**(5R)-5-Hydroxytriptolide (LLDT-8) induces substantial epigenetic mediated immune response network changes in fibroblast-like synoviocytes from rheumatoid arthritis patients**

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# Abstract

*Tripterygium* is a traditional Chinese medicine that has widely been used in the treatment of rheumatic disease. (5R)-5-hydroxytriptolide (LLDT-8) is an extracted compound from *Tripterygium*, which has been shown to have lower cytotoxicity and relatively higher immunosuppressive activity when compared to *Tripterygium*. However, our understanding of LLDT-8-induced epigenomic impact and overall regulatory changes in key cell types remains limited. Doing so will provide critically important mechanistic information about how LLDT-8 wields its immunosuppressive activity. The purpose of this study was to assess the effects of LLDT-8 on transcriptome including mRNAs and long non-coding RNA (lncRNAs) in rheumatoid arthritis (RA) fibroblast-like synoviocytes (FLS) by a custom genome-wide microarray assay. Significant differential expressed genes were validated by QPCR. Our work shows that 394 genes (281 down- and 113 up-regulated) were significantly differentially expressed in FLS responding to the treatment of LLDT-8. KEGG pathway analysis showed 20 pathways were significantly enriched and the most significantly enriched pathways were relevant to [Immune reaction](http://r.search.yahoo.com/_ylt=A86.JyRxrUFWl28ANDInnIlQ;_ylu=X3oDMTByb2lvbXVuBGNvbG8DZ3ExBHBvcwMxBHZ0aWQDBHNlYwNzcg--/RV=2/RE=1447173617/RO=10/RU=http%3a%2f%2fwww.thefreedictionary.com%2fimmune%2breaction/RK=0/RS=y5lS2HvWhcMog0MxG0yEKN1yS0c-), including cytokine-cytokine receptor interaction (*P*=4.61×10-13), chemokine signaling pathway (*P*=1.01×10-5) and TNF signaling pathway (*P*=2.79×10-4). Furthermore, we identified 618 highly negatively correlated lncRNA-mRNA pairs from the selected significantly differential lncRNA and mRNA including 27 cis-regulated and 591 trans-regulated lncRNA-mRNAs modules. KEGG and GO based function analysis to differential lncRNA also shown the enrichment of immune response. Finally, lncRNA-transcription factor (TF) and lncRNA-TF-mRNA co-expression network were constructed with high specific network characteristics, indicating LLDT-8 would influence the expression network within the whole FLS cells. The results indicated that the LLDT-8 would mainly influence the FLS cells systemically and specially in the process of immune related pathways