行政院國家科學委員會專題研究計畫成果報告

不同胃癌突變表現型的基因變化特徵(1/3)

計畫類別：■個別型計畫　□整合型計畫

計畫編號： NSC89-2314-B002-256

執行期間： 88**年** 8**月** 1**日至** 89**年** 7**月** 30**日**

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整合型計畫：總計畫主持人：
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執行單位：台大醫學院內科

中華民國八十九年五月二日

中 文 摘 要

由微衛星體不穩定性(MSI)和微衛星體有關的突變來判定腫瘤的突變表現型，在癌症的發生扮演重要角色。目前已知有部份的胃癌具有突變表現型，為了更進一步了解此變化在胃癌的意義，吾人依據 10 個微衛星體標記變化的情形將 100 個散發性胃癌患者分成高頻率微衛星體不穩定性(MSI-H)、低頻率微衛星體不穩定性(MSI-L)和微衛星體穩定性(MSS)三種表型，進一步分析 TGFβRII, IGFIIR, BAX, MSH3, MSH6, E2F4, MSH2, MLH1 和 p53 等基因突變和 MLH1/MSH2 基因，甲基化及蛋白表現的情形，結果發現 27%的胃癌至少有一個微衛星體不穩定性，其中 14%為 MSI-H,13%為 MSI-L。比較 MSI-H, MSI-L 和 MSS 的臨床病理特徵發現 MSI-L 和 MSS 並無差別，但 MSI-H 則有較高頻率為竇部、腸道型、幽門螺旋桿菌血清陽性和較低比率的淋巴結轉移。在相關基因變化方面，MSI-H 尚具有較高比率的 TGFρRII, IGFIIR, BAX, MSH3 和 E2F4 等基因的移位突變，以及較低比率的 p53 突變。此外，14 位 MSI-H 中有 13 位有 MLH1 基因啟動子的高度甲基化及蛋白質表現減少的情形。吾人初步結論為 MSI-H 胃癌有特殊的表現型及基因變化，其中 MLH1 基因的甲基化在此種腫瘤的癌化過程中扮演重要角色。相對於 MSI-H, MSI-L 及 MSS 則有不同的臨床病理特徵和較高頻率的 p53 突變，意謂在胃癌發生過程中可能有不同的致病機轉。

由於最近在大腸癌發現所謂突變表現型和甲基化表現型(methylator phenotype)有同時發生的情形，因此吾人第二年的重點在於以多種重要基因(p16, E-cadherin, p73, DAPK, GST, MGMT, TIMP-3, THBS1)分析其啟動子上的甲基化情形，另外並以比較基因雜交法分析不同表現型的基因體變化情形，來進一步釐清不同胃癌突變表現型的基因變化特徵。

關鍵語：胃癌，突變表現型，甲基化表現型，比較基因雜交法

Abstract

Mutator phenotype judged by microsatellite instability(MSI) and its associated mutations plays an important role in gastric carcinogenesis. A subset of sporadic gastric cancers (GC) exhibits MSI. To define the precise role of MSI in GC, a total of 100 patients with sporadic GC were classified into three groups, i.e., high-frequency MSI (MSI-H), low-frequency MSI (MSI-L) and microsatellite stable (MSS) based on ten microsatellite markers. Mutational analyses of TGFâRII, IGFIIR, BAX, MSH3, MSH6, E2F4, MSH2, MLH1 and TP53 genes, and methylation and protein expression of MLH1 and MSH2 were performed and correlated. Twenty-seven percent of GC showed MSI at least in one locus and could be further graded as MSI-H (14%) and MSI-L (13%). No clinicopathologic difference was noted between GC with MSI-L and MSS. Compared with GC with MSI-L or MSS, GC with MSI-H had a significantly higher frequency of antral location, intestinal subtype, H. pylori seropositivity, but a lower incidence of lymph node metastasis, and displayed a higher frequency of frameshift mutations of TGFâRII, IGFIIR, BAX, MSH3, and E2F4 genes but a lower incidence of TP53 mutations. Furthermore, hypermethylation of MLH1 promoter was responsible for the loss of protein function in 13 of 14 MSI-H tumors. It was concluded that a specific phenotype and a distinct profile of genetic alterations exist in MSI-H GC. We speculate that epigenetic inactivation of MLH1 by methylation plays a crucial role in initiating such a pathway of carcinogenesis. In contrast, GCs with MSS and MSI-L exhibit clinicopathologic features that are distinct from MSI-H tumors and have a higher frequency of TP53 mutations, suggesting that they may evolve through entirely different pathway.

Recently, CpG island methylator phenotype with concordant methylation at a number of loci has been reported in a certain portion of colon cancer. To extend our study, we will analyzed methylation status at multiple important genes (p16, E-cadherin, p73, DAPK, GST, MGMT, TIMP-3, THBS1) and compared the global changes using comparative genomic hybridization among different subtypes to further characterize genomic alterations in GC with different mutator phenotypes.

Key Words: Gastric cancer, mutator phenotype, methylator phenotype, comparative genomic hybridization.

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