Gastroenterology and Hepatology From Bed to Bench

EDITORIAL

Human Leukocyte antigen-G (HLA-G) and gastrointestinal malignancy

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Malignant conditions can affect any part of the gastrointestinal (GI) tract, including the esophagus, stomach, biliary system, pancreas, small intestine, large intestine, rectum and anus (1). Currently, conventional TNM staging is the most important prognostic factor for determining the clinical outcome of GI cancer. However, clinical studies have shown that patients with similar stages of the disease may have various outcomes and tend to have clear discrepancy in survival rates (2-5). Because tumor detection and treatment at an early stage can significantly improve patient survival, there has been great interest to find new molecular prognostic markers that can help identify patients at a higher risk of death (6).

Human leukocyte antigen G (HLA-G) is a non-classical major histocompatibility complex (MHC) class Ib antigen that expresses as seven isoforms, including four membrane-bound (HLA-G1 to HLA-G4) and three soluble (HLA-G5 to HLA-G7) forms (7). It has been demonstrated that HLA-G plays important role in immune tolerance during pregnancy (8).

In recent years, there has been strong evidence shown to suggest that the presence of intratumor tumor-infiltrating lymphocytes (TILs) reflects an immune response between tumor cells and immune effector cells. Several studies have shown that the presence of TILs is a prognostic factor for predicting patient survival in various types of cancer (9-13).

A consequence of immune-mediated selective elimination of tumor cells is a changing of the tumor phenotype during tumor development, which has recently been referred to as 'cancer immunoediting' (14). Cancer immunoediting is a process that includes three essential phases: elimination, equilibrium, and escape. HLA-G has been postulated to play a role especially in the escape phase of cancer immunoediting (14). The aberrant expression of HLA-G by tumor cells has been suggested to be part of the strategy to escape from the host's immunosurveillance by suppressing tumor reactive CD4+ T-cell proliferation and inhibiting NK-cell-mediated and T-cell-mediated cytolysis (3, 7, 11-13).

In non-pathological situations HLA-G expression is largely restricted to extra-villous cytotrophoblastic cells, placental chorionic endothelium, activated monocytes, thymic epithelial cells, nail matrix, cornea, and erythropoietic lineage cells from the bone marrow, and is not found in other healthy tissues expressing MHC class Ia antigens (15). In 1998, Paul *et al.* described, for the first time the expression of HLA-G in solid tumors (16), and the number of papers published on HLA-G in cancer has increased in recent years such as for melanoma, renal cell carcinoma, carcinoma of the lung, breast carcinoma, lymphomas, ovarian carcinoma, endometrial adenocarcinoma, and various gastrointestinal cancers including pancreatic ductal adenocarcinoma, ampullary cancer, biliary cancer, colorectal cancer, and gastric carcinoma (1-5, 11-

13,17-18). Remarkably, the detection of HLA-G was reported to correlate with certain clinicopathological parameters in some malignancy (2-5, 18). These studies all indicate that HLA-G might serve as a clinical marker for the diagnosis or prediction of clinical outcome of cancer. We focus on the prognostic effect of HLA-G expression in gastrointestinal cancer.

Gastric cancer, being the fourth most common cancer in the world, is a major health problem (19). In a paper by Yie *et al.* (3) it was documented that HLA-G protein was expressed in a majority of the primary site of gastric carcinomas and significantly correlated with tumor location, histological grade, depth of invasion, histological grade, host immune response, lymph nodal metastasis, and clinical stages of the disease. Moreover, HLA-G expression had a strong and independent prognostic value in human gastric cancer. It has been hypothesized that, the more aggressive cancers, which have less organized genetic control, may have more frequent HLA-G expression. Yie *et al.* showed a higher occurrence of HLA-G expression in cancers of the gastric cardia, which have the worst prognosis, as compared to cancers of the gastric body or antrum (3). These findings provide evidence to support foregoing hypothesis. Surprisingly, the results that were obtained by Ishigami *et al.* indicated that HLA-G may be involved earlier in the course of malignant transformation, decreasing in later invasion stages (18). Du *et al.* indicated that HLA-G expression was strongly associated with tumor progression and involved in tumor evasion by raising the frequency of infiltrating Tregs locally. Therefore, HLA-G expression is a factor that should be taken into account when considering immunotherapy as treatment option, and is also a promising predictor for prognosis in GI cancer patients (20).

In colorectal cancer, 40% of the patients that were diagnosed with a tumor-negative nodal status unfortunately will develop recurrent disease during their lifetime and the role of adjuvant chemotherapy in this setting is still unclear. Hence, identifying patients with high-risk colorectal cancer would be of great benefit for improving the treatment strategies (2).

The study published by Ye *et al.* revealed that there was a strong correlation between HLA-G expression and the different stages of colorectal cancer, where HLA-G positive staining was found in 43% of stage I patients and in 70–71% of patients with stages II to IV (2). These results strongly show that HLA-G expression is a highly specific marker associated with advanced tumors. Also, they found a significant correlation between the overall survival rate and the HLA-G status independent of the disease stage (2).

Esophageal squamous cell carcinoma (ESCC) remains a malignancy with a poor prognosis and the majority of patients have disseminated disease at diagnosis (4). Yie *et al.* demonstrated that the HLA-G protein was expressed in 90.9% of the specimens containing ESCC (4). This result was higher than what was found in a previous studies on colorectal cancer (65%) or gastric cancer (70 %) using the same anti–HLA-G monoclonal antibody (3, 2). According to these results it can be infer that more aggressive cancers with less organized genetic control may have more frequent HLA-G expression. In addition to altered genomic control, tumor environmental factors such as stress, cytokines and agents used in chemotherapy have been proposed to affect the up-regulation of HLA-G expression (21). It is known that interferon-γ up-regulates the expression of HLA-G (22). Therefore, the detection of HLA-G expression may be important in planning adjuvant therapy. Taken together, accumulating data suggest that tumor expression of HLA-G is an important prognostic indicator for GI cancer patients (1-5, 11-13).

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