Genetic Susceptibility to Gastric Carcinoma

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Abstract

Gastric carcinoma (GC) is the second leading cause of cancer-related death in the world, with an estimated 880,000 new cases and 650,000 deaths each year. Genetically, it is possible to distinguish two main forms of GC: an hereditary form in which the initiating genetic alteration is inherited and the remaining mutations are acquired somatically; and a sporadic form in which every mutation is of somatic origin and where the environment is thought to play a major role. Germline mutations of the tumour suppressor gene CDH1, that codes for the cell adhesion molecule E-cadherin, are the cause of the hereditary diffuse GC (HDGC) syndrome. Families carrying CDH1 mutations have a high incidence of diffuse GC, usually in young individuals (less than 45 years of age). The identification of such mutations has proven invaluable in the clinical management of such families and in GC prevention in CDH1 mutation carriers. The model of HDGC has been also providing valuable insight into the molecular mechanisms underlying the involvement of E-cadherin in onset and progression of cancers of epithelial origin. In the setting of sporadic-type GC it has been shown that individuals infected with Helicobacter pylori, a stomach colonizing bacteria, have an increased risk of developing GC. The risk for developing this type of tumour relates to the physiologic and histologic changes that H. pylori infection induces in the stomach. However, a striking difference exists between the number of infected individuals and the number that go on to develop malignancy. Hence, progression toward disease is likely to depend on the combined effects of bacterial pathogenicity, host susceptibility, and environmental factors. Recently it has been suggested that host genotyping (pro-inflammatory polymorphisms) as well as H. pylori genotyping (virulence factors) can be important in identifying individuals who are at greatest risk for developing GC. As a consequence, it would become possible to target such individuals with selective prophylactic interventions designed to prevent/reduce the incidence of the disease.