STUDY BREAK

Bacterial Cancer

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Rarely, do we think of cancer as "bacterial", such that we are often told that "cancer is NOT contagious"

Persistent bacterial infections cause persistent irritation of the host's defense systems, which when ineffective in eradication of the infection, result in a multitude of self-destructive damages. This in some cases occurs to such severity that the resulting cellular hyper-proliferation provides grounds for increased chances of writing errors (gene mutations) and decreased chances of corrections (gene repair). This is the basis of inflammation-induced cancer where presence of pathogens or other stimuli induce a chronic state of inflammation, yielding an array of defective cycles.

Normal flora or pathogen

A very popular example is the chronic infection of the vast majority of humans with *Helicobacter pylori* (Hp). Hp has infected and lived with humans for over 50,000. Such a long history of co-existence has even encouraged some to erroneously categorize Hp, as a member of the "normal flora". This scenario would be acceptable, except for the fact that Hp is a major cause of disease in humans. The established Koch's postulate, firstly by human volunteers and then laboratory animals, disqualified Hp as a member of the normal flora. Since Hp is picked up during childhood, such chronicity of infection (for several decades) allows for several multifaceted interactions to transpire between the "infecting microorganism", the "infected host" and the "surrounding environment". The whole of this triad (host/pathogen/environment) constitutes a number of potential susceptibility/risk factors, the combination of which identifies the small fraction (2-3%) of the infected subjects who develop this silent and mortal cancer, at later decades of life. Thus, Hp has been declared as a type I carcinogen, by the International Agency for Cancer Research (IARC) in early 1990's.

Dangers of chronic inflammation

Rudolph Virchow (1821-1902), a famous German pathologist, simplified "cancer" as a "wound that never heals". In the case of Hp infection, the bacteria colonize a very convenient location in the stomach (underneath the mucus layer), where they firmly adhere to the apical lining of the gastric epithelium, while protected from the destructive gastric acid (by means of its alkaline producing urease) and the flood of peristalsis (by means of its multiple array of adhesins; i.e the blood group binding antigen: BabA). The various virulence factors (i.e. CagA, VacA, NapA, HrtA, etc) produced by Hp pass through the epithelial lining, reaching the bloodstream recruiting the first line of the heavily-armed troops (the innate immune cells: neutrophils, eosinophils and basophils) to the basal side of the epithelial membrane, with distinct orders to contain and eliminate the infection. However, being unable to reach the invader (Hp) at the apical (luminal) side, they not only fail to eradicate the infection, but the constant supplies of bacterial antigens aggravate them, resulting in the release of their ammunition (defensins, hydrolyzing enzymes, toxic nitrogens and oxygens, etc.), which actually miss the pre-assigned target (Hp) and inflict damages on the surrounding tissue ("active" inflammation). Considering the source of antigens (Hp) remains undefeated on the apical side, the "second line" of defense (adaptive immune cells: antibody producing/helper/cytotoxic lymphocytes) are called in and added to the "first line". These, too, encounter the same ordeal and end up persisting and releasing their warheads (cytokines, chemokines and antibodies), sustaining "chronic" inflammation. To add insult to injury, Hp expresses antigens (i.e. Lewis histo-group determinants in O-specific chains of its LPS) that mimic host proteins, which may either trigger an auto-immune response, or at least, aid in its camouflage and persistence. Altogether, the body remains under attack by its own troops for as long as the clever invader (pathogen) remains out of reach.

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CagA: a bacterial oncoprotein

Once Hp is securely attached to the apical side of the gastric epithelial membrane, it forms a syringe (type IV secretory system; T4SS: CagM, CagT, Cag3, CagX, CagY), originating from its horizontally acquired cag pathogenicity island (cagPAI), which injects a multi-potential effector protein, namely CagA, into the epithelial cells. CagA (cytotoxin associated gene A) has proven oncogenic in such a multitude of ways that it can rightly stand for "cancer associated gene A". Upon injection of CagA into epithelial cells, it undergoes two phosphorylation-dependent and –independent pathways which results in alterations in cellular morphology (cytoskeletal rearrangement), proliferation and differentiation. As a consequence, epithelial tight junctions are impaired, the hummingbird phenotype (cell scattering and elongation) is observed and the inflammatory pathways are activated. Moreover, CagA takes part in the aberrant hypermethylation (silencing) of tumor suppressor genes (p53, MGMT, PTEN, p16, etc) and deregulation of cancer-associated microRNAs (miR-21, miR-26a, miR-101, let-7, etc).

Gastric oncogenesis

It is believed that the intestinal type of gastric adenocarcinoma is the end result of a cascade of histopathologic changes including non-atrophic gastritis, atrophic gastritis, intestinal metaplasia (gastric to intestinal trans-differentiation) and dysplasia (dedifferentiation), which is primarily triggered by Hp infection. At which point during this stepwise process does Hp become dispensable to the carcinogenic process, namely the "point of no return", remains unclear. Loss of balance between cellular proliferation and apoptosis may explain the development of a tumor. At the stage of tumor initiation, mutagenic changes take place (including initiation of plasticity; epithelial to mesenchymal transition: EMT). At which time the tight regulation on cellular proliferation, differentiation and survival is lifted, giving way to tumor promotion (mitogenic/epigenetic changes and accumulation of pre-neoplastic cells), followed by tumor progression (higher rates of mutations creating grounds for malignant transformation), eventually leading to metastasis of the neoplastic cell *via* the bloodstream to distant sites, where additional tumors are established (mesenchymal to epithelial transition: MET) and expanded.

Having come to the conclusion that a bacterium (Hp) causes cancer (of the stomach) and stomach cancer is the third leading cause of cancer mortality worldwide, is antibiotic therapy of infected subjects a simplified solution to a very complicated problem?!

More details in:

Role of Bacteria in Oncogenesis. AH. Chang and J Parsonnet. Clin Microbiol Rev; 2010. Vol. 23, No. 4: p. 837–857.

Mass Eradication of Helicobacter pylori to Prevent Gastric Cancer: Theoretical and Practical Considerations. YC Lee *et al.* 2016. Gut and Liver, Vol. 10, No. 1: pp. 12-26.

Pathogenesis of Helicobacter pylori infection. S Backert *et al.* 2016. Helicobacter; 21 (Suppl. 1): 19–25

Pathogenic mechanisms of the oncoprotein CagA in H. pylori-induced gastric cancer. Yin Chen *et al.*2016. Oncology Reports. Ahead of Print.

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