牙周病主要致病菌 Porphyromonas gingivalis 調控人類臍靜脈內皮細胞表現 Interleukin-6 及其接受器之訊息機制探討

Regulatory Mechanism of Interleukin-6 and Its Receptors in Human Umbilical Vein Endothelial Cells Infected by Invasive and Non-invasive Porphyromonas gingivalis

中文摘要

牙周病是經由 Porphyromonas gingivalis 感染所引發的慢性發炎反應，近年來許多文獻報導指出，牙周病會增加患者罹患心血管疾病的機率，發炎反應的三個指標：C-reactive protein (CRP)、fibrinogen (Fb)、interleukin-6 皆對於增加心衰竭與中風之危險有相關聯性；其中 interleukin-6 又爲冠狀動脈疾病的獨立性危險因子。本研究藉由探討人類臍靜脈內皮細胞在受到牙周病主要致病菌 Porphyromonas gingivalis (以下簡稱 381) 感染，誘發 interleukin-6 及其接受器表現之訊息傳遞來討論牙周病增加心血管疾病危險因子之機制。另外，利用另一突變菌株，insertionally inactivated fimA (fimA mutants，以下簡稱 DPG3)，比較細胞受到侵入型與非侵入型細菌感染後訊息傳遞機制之差異。結果顯示，細胞分別受到兩菌株感染後皆可誘發 interleukin-6 產生及調控 IL-6 receptor complex (IL-6R 、gp130) 的表現，但是兩者有程度上的差異。P. gingivalis 誘導的 IL-6 所引發的訊息傳遞路徑包含有 STAT3 以及 ERK 的活化。在我們的結果顯示 JAKs/STAT3 路徑只參與在由 381 所調控的 receptor 表現，由 real-time PCR 實驗結果推測，可能因爲 DPG3 不調控 IL-6 receptor 的 de novo synthesis；在 381 的刺激下，ERK 磷酸化會活化下游的 I- B 使得 IL-6 持續分泌，而在 DPG3 的刺激下，雖然也會磷酸化 ERK 的表現，卻不影響下游的 I- B ，因此推測有其他轉錄因子參與調控IL-6分泌。在我們的實驗模式中，經由牙周病致病菌 P. gingivalis 感染人類臍靜脈內皮細胞後誘導 IL-6 的產生並且調控 IL-6 receptor 的表現造成訊息傳遞的迴路，使得細胞本身自我調控產生 IL-6 的大量分泌；然而，過度的刺激會讓免疫反應所造成的損害性大過於修復性。因此，藉由探討牙周病菌對於臍靜脈細胞的感染發炎機制，可進一步的了解牙周病與心血管疾病間的相關聯性，並期望在將來可由致病機轉中找出減低牙周病患者罹患心血管疾病的危險因子之方法。

英文摘要

Porphyromonas gingivalis is an oral pathogen that causes a chronic local inflammatory disease, periodontal disease, which results in the destruction of the periodontal ligament and alveolar bone. Recent studies have focused on the association of P. gingivalis-mediated periodontal infection and systemic diseases. Several reports support a definite relationship between periodontal infections and certain systemic conditions including atherosclerosis and cardiovascular disease. Therefore, markers of systemic inflammation, such as C-reactive protein (CRP), fibrinogen, different cytokines; especially interleukin-6 (IL-6) have been studied as potential new risk factors. It has established that the periodontal pathogen Porphyromonas gingivalis is capable of invading aortic, heart, and human umbilical vein endothelial cells (HUVEC). Interactions of P. gingivalis with endothelial cells and the subsequent host cell response to infection may be important in the pathogenesis of atherosclerosis. In this study, we coculture HUVEC with live P. gingivalis strain, 381, or insertionally inactivated fimA mutant, DPG3 to compare the results. We demonstrated that P. gingivalis upregulated IL-6 and IL-6 receptor in HUVEC. The results showed that both P. gingivalis strains can modulate IL-6 expression in endothelial cell, but there is difference in the expression level. The STAT3 and MAPK activation were involved in P. gingivalis induced IL-6 signaling pathway. Our data showed that STAT3 activation was only involved in 381-regulated IL-6 receptor expression. After 381 stimulated, IL-6 production was via ERK and I-B activation, In contrast, there may be other transcription factors down stream of ERK to regulate IL-6 secretion in HUVEC infected with DPG3. Our results revealed the signaling pathway and IL-6 receptor complex expression by invasive and non-invasive P. g. Our data showed an experimental link between P. gingivalis infection and vein endothelial cells. It would activate IL-6 signaling transduction and result in excess IL-6 production in HUVEC infected by P. g. The results suggested that P. gingivalis infection would induce inflammatory response in endothelial cells; therefore accelerates atherosclerotic changes and increases CVD risky