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Topic Paper: Microbial Induced Cancer in Humans

The human body is home to trillions of microbes that interact with human cells through several different relationship patterns, these relationships can differ depending on the microorganism. These relationships can include anywhere between a beneficial symbiotic to a disastrous life-threatening pathogenic relationship. The vast majority of microbes that interact with humans are very beneficial to life as more than 20% of the small molecules in human blood comprises of these helpful microorganisms. (Rook et al, 2017) Most of the beneficial microorganisms, which are known as normal flora help the body's digestion, help repair damaged tissue, and help fend off invading pathogenic microbes. On the other side of the scale pathogens are not normal flora and they aren't common in the world of microbiology as they make up far less than 1% of the total microbe population. Pathogens can be categorized into different groups such as bacteria, viruses, fungi, protozoa, worms, and prions. Pathogens have a range of conditions that span from microbes that can cause mild food poisonings such as *E. coli* and other microbes that cause fatal conditions such as prions that cause Creutzfeldt-Jakobs disease and *H. pylori* that cause gastric cancer. It is estimated that nearly 15-20% of all cancers are caused by a related microbial infection. (De Flora and Bonanni, 2011)

Cancer is a significant mutation of the cell's genomic DNA that is uncorrected, but more specifically it's the mutation of the tumor suppressor and proto-oncogenes. The mutations in proto-oncogenes and tumor suppressors cause unchecked accelerated growth causing cancerous

cells to grow into tumors. Tumor suppressor and proto-oncogenes act as mechanisms to fight over-proliferation of cells. (Alberts et al, 2002) Proto-oncogenes usually function as a barrier to stop over cell proliferation and contribute to growth, but when mutated turns into oncogenes and becomes activated. When oncogenes activate it turns into uncontrollable cell proliferation, which then leads to cancer. Some proto-oncogenes transform into oncogenes due to inherited genetic material defects as well as acquired mutations through one's lifetime. An important example of an oncogene is the Cyclin D1 which can lead to cancers in the esophagus, colon, pancreas, and more when the oncogene is activated.

Tumor suppressor genes act in the opposite direction as an oncogene. When activated the tumor suppressors are important functional genes that slow cell division, repair DNA mistakes, or command cells to die through apoptosis. Out of control cell growth possibly occurs when these genes don't function optimally, the deactivation of tumor suppressor genes can then lead to cancer. Deactivation of tumor suppressor genes is supported by the hypothesized two-hit system by Dr. Alfred G. Knudson. The two-hit system states that two mutations of the alleles in the gene is required to cause cancerous tumors. (Paige, 2003) This idea means two alleles of the gene must mutate in order to cause the deactivation of tumor suppressor genes. The most frequently seen tumor suppressor inactivation is with the BRCA1 and BRCA2 genes. (Chial, 2008) If the oncogenes are deactivated, they cause uncorrected cell proliferation, which can lead to breast cancer. Often, at least one hit on the BRCA gene allele is hereditarily acquired and the other hit is usually acquired by induced damaging actions. Sometimes, both hits on the alleles can be hereditarily acquired which leads to no choice but the deactivation of the tumor suppressor genes. The most important distinction between oncogenes and tumor suppressor genes is the

difference in activation and deactivation. When oncogenes are activated and when tumor suppressor genes are that's when they catalyze cell proliferation, which then can cause cancer.

When normally thinking about a pathogen people tend to think of them as hostile foreign invaders that cause serious damage to humans. In reality, these microbes are doing what any other organism does, survive, and pass genetic information along to offspring. (Alberts et al, 2002) The human body is a nutrient-rich ecosystem for microbes and provides many opportunities for microbes to thrive. This fact is the reason why pathogenic microbes find opportunities to enter the human body through infections or infected food and water. Most pathogens that infect humans hardly ever become symptomatic as the non-normal flora immediately get killed. These pathogens are distinct from the normal flora in the body which has the immune system recognize foreign invaders and respond by eliminating them. In order for these pathogens to survive, they must colonize a host before being detected and replicated under the host's resources. Once replicated, these pathogens then look to exploit other host cells to continue to reproduce and evolve to eventually become symptomatic. When the pathogenic microbes infect enough cells, they constantly challenge the immune system antimicrobial agents.

There are several microorganisms known to directly cause cancer. These opportunistic pathogens attack and cause mutations of the proteins that support the normal functioning of proto-oncogenes and tumor suppressors. The most common microbes to cause cancers are the human papillomavirus (HPV) causing anogenital cancer, *H. pylori* bacteria causing gastric cancer, and Hepatitis B and C viruses causing hepatic cancers. (Vandeven and Nghiem, 2014) There are three different ways pathogen microbes to induce cancers. The classification systems discussed by Martin Blaser in his paper Understanding Microbe-Induced Cancers (Figure 1) starts with class A microbe such as HPV as they target host immunity and assists in lymphomas

via immunosuppression. Class B microbes such as the hepatitis virus or *H. pylori* directly promote malignancies by interactions with parenchyma, whether epithelial, endothelial, or mesenchymal cells. In Blaser's class C group, he postulates microbial disruption in hormonal regulation disruption, which significantly promotes cancer in the breast, ovaries, endometrium, and testicles. (Blaser, 2008) All microbial pathogens disrupt normal functioning in the immune system effectively suppressing the immune system. Immunosuppressive microbes such as HIV/AIDS increase the chance to develop different types of opportunistic cancers.

Cancer development is a special situation that is caused by a significant uncorrected mutation in the cell's genomic DNA. Looking at the properties of microbial flora, it is seen that pathogens have their special place in the microbiology kingdom. There is a direct connection between both pathogenic microbes and cancer development as nearly 20% of human cancers are connected to microbes. (Whisner and Aktipis, 2019) There were distinct different ways that a pathogen can promote cancer development by modifying normal functions in cell communication. Although, microbes are only 1/5 of the reason behind cancer development, it is still a researched topic in the medical and microbiology field. With there being trillions of different microbes on Earth humans have hardly made a dent into research in the unknown. It is vital to continue research about this topic as several different pathogens that have yet to be discovered and researched. Knowing the effects of these unknown pathogens can significantly help the development of a vaccine or cure such as the HPV vaccine.

The reason why I wrote about cancer-inducing microorganisms is due to my enthusiasm for cancer research. I've done several papers on cancer, its effects, and its development in humans. I haven't yet written a paper about microbes inducing cancer so that was interesting to research and learn about. Throughout my undergraduate research so far on cancer, I have great

interest one day in becoming an oncologist. Taking microbiology for the first time, it is a very fun lab course as I was given independence on my lab time before COVID-19 restricted us. Combining my interests in cancer research and microorganism properties from the field of microbiology gave me the idea of writing this paper. Thank you for the instruction throughout the course.

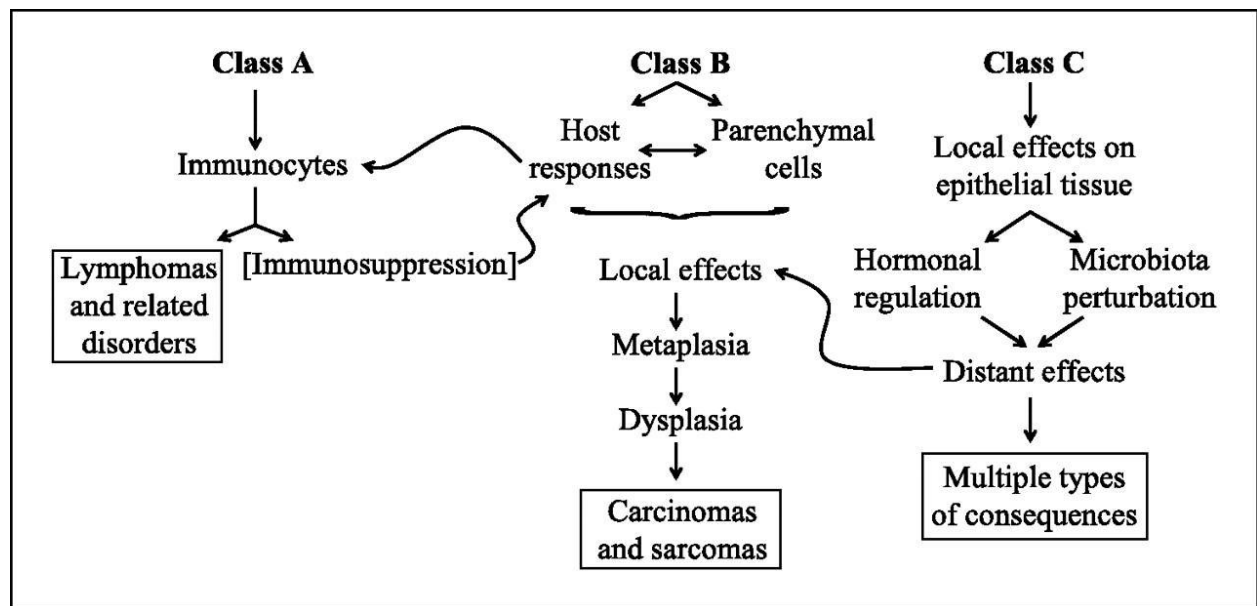


Figure 1: Classification System Flow Diagram (Blaser, 2008)

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