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Role of Immunotherapy for *H. pylori* in Gastric Cancer

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Abstract

Gastric cancer is a widely well-known challenging health problem in the world, which has been deemed associated with Helicobacter pylori (*H. pylori). H. pylori avoid the endogenous immune reactions.* . An effective production of antibody against *H. pylori* is critical. There are known conventional as well as experimental treatments associated with against H. pylori. Immune therapy may be considered a cornerstone of treatments. Immunization *against H. pylori* may be deemed as safe and effective among many populations. *H. pylori* colonize the gastric mucosa of more than half of the world. Most of the aggravation associated with its infection is deemed as innocuous and/or clinically asymptomatic to treat. However, it may lead to perpetual gastritis, peptic ulcer, gastric mucosa-related lymphoid tissue lymphoma, and gastric cancer.

The actual role of immune system for gastric cancer is discussed. Lately, T regulatory cells (T reg) have been inferred to be a vital part in *H. pylori*-related advancement. Additionally, T reg-actuated tolerance has been suggested as a plausible tool that presumes less serious infection. A number of clinical trials have been shown the mechanism of immune response against *H. pylori* in line with the induction in gastric cancer.

Keywords: *Helicobacter pylori*, Vaccines; T Regulatory Cells; Gastric Cancer; Lymphoid Tissue; Lymphoma; Git

Abbreviations

TLR : Toll-like Receptors;

ADCC: Antibody Dependent Cell Mediated Cytotoxicity ;

MALT : Mucosa-Associated Lymphoid Tissue;

Treg : T Regulatory Cells;

PAP-GM-CSF: Prostatic Acid Phosphatase and Granulocyte Macrophage-Colony Stimulating Factor;

DC : Dendritic Cell;

MHC: Major Histocompatibility Complex

Introduction

Gastric cancer is the second leading cause of death among patients with cancer. *H. pylori* is a gastric pathogen which colonizes of approx. half of the world's GI track. An infection with *H. pylori* causes chronic inflammation and considerably increases the risk associated with developing gastric cancer, gastric ulcer and duodenal ulcer condition. Infection with H. Pylori is considered a major risk associated with gastric cancer related deaths worldwide [1]. *H. pylori* are often a spiral-shaped bacterium which raises from the mucus level that coat inside of the human stomach. *H. pylori* are colonized within the gastric Mucosa; therefore, it is uniquely adapted to the acidic environment. The production associated with ammonia all around *H. pylori* neutralizes the level of acidity of the stomach, turning it into additionally an agreeable environment for bacterium. Also, the helical model of *H. pylori* permits it to reside into mucus layer; which is less acidic as opposed to inside of space, or lumen, of the stomach. *Additionally, H.pylori* may also attach to the tissue which is gathering the interior surface of the stomach. The immune response of the body associated with the inner wall of the stomach is limited. Therefore, a proper response against H. pylori is effectively provided. Furthermore, H. pylori adapts to the local immune reactions, thus, it is rendered to be immune during the potential eradication process. There are many factors leading to gastric carcinoma. Precancerous pathways leading to gastric cancer is provided below (Figure 1).

H. pylori is directly known to be associated with duodenal and gastric ulcer [2]. The complete clinical understanding of its associated disorders is debated. Neoplasm of the gastro intestinal track; including but not limited to, low grade B cell gastric lymphoma of mucosa associated lymphoid tissue and carcinoma of the stomach called MALT lymphoma are deemed to be associated to infection with H. pylori [2].

Stomach cancer stems from the inner layer or epithelium of the stomach. Adenocarcinoma; which is the most common type of stomach cancer, starts in the glandular tissue of the stomach. This accounts for 90% to 95% of all stomach cancers. Signs and symptoms associated with stomach cancer are: Discomfort and/or pain in the stomach, nausea and vomiting, weight loss, difficulty swallowing, haematemesis, melena, and feeling full or bloated after a small meal. Smoking increases the risk of developing gastric cancer by 40 to 82 % [3].The general sites associated with smoking related gastric cancers are within the upper part of the stomach near the esophagus [4,5]. Some studies suggest an increased risk of acquiring gastric cancer with alcohol consumption as well [6].

Mechanism of *H. Pylori* pathogenesis in Gastric Mucosa

The following enzymes secreted from the Bacterium secretes several enzymes are known to play an important role in altering the integrity of mucus and epithelial cells [8].

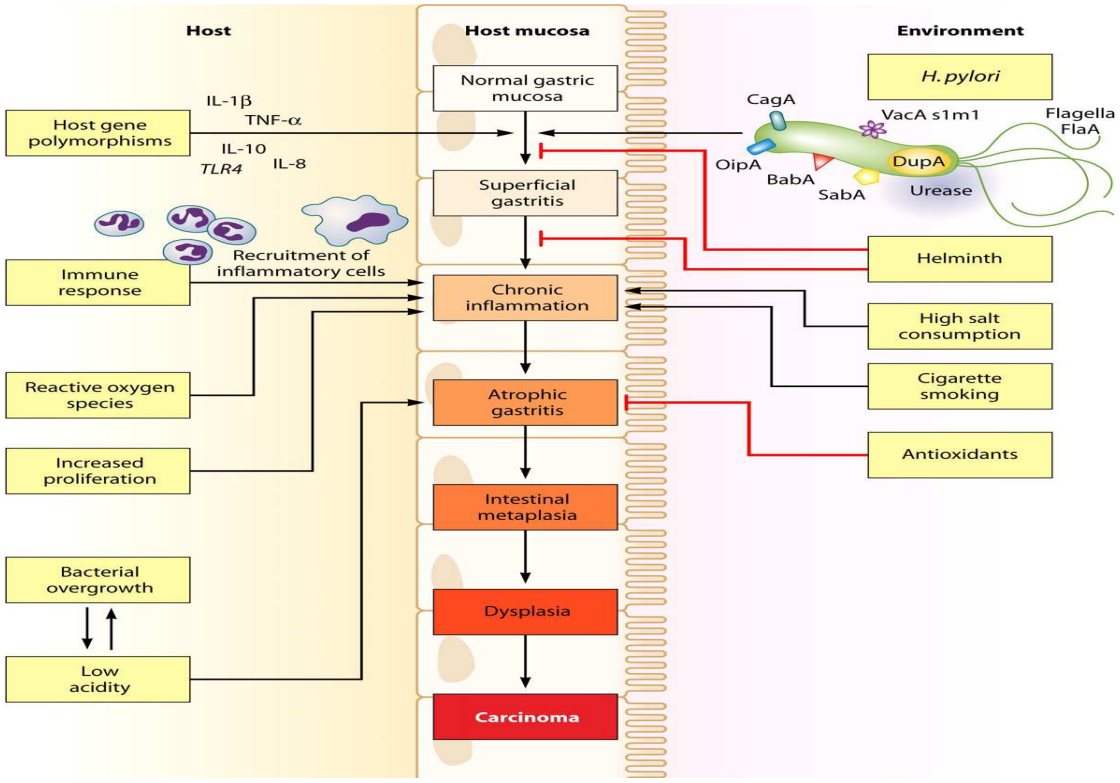

Figure 1. Multifactorial pathway leading to gastric carcinoma. Many host, bacterial, and environmental factors act in combination to contribute to the precancerous cascade leading to development of gastric cancer [7].

1) Glycosulfatase: Reduced capacity to retard hydrogen ion diffusion and causes loss of mucus viscosity. Therefore Mucus secretion is also reduced.

2) Urease Enzyme: They produce Ammonia which is directly toxic to gastric Epithelial cell

3) Phospholipase: Phospholipids membrane gets degraded.

4) Alcohol dehydrogenase: In presence of Ethenol, toxic acetaldehyde is produced.

5) Cytotoxin : which also responsible for damage of Epithelial cell.

Types of Gastric Carcinoma

1) Intestinal-Type Adenocarcinoma: initially, transition of normal mucosa to chronic superficial gastritis takes place, which is followed by atrophic gastritis and intestinal metaplasia. This progresses to final stage which is dysplasia and adenocarcinoma. Noted: Approximately 95% of all gastric cancers are adenocarcinomas

2) Diffuse-Type Gastric Cancer: They are infiltrated neoplastic cells which do not form glandular structure. The remaining 5% are lymphomas (second most common, includes MALT lymphomas), sarcomas (including leiomyosarcomas and Kaposi's sarcomas), GISTs, carcinoids, and squamous cell carcinomas.

   There are 2 distinct histologic subtypes of gastric adenocarcinomas: intestinal, diffuse; a Intestinal type – retained glandular structure, which is deemed to be more localized. A Diffuse type – no glandular structures, more spread out per se.

Symptoms of Gastric cancer

There are following sign and symptoms of gastric cancer in early stages and standard stages:

At early stage following symptoms are clearly identified with no treatment per se [9]. Depends on the patients' life style, symptoms may be observed.

(a) A bloated feeling after eating

(b) Indigestion and stomach discomfort.

(c) Mild nausea.

(d) Heartburn

(e) Loss of appetite

Upon further clinical progression of the underlying neoplasm, few more symptoms are observed. [9] Other organs are potentially involved at this stage of the disease progression:

(a) Vomiting

(b) Melena

(c)Weight loss

(d) Trouble in swallowing

(e) Ascites (build-up of fluid in the abdomen)

(f) Jaundice

(g) Epigastric pain

Helicobacter Pylori, pathology and associated malignancies:

While over 80 percent of infected people are asymptomatic, it has been suggested that it may play an important role in the natural stomach environment [10]. It is microaerophilic; i.e., it takes up oxygen. It contains a hydrogenase which might be utilized to get vitality by oxidizing atomic hydrogen (H_2) delivered by intestinal microorganisms.

Infection is more predominant in developing countries. Its incidence rate is decreasing in Western countries. *H. pylori*'s helix shape (from which the generic name is derived) is thought to have evolved to penetrate the mucoid lining of the stomach [11, 12]. Up to 85% of individuals who are infected with *H. pylori* don't experience the known signs and/or symptoms associated with its contamination. Heightened symptomology may show up as an intense gastritis/ ache (stomach throb) and/or vomiting. Intensification of the pyloric antrum is more tending to instigate duodenal ulcers, while irritation of the corpus is more disposed to early gastric ulcers as well as gastric carcinoma. Additionally, it is conceivable that *H. pylori* assumes a part just in the first stage which prompts regular never-ending aggravation(pain, vomiting, etc.), yet not furthering in its later stages which may be prompting carcinogenesis. A meta-analysis concluded that the destruction of *H. pylori* diminishes gastric tumor chance in infected people, suggesting that the loco regional disease of *H. pylori* establishes a relative hazard variable of 65% for gastric growths as far as outright hazard the expand was from 1.1% to 1.7% [13].

The smoking tendency in addition to weight control plans including salted, smoked sustenances, and prepared meats, collectively build the danger of non-cardia gastric carcinoma. In parallel, abstainingfrom food rich in new vegetables lessen the danger of non-cardia gastric carcinoma in *H. pylori*-contaminated patients. There is no distinction between non-cardia gastric carcinoma, in its relationship to H*. pylori* disease with cardia gastric carcinoma. Especially, when considering the cytotoxin associated gene A (CagA) status. The CagA protein of *H.*

pylori delivered into gastric epithelial cells via bacterial type IV secretion, is an oncoprotein that can induce malignant neoplasms in mammals [14]. (Figure 2)

Immunotherapy and Gastric Carcinoma

Researchers have successfully tried to prove that natural defense mechanism may be utilized as an effective treatment plan.

The immunotherapeutic modalities have been plied to different types of cancers. The potential deployment of immune based theory to treat the GI malignancies are considered and utilized. . The use of Immunotherapy is based on monoclonal antibodies, cytotoxic immunocytes, or gene transferred vaccines. In case of Gastric cancer, there are two tactics in use:

1) Activate tumor specific cytotoxic T cell so that they lyse the tumor cells

2) Treatment by stimulating the target molecules or proteins expressed on the carcinoma cells

Tumor specific T cells are prevalently identified in patients with in GI cancers [15-17]. T-cell infiltration into GI tumors could be deemed as correlated with improved prognosis in a few types of GI cancers [18-20]. Prevention of blocked antitumor T-cell reactions corresponds to a poor prognosis in a some GI cancers [21, 22]. Various other treatment protocols to stimulate immunity against GI malignancies are under consideration. They are: Monoclonal antibodies, vaccine based immunotherapy and adoptive cell transfer.

Monoclonal antibody Therapy (mAb)

Monoclonal antibody (mAb) Therapy has been playing a significant role in treatment for Gastric cancer. The list of the US Food and Drug Administration (FDA) approved mAb treatments focusing on gastric malignancies include: Cetuximab, bevacizumab, panitumumab, and trastuzumab. Their mechanism of actions is: blocking growth factor/receptor interactions, down regulating proteins required for tumor growth, and activating effector mechanisms of the immune system (including complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity [ADCC].

Mitotic active cells are affected for normal and cancerous cell, Cetuximab and Panitumumab target EGFR and becomes first line therapy for EGFR-expressing metastatic cancer. Bevacizumab would be considered as the first or second line of therapy and target VEGF as well. Trastuzumab is the first or second line of therapy for HER2-positive metastatic gastric or gastroesophageal adenocarcinoma, which target human epidermal growth factor receptor 2. Immunomodulatory mAb therapies directly target immune cells, as opposed to tumor antigens e.g. Ipilimumab. Many more of the Immunomodulatory mAb therapies are being investigated for gastric cancer [23].

Adoptive cell transfer therapy

The segregation of antigen-specific cells, their *ex vivo* expansion and consequential activation, with subsequent autologous administration is considered the cornerstone of adoptive cell transfer therapy and antitumor immune responses. The molecular identification of tumor antigens and the aptitude to display the persistence and transport of transferred cells has provided the ability to work with the mechanisms of tumor immunotherapy. The efficacy associated with the cell-transfer therapies for the treatment of patients with gastric cancers is well appreciated.

In short: Adoptive cell treatment focuses on passive transfer of tumor specific T cells into a tumor-bearing host which focuses on deterring the tumor. These treatments are tailored for every patient. As this has not been possible in mAbs therapy. Lymphokine-activated killer (LAK) cells in patient with advance cancer were produced by culturing peripheral lymphocytes in high concentrations of IL-2; then, tumor cells are lysed by the production of produce cytotoxic cells24 Adoptive cell treatment with autologous tumor-infiltrating lymphocytes (TILs) works with lymphocytes. Adaptive cell treatment with TILs detached from resected tumors when administered in combinations to patients with IL-2 has showed a 50% reaction in patients with metastatic melanoma. TILs which are isolated from a type of GI tumors may deemed as effective in ; as a new approach, patients with metastatic GI cancers [25, 26].

Vaccine Based immunotherapy

1. Generally vaccines activate and expand tumor-specific T cells as effector T cells. They may act by increasing already existing immunity, by inducing new immunity, or by anti- tumor response alike. Tumor specific T cell can be brought upon by peptides stemmed from tumor-related antigens at the T cell sites. Immature dendritic cell (DCs) with high phagocytic capacity which are gathered in peripheral tissues, are more so localized to tumor growing sites. They up antigens which are digested into small oligopeptides. They bound to significant major histocompatibility complex (MHC) class I/II elements for presentation to Cd8+ and to Cd4+ helper cytotoxic T Cells. 27
2. Tumor antigen-pulsed DC-based antibodies have been confirmed to activate both Cd8+ and Cd4+ T-cell reactions in patients with advanced malignancies [27]. Although clinical trials utilizing DC-based immunizations in patients with advanced malignancies which have encouraged in leading into positive immunologic endpoints, their actual clinical manifestations are not seen [28-30]. One exception is the utilization of

sipuleucel-T: Sipuleucel-T is a DC-containing cell antibody loaded with a combination protein of prostatic acid phosphatase and granulocyte macrophage-colony stimulating factor (PAP–GM-CSF). It has been indicated to increase overall survival (OS) in patients with metastatic prostate cancer [31]. Sipuleucel-T is the first therapeutic tumor immunization to get FDA approval(APC8015, trade name **Provenge**) manufactured by Dendron Corporation [32].

H. pylori Treatment plan in action with Immunity response

H.pylori induces immune reactions at both T and NK cell level. H.pylori infection stimulates both innate effectors and a complex mix of Th17, Th1, and T regulatory cells (Treg) adaptive immune responses [33-35]. Treg cell inhibits cytotoxic lymphocytes and/or helper T activity. Tregs are characterized by the CD4+CD25+FOXP3$^+$ phenotype. Tregs are known in mainitining immunological tolerance to self-antigen with suppressing excessive immune response [36].

Th1 response drives an inflammation that; if maintained to be prolonged, results in pathological squealae. Polarized Th2 response alone does not guarantee protection, suggesting that specific Th1 response appropriately turned by Th2 cells would lead to a balanced and protective response [36-39]. Just a few advances in the information of the direct activity of both bacterial/ host considers in determining the result of *H. pylori* contamination, which needs to be further investigated [40]. While different variables create modes of parallel concurrence in order to keep up with the colonization in the gastric tissue and simultaneously disregarding the robust immune reaction, *H. pylori* initiates mechanisms of escaping [41,42]. Of Note: The host hereditary background, especially destructive *H. pylori* variables; as a prime example, CagA, can break this modality which may lead to a pathological manifestation of malignancy.

Immunomodulation and Immune Evasion by *H. pylori :*

H. pylori mayadhere in its host with an adoptive immune and robust innate reaction. FoxP3 + CD25hi regulatory T cells (Tregs) collect in the gastric mucosa of *H. pylori* -infected patients; specifically in children, are documents [43]. *H. pylori* is competent for actively tipping T-cell reactions towards a regulatory phenotype, yet suppressing Th17-driven immunity and reassuring a level of persistence [44]. A proposed collaboration between *H. pylori* with DCs seems to principally prime Treg over Th17 reactions and fail to create pro-inflammatory cytokines [45]. A proposed theory of immune escape was recommended by Sayi et al [46]. They proposed that special ligation of the anti-inflammatory TLR-2, instead of other TLRs, by Helicobacter PAMPs may sustain an immunoregulatory manifestation over effector reactions [47].

H. pylori interaction with Regulatory T cells

Regulatory T cells are immunosuppressive cells by nature [47] There are a diverse subsets of Treg cells(i.e, CD4+CD25+ regulatory *T cells*). The primary characteristic for Cd4+cd25 high Treg cells is its ability to stimulate and/or suppress immune reactions [48,49]. A few studies propose that Cd4+cd25 high Treg cells prevent multiplication of Cd8+ T cells and effector Cd4+cd25-T cells by capturing the expansion of these cells at G1-S interphase of the cell cycle [50]. Human CD4+CD25+ cells; despite some consistent characteristics, proposed contrasting results. Especially, in regards to potential involvement of TGFbeta and production of IL-10. There were different techniques employed to isolate human CD4+CD25+ T-reg cells; which may result in the comparison of T-reg populations that differ in their cellular presence and/or activation state, and the function of T-reg in human may be hinging upon many variability of the culture conditions and TCR stimuli. Noted: The strength of the TCR signal produced to the cell cultures governs its functional. In contrast: Stronger stimulation has a greater and more rapid effect on the T-resp cell as opposed to T-reg cell. There are further studies needed to identify the human CD4+CD25+ regulatory T cells and their possible mechanism(s) of function. *Patients with H. pylori*- infection have a rise in number of CD4+CD25 T cells in both the stomach and duodenal mucosa as opposed to. Noted: These cells express FOXP3 which is a gene for the advancement and action of Treg cells and the known abnormal levels of the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) proteins. Furthermore, mucosal CD4+CD25 high T cells are also available in people with asymptomatic *H. pylori* infection as well as in patients with the ulcer of duodenum. The frequencies of CD4+CD25 high cells are expanded in the stomachs of patients who are infected with *H. pylori*-and gastric adenocarcinoma. It is considered that the regulatory T cells would suppress mucosal reactions and add to the contribution of the insistence of H. pylori infection. The reduction of the gastric inflammation in infected children related with a checked increase in the quantity of Treg cells and the levels of their cytokines I (i.e., TGF-beta and IL-10. IL- 10-delivering T lymphocytes) are important in controlling instigated by *H. pylori* irritation.

Conclusion

Gastric cancer is a highly lethal disease and H. pylori-induced gastritis is the strongest singular risk factor for gastric cancer. The main reason for the potential deployment of immune based theory is to treat the GI malignancies and have been considered and utilized. Monoclonal antibody therapy, vaccine based immunotherapy and adoptive cell transfer therapy contributes a pivotal role in the treatment of gastric cancer. Many more of the Immunomodulatory mAb therapies are being investigated for gastric cancer and the efficacy related to cell-transfer therapies are well appreciated. Furthermore, it is

mandatory to identify the most effective biomarkers, and early diagnosis to detect the cancer growth as an important part of that therapy.

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