INTRODUCTION

Inductive and sequential transformation of gastric cancer has been an excellent model for experimental search on genetic alterations and marker definitions. The development of gastric cancer is unique wherein several etiological agents, either alone or in conjunction feed into few common prognostic pathways whose manifestations can be histologically staged or verified. Ninety percent of gastric cancer is sporadic involving nongenomic factors such as chronic infection with *Helicobacter pylori* and food habits, especially the intake of high-salt diets that, in common, initiates a chronic inflammation response. A link between the chronic inflammation and neoplastic transformation can be serially investigated in gastric cancers, and definitive boundaries can be laid between the reversible and nonreversible changes in the protoplasmic properties of the inducted cells. Intestinal metaplasia has long been considered as the intermediate stage, progression beyond which irreversibly commits the cells for neoplastic transformation. Several molecular biomarkers have been considered for defining the early diagnosis and prognosis of gastric cancer with much emphasis on mucins (MUCs) and its epitopes. In this chapter we will review the molecular shifts in the expression of biomarkers, including the evaluation of MUC2, during the progression of gastric cancer with emphasis on methodology and molecular basics for diagnosis.

MOLECULAR MECHANISM OF GASTRIC CANCER

The pathogenesis of gastric cancer represents a classic example of gene-environment interactions. A strong association seen between *H. pylori*, a class I carcinogen (WHO), and gastric adenocarcinoma suggests that bacterial factors and host responses play a vital role in initiation and progression of the disease. It was reported by Mandell *et al.* (2004) that the persistence of *H. pylori* infection sensitizes the pattern recognition receptors (Toll-like receptors or TLR) and cellular mediators of inflammation that result in chronic Th1 mediated inflammatory response. Besides, abrogation of T cell mediated response or a skewed response towards Th2 polarization protects the C57BL/6 from *H. pylori* induced atrophy and cancer, suggesting...
that chronic exposure to increased amount of proinflammatory cytokines, such as Interleukin-8 (IL-8), IL1β, tumor necrosis factor-α (TNF-α), and the inflammatory mediator NFκB represents the switch between the temporary inflammation process (healing process), chronic lesion, and gastric cancer.

Inflammatory cytokines activate several signaling cascades that feed into apoptotic and proliferative responses. In C57BL/6 mouse models, Cai et al. (2005) showed that infection with *H. pylori* causes a concomitant increase in apoptosis and proliferation resulting in the loss of parietal and chief cells (atrophy) that developed along the sequence of intestinal metaplasia (expression of mucus metaplastic cells), dysplasia and invasive carcinoma. Indeed, El-Omar et al. (2003) clearly showed that Th1 cytokines such as IL1β induce gastric secretion, inhibit acid secretion and promote apoptosis, and along with TNFα and INFγ upregulate Fas antigen on gastric mucosal cells leading to alterations in cell growth. However, subsequent adaptive changes in the Fas signaling appear to increase the proliferation of cells and maintain homeostasis. Though the imbalance in apoptotic and proliferation ratio could contribute to progression from premalignant to malignant conditions, the microenvironment that favors this outcome has not yet been clear. The expansion of proliferative zone throughout the gastric glands suggests that additional cell populations or recruitment of cells might contribute to the proliferation under these circumstances. In addition, sustained hypoxia within the acidic inflammatory environment induces angiogenic signals that promote neovascularisation with defective podocyte coverage on the endothelium.

Recruitment and activation of cell mediators of inflammation (macrophages and monocytes) to the site of gastric lesion release products of oxidative burst such as superoxide free radicals and nitric oxide that might exert an oncogenic effect through direct DNA and protein damage, inhibition of apoptosis, mutations in genes involved in cellular repair functions (such as P53), and promotion of angiogenesis. Loss of heterozygosity (LOH) that is seen frequently associated with gastric carcinomas is also mediated by inflammatory response. Erosion of gastric mucosa by the persistent inflammatory process exposes the fragile niche of gastric stem cells to the inflammatory assault. The compensatory proliferative response of the resident stem cells to the erosion of gastric mucosa fail to repair the lesion due to high incidence of apoptosis of the transit multiplying populations. The hallmark of persistent inflammation is, therefore, defined by Coussens and Werb. (2002) as rapid proliferation with concomitant cell loss by apoptosis that fails to repair the lesion. Van den Brink et al. (2002) reported that parietal cell loss during gastric atrophy and progression to metaplasia is associated with a reduction in the amount of numerous secreted signals such as sonic hedgehog (SHH), which modulate the growth and differentiation of gastric progenitors. Studies by Cai et al. (2005) further revealed that a combination of parietal cell loss and chronic inflammation is a necessary event for progression along the metaplasia-dysplasia-carcinoma pathway.

Persistence of multiplication signals remains the principle cause for genetic mutations in the dividing cell population. Gopal et al. (2007) and Sakakura et al. (2005) pointed out that the spectrum of