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Anti-invasive effects of kaempferol in hypoxia-induced fibroblast-like synoviocyte through suppressing of HIF-1α/CXCR4 signaling pathway

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Rheumatoid arthritis (RA) joints are in a hypoxic condition. Hypoxia-induced migration and invasion of fibroblast-like synoviocytes (FLSs) are considered to play a critical role in the pathogenesis of RA. Among the key genes upregulated by hypoxia-inducible factor-1α (HIF-1α), CXC chemokine receptor 4 (CXCR4) plays an important role in FLS migration and invasion. Our previous studies have shown that kaempferol exerts anti-arthritic effects by inhibiting FLS migration and invasion under normoxic conditions. However, the effect and molecular mechanisms underlying the effect of kaempferol on hypoxia-induced FLS migration and invasion are poorly understood. In the present study, we assessed the effect of kaempferol on hypoxia-induced FLS migration and invasion. Results showed that kaempferol suppressed hypoxia-induced FLS migration and invasion. In addition, we also found that celastrol inhibited hypoxia-induced CXCR4 expression at both the mRNA and the protein levels in RA-FLSs. Meanwhile, it is revealed that kaempferol inhibited the transcriptional activity of CXCR4 under hypoxic conditions by suppressing the binding activity of HIF-1α in the CXCR4 promoter, and blocked hypoxia-induced accumulation of nuclear HIF-1α. Furthermore, treatment with HIF-1α inhibitor reduced the hypoxia-induced expression and transcriptional activity of CXCR4. In conclusion, our results indicate that kaempferol inhibits hypoxia-induced migration and invasion via suppression of HIF-1α mediated CXCR4 expression in FLSs under hypoxic conditions. These results provide a strong rationale for further testing and validation of the use of kaempferol as a new alternative for using in the treatment of RA.

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