Topic: The relationship between gut microbiome and cancer

- Can changes in gut microbiome lead to gastrointestinal cancer, colorectal cancer, etc.?
- Nutrition effect on gut microbiome
- Microbiome effect on immune system (is this related to cancer?)
- Does dysbiosis increase risk of cancer?

Key Components:

- Gut Microbiome:
    - Collective genomes of microbes within the gut
    - Influence local immune responses
    - Produce metabolites
    - Metabolites are used to communicate

Information:

- Loss of bacterial diversity and atrophic gastritis is associated with esophageal cancer

Sources:

- Frontiers | Understanding the role of the gut microbiome in gastrointestinal cancer: A review
- The Influence of the Gut Microbiome on Cancer, Immunity, and Cancer Immunotherapy: Cancer Cell
- Functions of Gut Microbiota Metabolites, Current Status and Future Perspectives - PMC

Abstract:

Among the most common types of cancer is gastrointestinal cancer. Digestive cancers account for roughly one-third of cancers that result in death. Mutations in genes relating to genome integrity (TP53, BRCA2), chromatin remodeling (ARID1A), cell adhesion (CDH1, FAT4, CTNNA1) all contribute to gastrointestinal cancer. Due to increasing research on microbial effects on cancer, it has been shown that gut microbiomes can promote cancer. This literature review will analyze current studies and summarize the latest research regarding gut microbiome relationship with cancer, as well as address any questions that remain unanswered.

Introduction:

The microbiome and cancer is an emerging topic which has gained a lot of popularity in recent years. The microbiome is essential for regulating local immune responses. Gt microbiota produce metabolites which are helpful for maintaining body function. Cancer prevention is pivotal, and understanding the interactions between gut microbiota and immune responses can be significant in finding ways to prevent it. The microbe population find in the gut has variable

nature as its composition is influenced by hosts genetics, diet, lifestyle, and microbial exposure at birth. The microbiome is variable between various subjects. The effect of microorganisms on cancer could be approximately 20% of cancers human being suffer from. This could also be associated with lack of physical activity, and obesity. This review will examine the role of gut microbiota and the development of digestive cancers.

Microbiome:

Three main bacterial strains have been identified as independent of individual factors. Each individual has either one of three of these strains. The enteotype is linked to specific functions of the subject. Number of microbiomes is high in oral cavity. It contains more in the stomach as well. The gut microbiome is a set of symbiotic microorganisms, which are bacteria, viruses, fungi, and protozoa, found in the digestive tract of mankind. In gut microbiome, a decrease in beneficial bacteria and in increase in pathogenic bacteria populations, changes in bacterial content, and deterioration of balance are defined as dysbiosis. Dysbiosis prevents regular functioning of the immune system and may play a role in pathogenesis. Dysbiosis has been linked to playing a role in tumor formation. Gut bacterial composition is largely determined at birth and early stages of life. In formula fed infants streptococcus bacteria provide colonization. Dietary patterns play a significant role in the modulation of the gut microbiome. Nutrition has the potential to affect gut microbiome composition and diversity.

Gastric tumor:

Involvement of helicobacter pylori in gastric cancer is best known example of microbial infection related to cancer. Studies have shown that deficiency of H. pylori increases the chance of tumor forming due to alterations of the physiology of the gastrointestinal tract which changes the composition of the microbiota. H. pylori inject cyto toxins VacA and CagA into host cells which activates ocogenic signal transduction pathways. Destruction of parietal cells stimulates cell. H pylori infection shows negative correlation to with esophageal cancer. Metabolic reprogramming promotes the development of tumors by connecting many pro-oncogenic molecules. Studies have confirmed that HFD can cause significantly increased hepatic retention of hydrophobic bile acids, which are associated with changes in intestinal microorganisms.

Deposition of bile acids are linked to the occurrence of liver cancer. The microbiome is defined as the collective genomes of microbes within a community, whereas the term microbiota refers to the microbes themselves in aggregate. Within a human organism, there are trillions of microbes--as numerous as human cells--which interact with the host constantly at numerous sites (including the skin and mucosal surfaces such as the gastrointestinal tract) throughout development. Therefore, it is not surprising that they play such a large role in numerous host functions including immunity. The crosstalk between microbiota and the immune system at the level of the gut is critical, and, not only allows for the tolerance of commensal bacteria and oral food antigens, but also

enables the immune system to recognize and attack opportunistic bacteria thereby preventing bacterial invasion and infection. In addition to influencing localized immune responses, these microbiota also have broader effects contributing to innate and adaptive immunity at multiple levels. This concept is supported in pre-clinical models; germ-free (GF) mice that lack intestinal microbiota are noted to have severe defects in immunity, with an absent mucous layer, altered immunoglobulin A (IgA) secretion, and reduced size and functionality of Peyer's patches and draining mesenteric lymph nodes (mLNs) Overall, there is compelling evidence that the microbiota help to shape the immune system as a whole.

Local immunity is promoted via recognition of pathogen-associated molecular patterns (PAMPs) (such as lipopolysaccharide and flagellin) by pattern recognition receptors (such as Toll-like receptors (TLRs) present on IECs as well as innate immune effectors within the gut). Metabolites produced by bacteria may also affect local immunity via production of short-chain fatty acids (SCFAs), which, among a number of key activities, have been shown to augment immunity via IgA production by plasma cells (Pabst, 2012). IgA acts primarily by blocking bacterial adherence to epithelial cells; agglutination, entrapment, and clearance; and also has direct effects on bacterial virulence (Mantis et al., 2011).

Draining lymph nodes for the gut lie within the mesentery of the small bowel and colon, where adaptive immune responses are further shaped by the gut commensals, impacting the differentiation of naive T cells within the mLNs. PAMPs act to induce maturation of antigen-presenting cells, such as dendritic cells (DCs), as they sample antigen from the lumen, either directly via interdigitation of dendrites through the mucosal layer or indirectly after processing and transphagocytosis by specialized IECs called M cells. Once activated, DCs travel to mLNs where they interact with and stimulate naive T cells to form $CD4_+$ T cells (Lathrop et al., 2011), specifically $CD4_+$ T regulatory cells (Tregs) and T helper 17 (Th17) cells, both of which have a tropism for the gut. DCs may also directly stimulate $CD8_+$ T cells.

After education in the mLNs, T cells can influence immunity at a number of different sites. They play a critical role in gut homeostasis, highlighted by mucosal tolerance induced by Tregs, and via production of immunosuppressive cytokines, such as interleukin-10 (IL-10). Importantly, there is ongoing crosstalk between gut commensals and mucosal T cells (such as Tregs), as maintenance of these cells at the level of the gut is facilitated by bacterial metabolites such as SCFAs; the fuction of SCFAs is dependent on their ability to inhibit histone deacetylase activity suggesting epigenetic regulation (Rooks and Garrett, 2016). In addition, some bacterial species have been shown to drive Treg development via alternative pathways dependent on

polysaccharide A and TLR signaling to DCs (Round and Mazmanian, 2010; Shen et al., 2012).

A specific subset of CD4+ cells proven to be important in gut microbiota interactions are Th17 cells. These cells are prominent within the lamina propria of the small and large intestine, and are critical in protecting against bacterial and fungal infections. Th17 cells also function in mucosal immunity as cytokine secretion from Th17 cells stimulates IECs to form tight junctions and to secrete anti-microbial proteins (Weaver et al., 2013). Th17 cells are markedly depleted in GF animals and can be induced by specific bacterial subsets such as segmented filamentous bacteria (Ivanov et al., 2008, 2009). IL-17 can cause further release of additional inflammatory cytokines and recruit neutrophils from the circulation to the gut microenvironment. In addition to influencing local immunity within the gut mucosa, microbiota can also shape systemic immune responses via immune cell priming. DCs primed by commensals typically do not pass into the circulation or travel to distant lymph nodes but can do so in certain settings. TLR signaling from microbial peptides to DCs and other innate immune effectors generates cytokines and interferons that act in both a paracrine and endocrine manner at distant sites; it is thought that this signaling in the gut creates immune system “tone.” That is, the systemic immune system is primed (potentially at epigenetic or transcriptional level) to enact a robust response in the setting of pathogens, and, in the absence of threat, to maintain a non-inflammatory state (Furthermore, B and T cells, including Tregs and Th17 cells, can, upon being primed by DCs presenting antigen derived from commensal organisms in draining mLNs of the gut, circulate systemically to facilitate immune responses at distant sites against the same organism or against other antigens by cross-reaction to similar epitopes (Stary et al., 2015). Interestingly, Th17 cells that emigrate can have significant plasticity in function, changing their cytokine output based on the existing local inflammatory or non-inflammatory statew.

Disruption of the delicate balance of commensal bacteria is seen in the setting of dysbiosis, which is characterized by a less-diverse and less-stable microbiota, with potential enrichment of opportunistic pathogenic bacteria (Frosali et al., 2015). Dysbiosis can lead to impaired local, locoregional, and systemic immune responses with breakdown of mucosal barriers, translocation of gut bacteria to the mLNs and into the peripheral circulation, alteration of the cytokine milieu within the gut mucosa and draining mLNs towards an inflammatory phenotype, and activation of Th17 cells and effector T cells, causing an influx of neutrophils and inciting a profound inflammatory state both locally and systemically (Levy et al., 2017).

Exemplification of the importance of eubiosis in preserving immunity is seen in response to vaccination. A highly diverse microbiota has been associated with improved adaptive immune responses to a variety of vaccines in infants (Huda et al., 2014). Specific

components of the microbiota can prime the immune system by activating TLR signaling pathways serving as a natural vaccine adjuvant (Oh et al., 2014). Thus, it is increasingly clear that the gut microbiota may affect not only local immunity but also systemic immune responses.