

## Punicalagin, a PTP1B Inhibitor, Induces M2c Phenotype Polarization via Up-Regulation of HO-1 in Murine Macrophages

Xiaolong Xu<sup>1,2,3\*</sup>, Jingxia Zhao<sup>1,2,3</sup>, Di Tingting<sup>1,2</sup>, Wang Yan<sup>1,2</sup>, Ping Li<sup>1,2</sup> and Qingquan Liu<sup>1,2,3</sup>

<sup>1</sup>Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, China

<sup>2</sup>Beijing Institute of Traditional Chinese Medicine, China

<sup>3</sup>Beijing Key Laboratory of Basic Research with Traditional Chinese Medicine on Infectious Diseases, China

Punicalagin (PUN) is the most abundant ellagitannin in pomegranate, a well-documented traditional Chinese medicine used for inflammatory diseases. We reported that PUN possesses considerable anti-inflammatory and anti-oxidant properties; However, its direct targets have not yet been reported. Here, we demonstrated that Protein Tyrosine Phosphatase-1B (PTP1B) serves as a direct target of PUN, with  $IC_{50}$  value of 1.04  $\mu$ M. Results from NPOI further showed that the  $K_{on}$  and  $K_{off}$  of PUN-PTP1B complex were 3.38e2  $M^{-1}s^{-1}$  and 4.13e-3  $s^{-1}$ , respectively. The active site Arg24 of PTP1B was identified as a key binding site of PUN by computation simulation and point mutation. Moreover, inhibition of PTP1B by PUN promoted an M2c-like macrophage polarization and enhanced anti-inflammatory expression, including IL-10 and M-CSF. Based on gene expression profile, we elucidated that PUN treatment significantly up-regulated 275 genes and down-regulated 1059 genes. M1 like macrophage marker genes, such as *Tlr4*, *Irf1/2*, *Hmgbl*, and *Stat1* were down-regulated, while M2 marker genes, including *Tmem171*, *Gpr35*, *Csf1*, *Il1rn*, *Cebpb*, *Fos*, *Vegfa*, *Slc11a1*, and *Bhlhe40* were up-regulated in PUN-treated macrophages. *Hmox-1*, a gene encoding HO-1 protein, was preferentially expressed with 16-fold change. Inhibition of HO-1 obviously restored PUN-induced M2 polarization and IL-10 secretion. In addition, phosphorylation of both Akt and STAT3 contributed to PUN-induced HO-1 expression. This study provided new insights into the mechanisms of PUN-mediated anti-inflammatory and anti-oxidant activities and provided new therapeutic strategies for inflammatory diseases.

### Biography:

Xu Xiaolong was born in 1988, China. He received M.S.A and D.S.A from China Agriculture University in 2012 and 2015, respectively. Now he is a research associate in Beijing Hospital of Traditional Chinese Medicine and Beijing Institute of Traditional Chinese Medicine. He is also a research fellow in Beijing Key Laboratory of Basic Research with Traditional Chinese Medicine on Infectious Diseases. His main research interest is natural plant extract on inflammatory diseases including Sepsis, IBD, Shock and so forth.