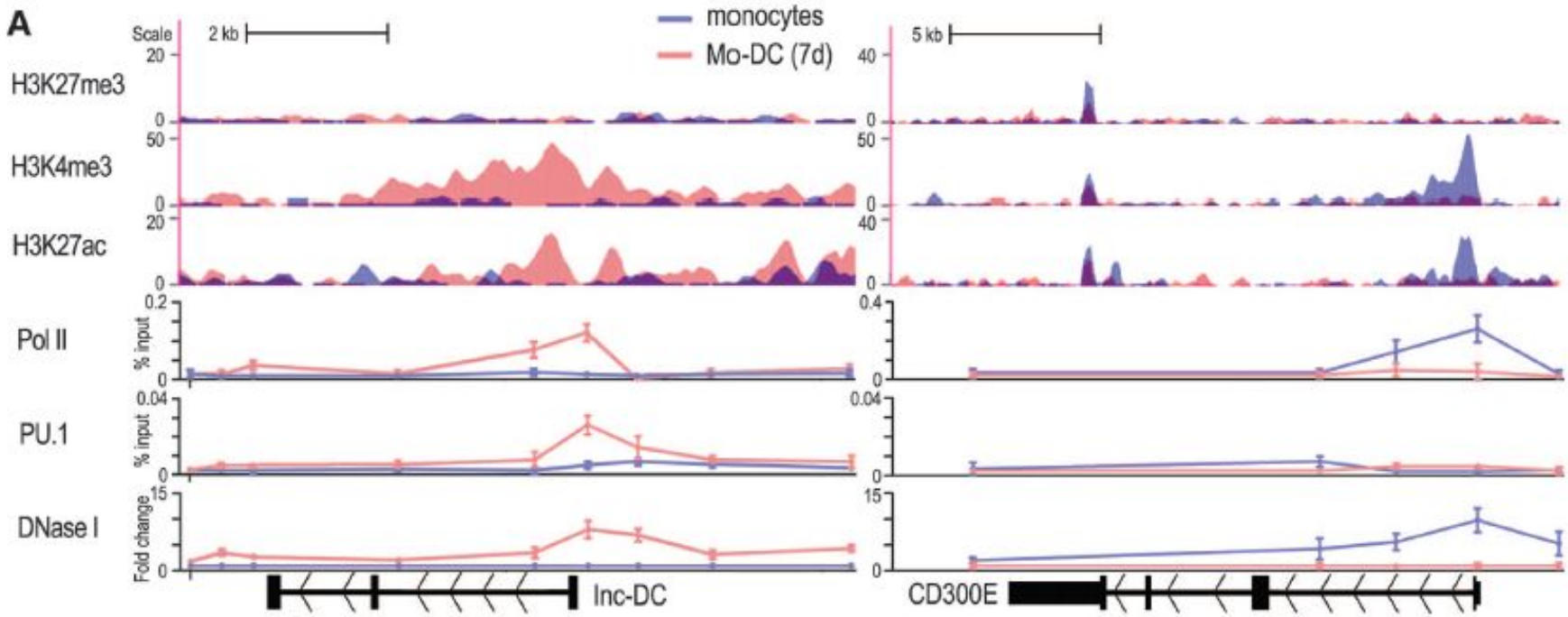
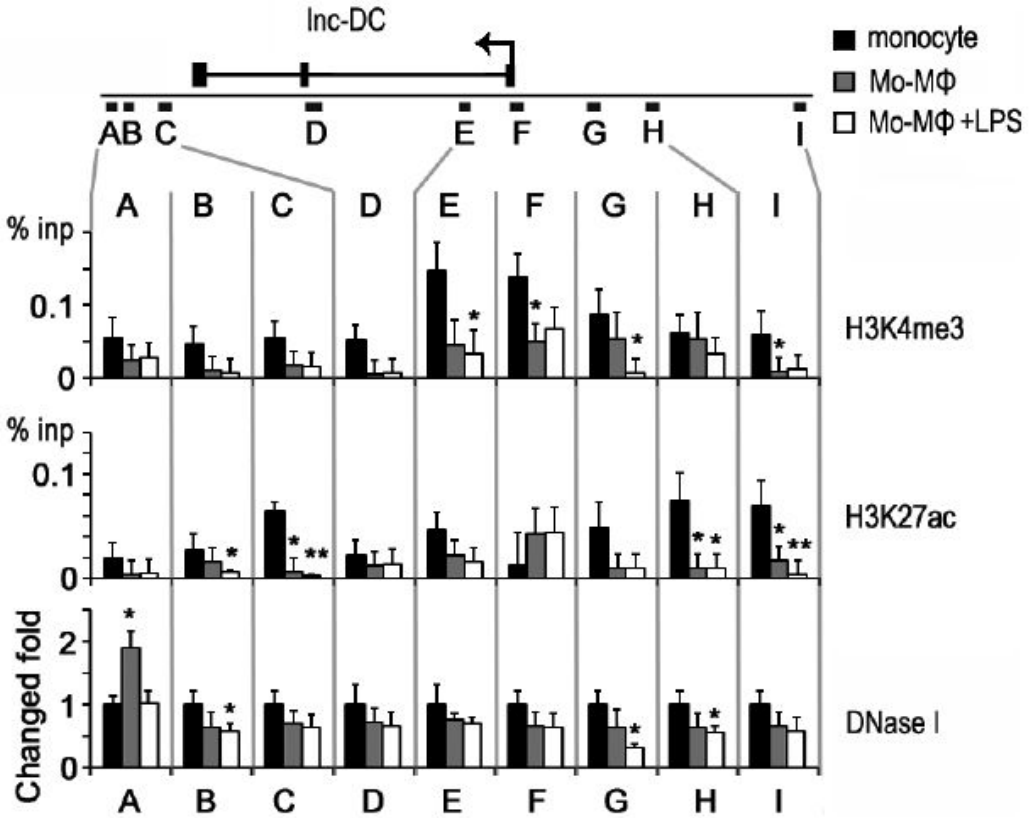


Fig S6. H3K4me3 and H3K27ac modifications and chromatin accessibility of lnc-DC gene remain at low levels during the differentiation and activation of Mo-MΦ.



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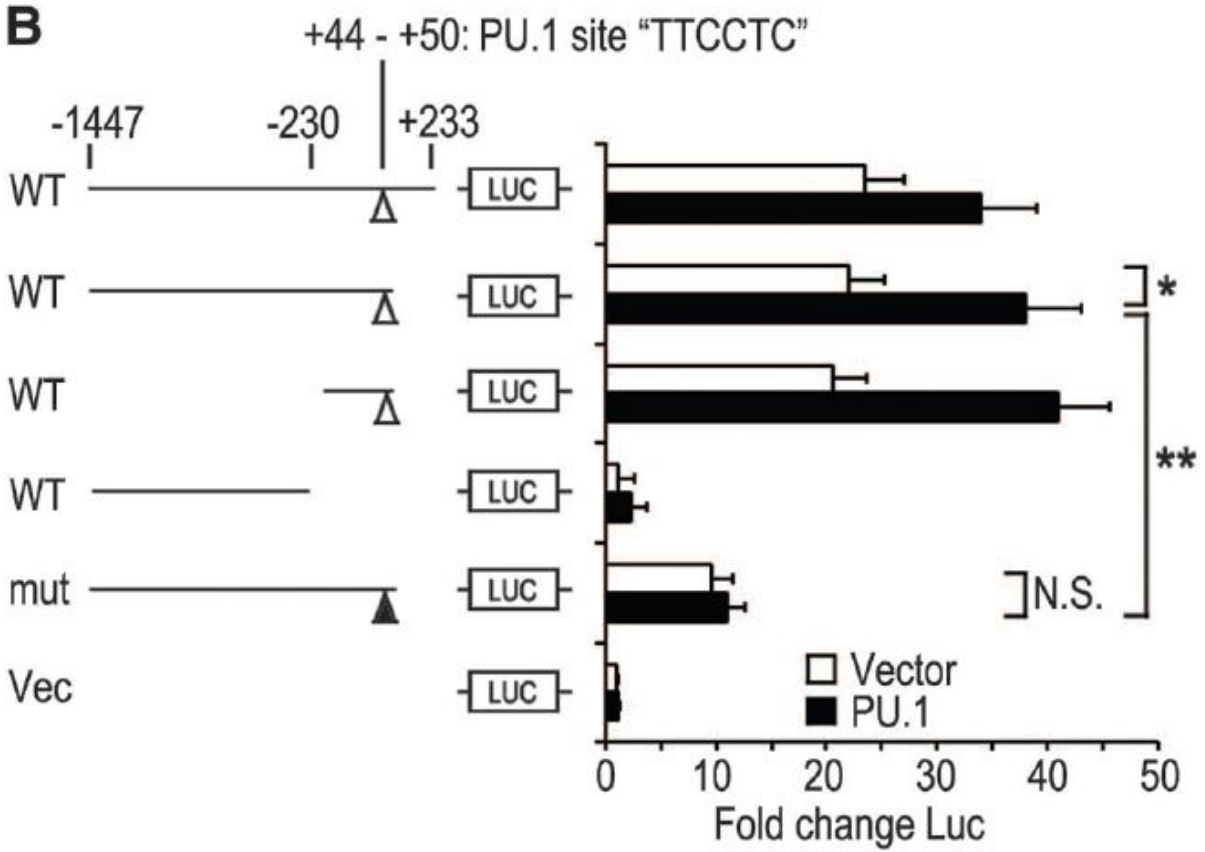
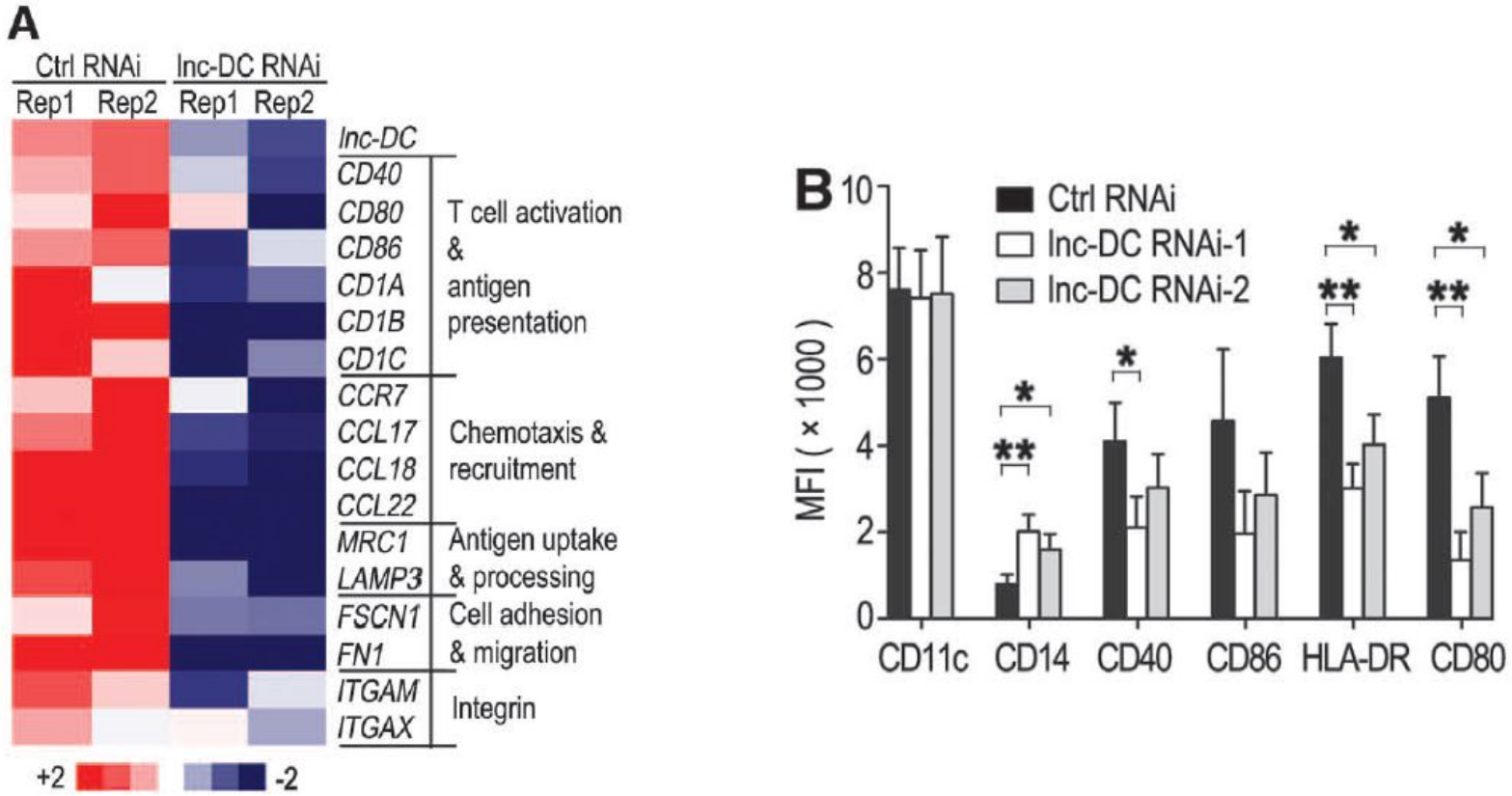


Figure 3. Knockdown of lnc-DC impairs DC differentiation and function



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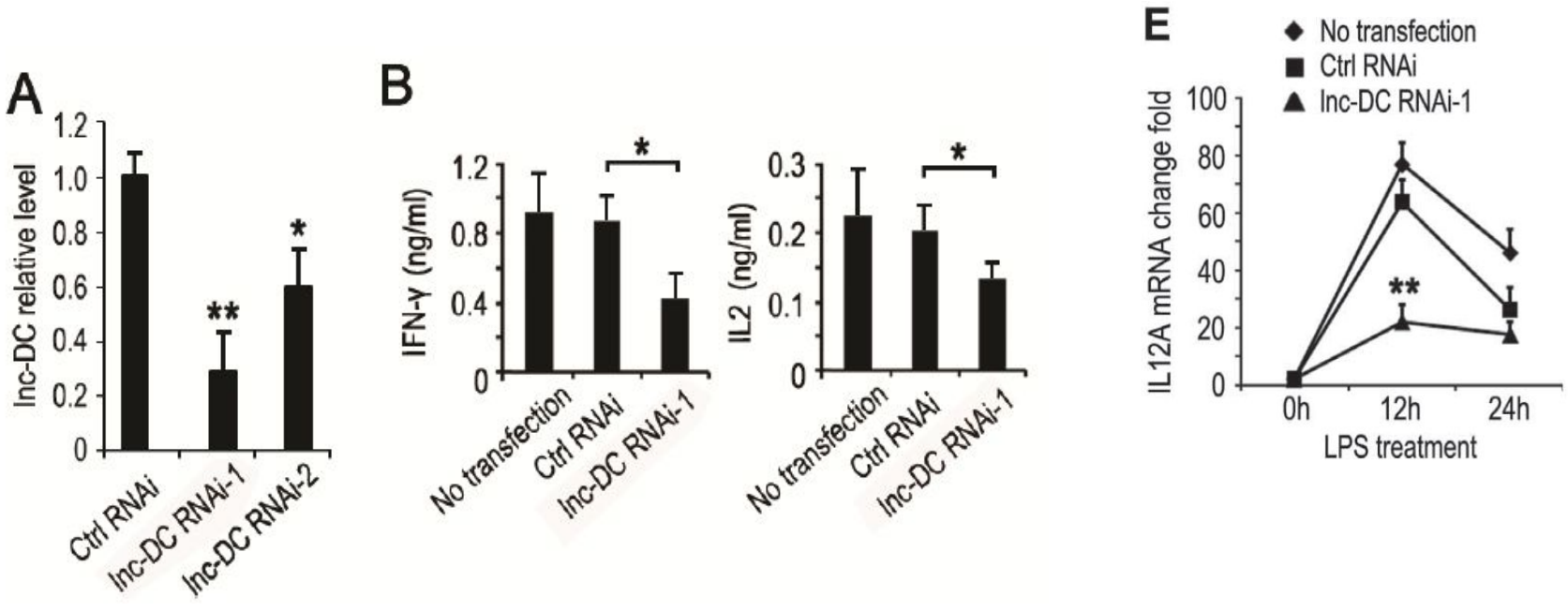

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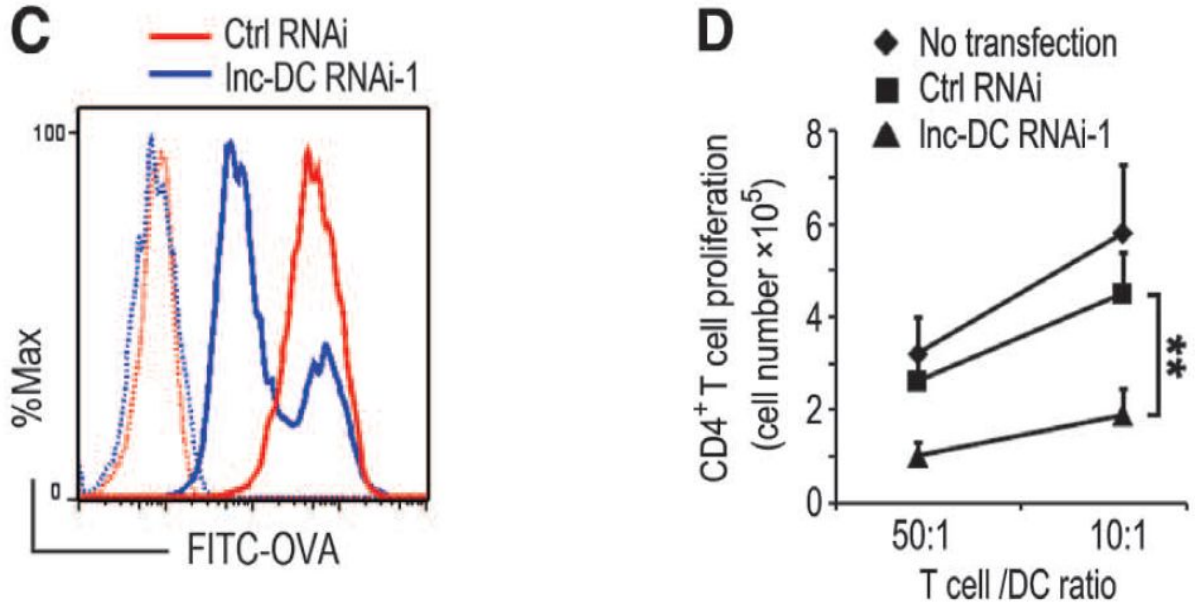
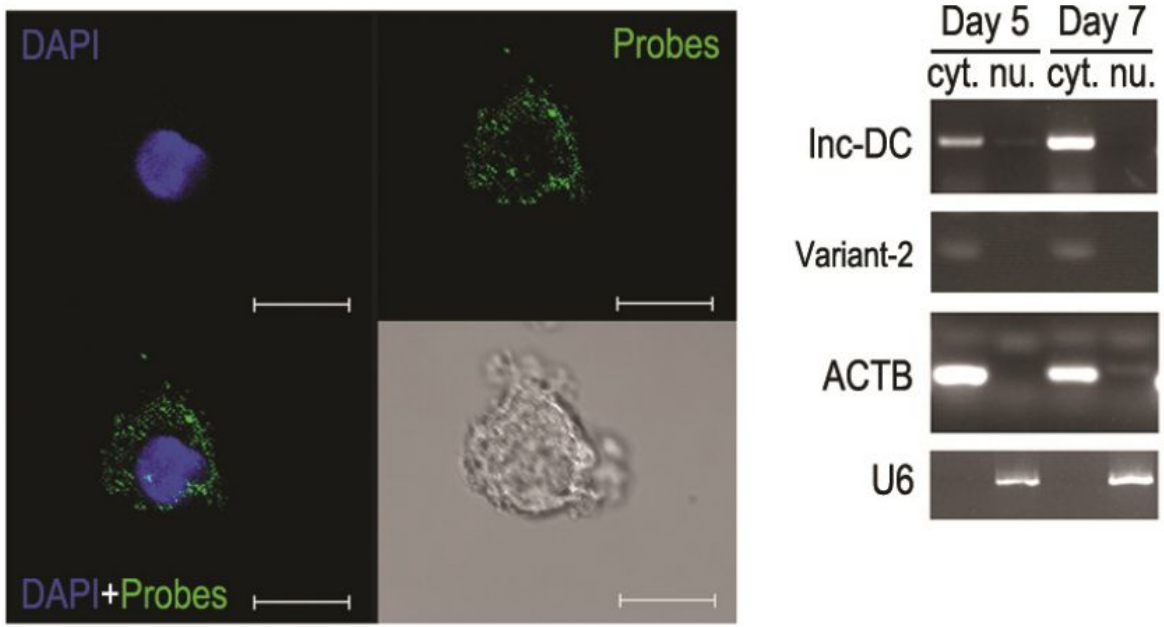


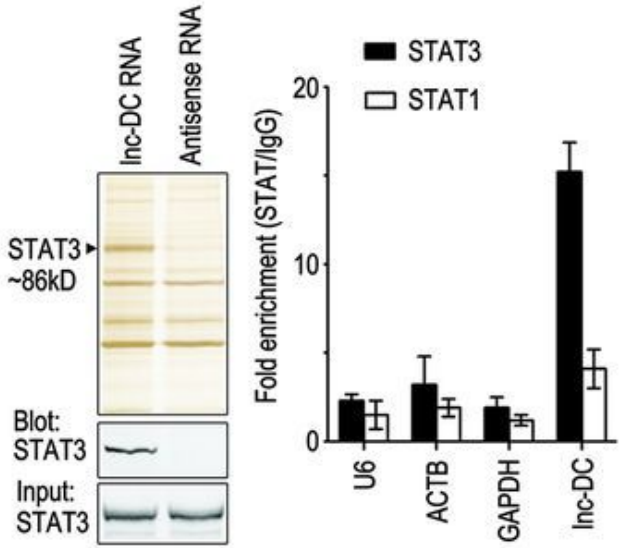
Fig S15. The cytoplasmic location of lnc-DC in human DC.

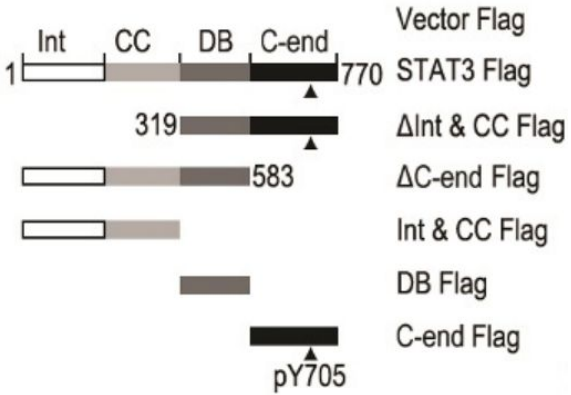


Mechanisms for cytoplasmic lncRNA action

- ❏ Sequestration of microRNA to restore mRNA translation
- ❏ Promotion of STAU1-mediated mRNA decay

Figure 4. lnc-DC directly binds STAT3 in cytoplasm to prevent Y705 dephosphorylation of STAT3 by SHP1. **Figure S18.** lnc-DC binds to the C-terminus of STAT3 protein.





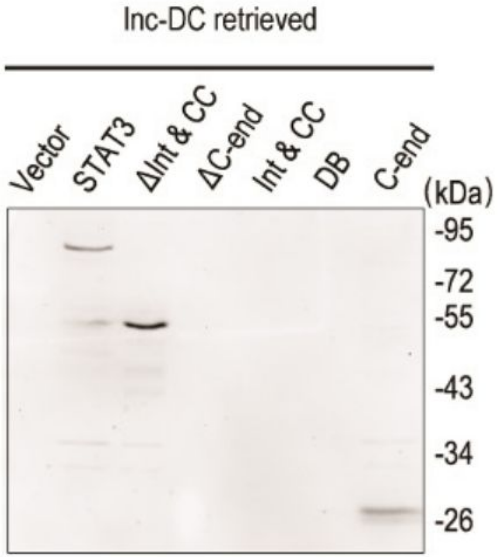


Figure 4. lnc-DC directly binds STAT3 in cytoplasm to prevent Y705 dephosphorylation of STAT3 by SHP1. **Figure S19.** lnc-DC promotes STAT3 signaling.

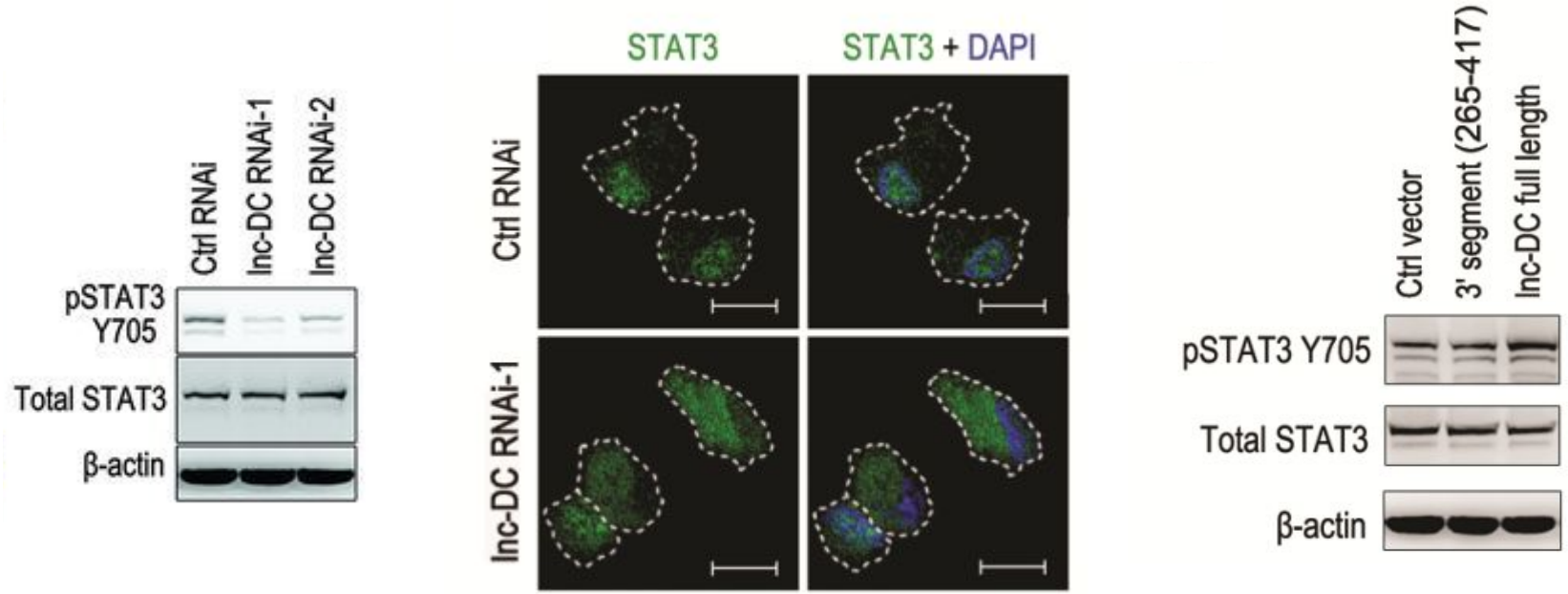
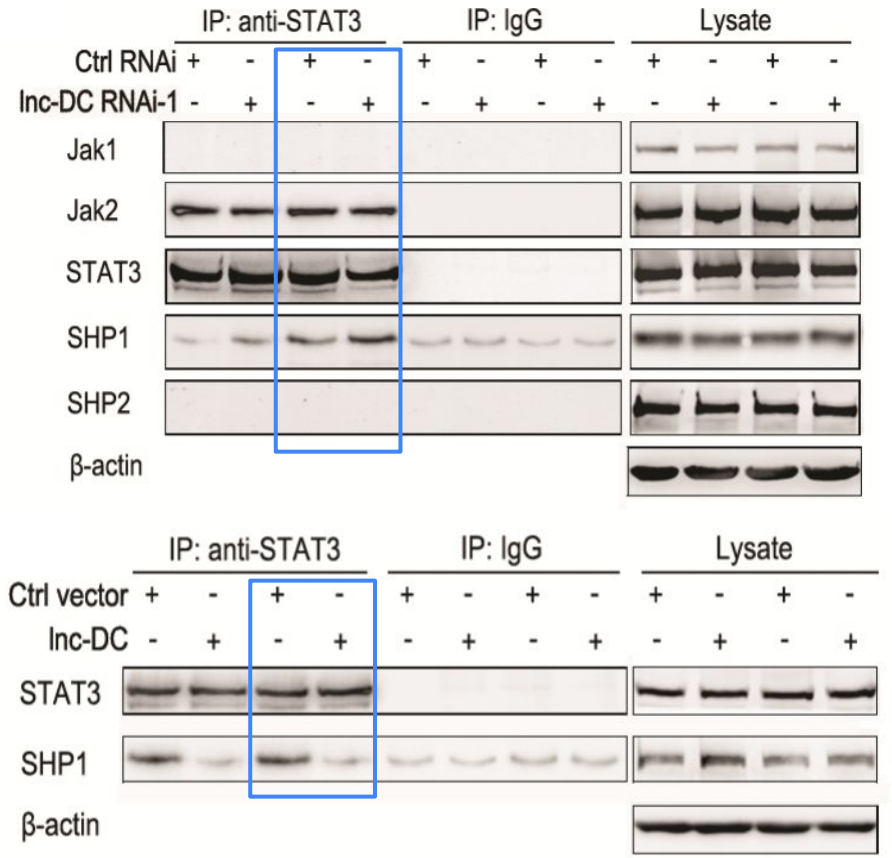
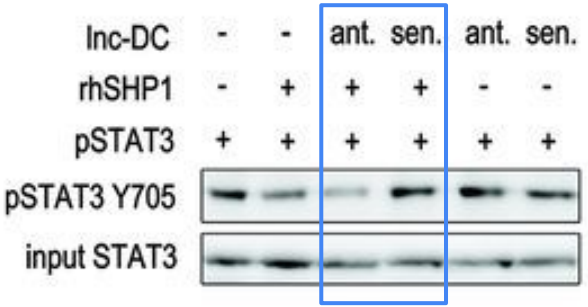
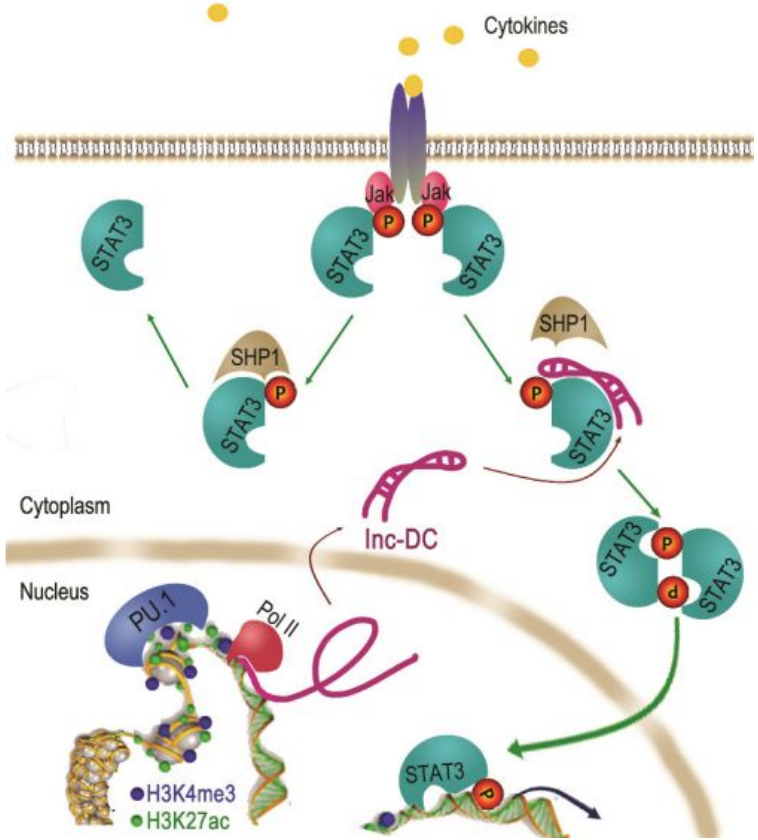


Figure 4. lnc-DC directly binds STAT3 in cytoplasm to prevent Y705 dephosphorylation of STAT3 by SHP1. **Figure S23.** lnc-DC impairs the interaction between STAT3 and SHP1.





Conclusion



During the process of DC differentiation from monocytes, histone modifications are increased, leading to chromatin structure opening, which allows the transcription of lnc-DC. Once exclusively expressed in DC, lnc-DC is translocated into cytoplasm, where it directly interacts with C-terminus of STAT3. The binding of lnc-DC to STAT3 preserves the phosphorylation of STAT3 from dephosphorylation by tyrosine phosphatase SHP1, which strengthens STAT3 signaling to promote DC differentiation