行政院國家科學委員會專題研究計畫成果報告

Epstein-Barr病毒相關胃癌的宿主易感性研究

計畫類別：■個別型計畫　□整合型計畫

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個別型計畫：計畫主持人：吳明賢醫師

整合型計畫：總計畫主持人：

子計畫主持人：

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執行單位：台大醫學院內科

中華民國九十年

中 文 摘 要

胃癌仍是全世界常見且預後欠佳的疾病。遺傳體質，環境因子和感染源三者間彼此交互作用而使胃癌發生。除了飲食因子和幽門螺旋桿菌外，最近也有報告顯示 EB 病毒和胃癌有關。吾人過去已報告與 EB 病毒有關的胃癌具特殊的表現型，這些特異的臨床病理特徵意謂 EB 病毒陽性的胃癌在腫瘤發生過程中可能與一般胃癌採不同的變化途徑。雖然過去已有一些有關 EB 病毒和胃癌的研究報告，但是針對其致病機轉的探討仍然不多。

大多數人在成年前即得過無症狀的 EB 病毒感染。為何只有一小部分的感染者發展成較嚴重的表現，如感染性單核球症(infectious mononucleosis)，B 細胞型淋巴瘤，和 EB 病毒有關胃癌等，目前仍不清楚。雖然不同病毒毒性有可能造成不同的染後果，但最近認為感染後宿主細胞素(cytokine)產生能力的不同也是造成不同預後的重要原因。為了探討細胞素啟動子(promoter)基因多型性是否影響 EB 病毒感染後的結果，吾人收集 30 例 EB 病毒陽性胃癌、120 例 EB 病毒陰性胃癌及 220 例對照患者，分析甲型腫瘤壞死子(TNF-α)-238 及-308 和介白質-10(IL-10)-1082 位置上的多型性，結果發現具高 TNF-α 製造力的對偶子(-308A)在 EB 病毒陽性的胃癌患者比例較對照組高(23.3% vs. 12.0%, $p<0.05$)；而具高 IL-10 製造力的對偶子(-1082G)則在 EB 病毒陰性的胃癌患者比例較對照組高(6.3% vs. 3.0%, $p<0.05$)。吾人資料支持遺傳因子可以透過不同 TNF-α 及 IL-10 製造能力而影響感染疾病預後的想法。

關鍵語： 胃癌、EB 病毒、細胞素多型性、宿主易感性

Abstract

Gastric carcinoma (GC) remains a common disease with a dismal prognosis in the world. Genetic predisposition, environmental factors and infectious agents interact in the development of GC. In addition to dietary factors and H. pylori infection, Epstein-Barr virus (EBV) has recently been shown to be associated with GC. In a previous study, we have described unique morphologic and phenotypic features in EBV-associated GC. These divergent clinicopathologic characteristics raise the possibility that EBV-positive GCs adopt different pathways during tumorigenesis. Despite the fact that there have been a number of studies on EBV and GC, studies looking into the pathogenesis for EBV-associated GC remain scanty.

Most people become infected with EBV before adulthood and remain asymptomatic thereafter. It remains unknown why only a small portion of EBV-infected individuals develop a range of diseases such as infectious mononucleosis, B cell lymphoma, and EBV-GC. Variation of virulence among different viral strains has been postulated to contribute to the variability of clinical outcomes in such an infection. Recently, it has been proposed that variability of generating host cytokines may be another reason to explain such variable clinical outcomes after exposure to microbial pathogens. To investigate whether genetic differences in cytokine promoter polymorphisms may affect variable outcomes after exposure to Epstein-Barr virus (EBV) infection, thirty patients with EBV-positive gastric carcinoma (GC), 120 patients with EBV-negative GC and 220 controls were enrolled. Promoter polymorphisms of the tumor necrosis factor alpha (TNF-α) at positions -238 and -308, and of the interleukin (IL)-10 at the position -1082 were determined. The frequency of the high TNF-α producer allele (-308A)

was significantly higher in EBV-positive GC compared with controls (23.3% vs. 12.0%, $p<0.05$), while the frequency of high IL-10 producer allele (-1082G) was significantly higher in EBV-negative GC compared with controls (6.3% vs. 3.0%, $p<0.05$). These data support the notion that genetic factors may modify the outcomes of infectious diseases through different TNF-α or IL-10 producing capability.

Key Words: gastric carcinoma, Epstein-Barr virus, cytokine polymorphism, Host susceptibility

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已發表之論文

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