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THERAPEUTIC VALUE OF CURCUMIN ON INITIATION AND DEVELOPMENT OF INFLAMMATION IN TAKAYASU'S ARTERITIS CAUSED BY HSP65-MEDIATED CCL2 OVEREXPRESSION

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Background: Takayasu's arteritis (TA) is a chronic inflammatory disease characterized with macrophages infiltration. During active stage, aorta adventitial fibroblasts (AAFs) proliferate excessively and produce numerous pro-inflammatory factors in the adventitia, which is the main target of TA therapy. Monocyte chemokine CCL2 may contribute to the infiltration of macrophages in TA arteries [1] but whether with relationship with HSP65, an antigen of Mycobacterium tuberculosis (M. TB) which might involve in the pathogenesis of TA [2] and activate AAFs to produce inflammatory factors, has not been reported. The treatment of TA is full of difficulties and contradictions [3]. Curcumin is a traditional Chinese medicine with anti-inflammatory effect [4], whether it is effective on TA and the underlying mechanism remains unclear.

Objectives: To explore the mechanism of TA inflammation triggered by M. TB associated antigen HSP65 activating AAFs, as well as the therapeutic value of curcumin in the initiation and development of TA.

Methods: We first verified high HSP65 expression in aortic adventitia of TA patients by IHC. mRNA-seq was used to profile DEGs between AAFs stimulated by HSP65 with or without pretreated with curcumin, and AAFs without any treatment. Then the key chemokine CCL2 screened by mRNA-seq was detected in the adventitia of TA aorta, and its correlation with HSP65 expression was analyzed by double-labelled IF. Subsequently, we explored how HSP65 affected the production of inflammatory factors by AAFs at cellular level and its related signal pathway. Simultaneously, we explored whether curcumin could hinder this process, and verified the effect of curcumin on serum CCL2 level in patients with TA. Finally, serum CCL2 and other inflammation indicators of TA patients at baseline and after 3 months treatment by curcumin were determined.

Results: HSP65 was highly expressed in the adventitia of TA arteries. DEGs analysis showed a key role of CCL2. The expression of CCL2 in adventitia of TA arteries was significantly higher than healthy subjects, and was correlated with HSP65. HSP65 facilitated the production of CCL2, IL-6 and IL-1 β by AAFs via activating TLR4-JAK2/AKT/STAT3 pathway, among which the change of CCL2 was the most remarkable. Curcumin reversed the upregulation of CCL2 induced by HSP65 in vitro, which was more obvious than that of MTX and tofacitinib. Finally, curcumin significantly downregulated the level of serum CCL2 of TA patients.

Conclusion: HSP65 initiates and promotes inflammation of TA by upregulated CCL2 in AAFs through JAK/AKT/STAT3 pathway, while curcumin can reverse this process and slow down the initiation and development of TA.

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Figure A. High expression of HSP65 and CCL2 in aortic adventitia of TA patients (n=8) than that of healthy controls (n=6).

Figure B. HSP65 increased production of CCL2 in AAFs through TLR4/JAK2-STAT3 pathway.

Figure C. Curcumin reversed inflammatory response initiated by HSP65 via inhibiting JAK2/AKT/STAT3 signal pathway in AAFs and significantly reduced serum CCL2 concentration of TA patients.

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