Cancer Due to Prolonged Inflammation

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What mechanisms are activated when your body is invaded by pathogens? How do these mechanisms interact with other pathways in the body? Scientists have considered these questions for years in order to determine exactly how we fight diseases and how we can amplify our body's defense system. Inflammation has long been accepted as the most standard, and perhaps the most effective, response that the body has in place to fight both external and internal pathogens. This mechanism is considered useful because it activates whenever a threat is present, and becomes inactive upon restoring health. However, in some instances this inflammation continues to propagate, now harming cells and threatening to expand throughout the body. This prolonged inflammation gives rise to multiples forms of cancer. In this article we will consider the mechanism of inflammation and how it is activated in the body. To understand how this mechanism can become

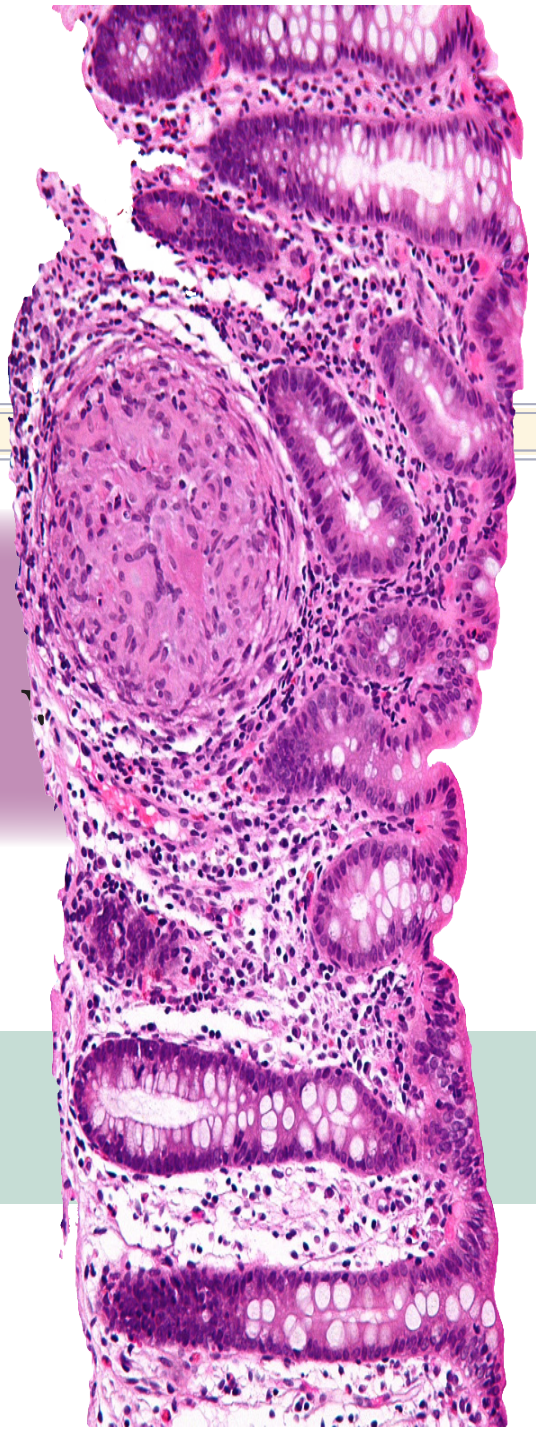

Figure 1:
Endoscopic biopsy showing granulomatous inflammation of the colon in a case of Crohn's disease.

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uncontrollable, we will look at the possible routes of mutation, factors that can trigger such mutations, and the negative effects they cause. Finally, we will consider everyday actions that cause this prolonged inflammation that can eventually develop into cancer.

Inflammation is a mechanism triggered when pathogens invade our sensitive, highly advanced immune system. When you are injured, either externally or internally, immune cells around the affected area release a variety of proteins and other factors that promote cell proliferation and regeneration. However, release of factors occurs only for a limited period of time, and positive feedback of the repaired area prevents the immune cells from releasing more factors. As the damaged cells are repaired or regenerated, they cease to excrete the chemicals that attracted the immune cells. This decrease in signaling factors conveys a stop message to the immune cells, which then cease their reparative mechanism and recede. This process of inflammation is vital in the body as it is responsible for reparative processes such as, "tissue remodeling, angiogenesis, and other wound-healing features" (Demaria, Pikarsky, Karin, Coussens, Chen, El-Omar, Trinchieri, Dubinett, Mao, Szabo, Krieg, Weiner, Fox, Coukos, Wang, Abraham, Carbone, Lotze, 2010).

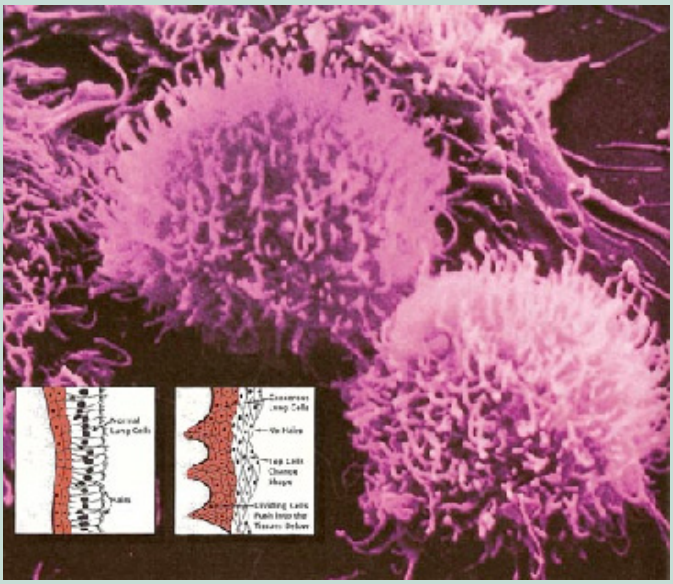

Figure 2. Inflammed cancer cells

Trouble can arise when these immune cells have been genetically damaged or attacked by mutagenic cells (initiated cells). When this DNA mutation occurs, the immune cells continue to proliferate at the site of an injury even though they are no longer needed (Coussens & Werb, 2002). This uncontrolled proliferation is a trademark of all forms of cancer, and hence we can see that there is a reflexive relationship between cancer and inflammation (Rakoff-Nahoum, 2006).

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Although the link between prolonged inflammation and cancer has become a major topic of study recently, the link between the two was noticed as early as 150 years ago. In 1863, Virchow observed that there was an unusually strong correlation between sites where chronic inflammation was present and sites where cancer later manifests (Lu, Ouyang, Huang, 2006).

Numerous studies have found that there are more factors involved than simply the uncontrollable production of cells that cause cancer. Rather, this proliferation requires the support of an environment that is, "rich in inflammatory cells, growth factors, activated stroma, and DNA-damage-promoting agents…" (Coussens & Werb, 2002). Thereby, it is now understood that not only is cell proliferation necessary, but it must also be supported by a cell environment that both supports the cell growth and its rate of regeneration. Both of these features combined promote neoplastic risk, which is

the probability of the appearance of abnormal tissue growth (tumors) (Coussens & Werb, 2002).

A supportive cell environment not only supports the expansion of cancer, but may also make it more deadly. After the initial infection, the mutated cells and the surrounding cell factors develop a type of communication system that can aid them in their proliferation. Cancerous cells themselves hijack some of the communication mechanisms present in the inflammatory system and use them to further their own growth and development throughout the host (Coussens & Werb, 2002). After hijacking these signaling systems, the tumor cells have a much more elaborate and powerful system at their disposal that they can then use to mutate beyond their initial purpose of reparation through the use of processes such

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as "transformation, survival proliferation, invasion, angiogenesis, metastasis, chemoresistance, and radioresistance…" (Aggarwal & Gehlot, 2009). This hijacking process progresses to the extent that the survival and proliferation of most types of cancer stem cells seem to be dependent on the activation of these inflammatory pathways (Aggarwal & Gehlot, 2009). Hence, through deep integration with the inflammation pathway, the cancer cells are able to further their own infection of the host.

The specific factors through which the inflammatory system can be commandeered into helping cancer cell proliferation are, "nuclear factor kappa B, reactive oxygen and nitrogen species, anti-inflammatory cytokines…" (Schetter, Heegaard, Harris, 2010). The collective activity of these factors can induce pro-tumorigenic inflammatory responses through changes in cell proliferation, cell death, cellular senescence, DNA mutation rates, DNA methylation, and angiogenesis (Schetter et al, 2010).

Nuclear factor kappa B, a particularly important factor, plays a role in perpetuating cancer when it is activated from its dormant state in the cytoplasm. The activation of this genetic factor causes a suppression of apoptosis, or cell death. Hence, since the cells are no longer able to die, they continue to grow and develop, promoting chemoresistance and tumorigenesis. While this factor seems to be clearly implicated in propagating cancer, it has also been found to be a potential therapeutic target. Most chemopreventative agents are thought to primarily suppress Nuclear factor kappa B production, indicating that it is a major factor in facilitating the spread of cancer. Further optimization of this method may lead to further developments in more efficient and successful cancer treatment and prevention programs (Bharti & Aggarwal, 2002).

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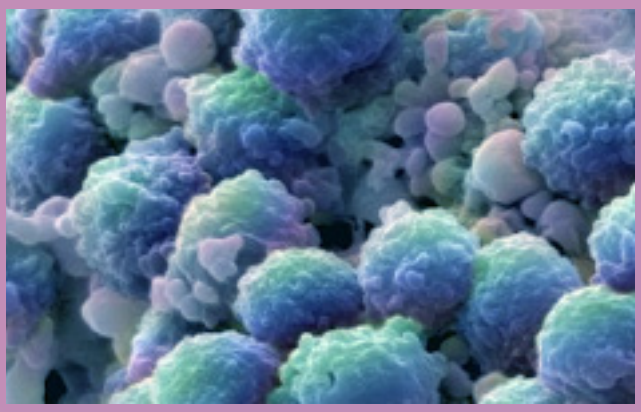


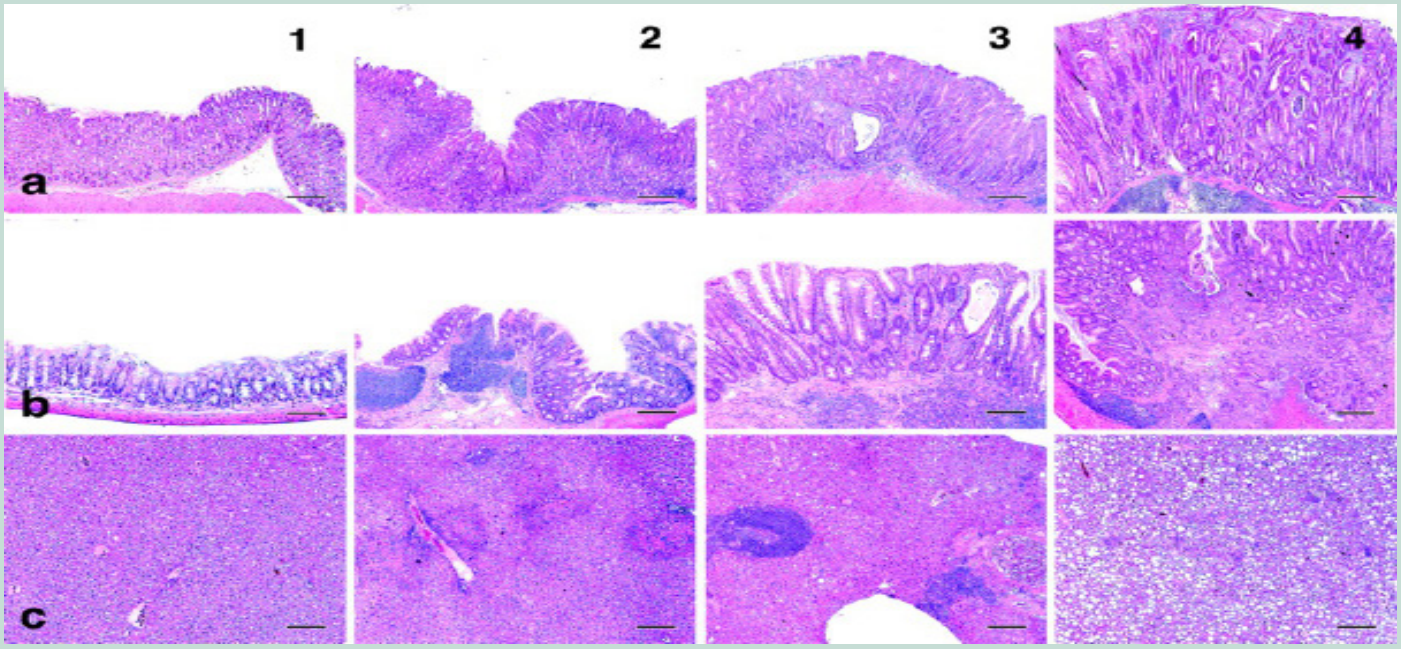
Figure 3. Prostate cancer cells

When considering cytokines, there are two types that are of interest: anti-inflammatory and inflammatory. Generally, anti-inflammatory cytokines play a vital role by acting as inhibitors regulating the inflammatory system after the necessary repairs have occurred. However, sometimes they may fail to properly control the inflammatory activity within the cell or overcompensate by decreasing the immune response from the necessary levels needed for protection. In the first case, when the anti-inflammatory cytokines are unable to properly control the inflammatory response, there is an increase in cell proliferation and growth, which then promotes cancerous growth (Opal & DePalo, 2000).

Cellular senescence refers to the aging of the cells. "Senescence, perceived as a cancer barrier, is paradoxically associated with inflammation, which promotes tumorigenesis" (Pribluda et al, 2013). This is because although cells that undergo senescence prevent cancer in that they lose their ability to produce viable offspring, they also increase their production of inflammatory cytokines. As discussed previously, these inflammatory cytokines prevent cytokine inhibitors from controlling the inflammatory response and allow it to perpetuate over a prolonged period of time, thus promoting tumorigenecity. (Ren, Pan, Lu, Sun, Han, 2009).

The factors discussed above play a major role in mutating a DNA sequence from its original strand to a more powerful viral strand. Mutation rate refers to the rate at which base pairs within a given sequence are mutated. A faster mutation rate is characteristic of developing cancer cells as their high rate of proliferation makes them more prone to mutation accumulation. A factor that is linked to increasing the mutation rate is known as miR-155, and further research may indicate that this is a viable therapeutic target for controlling these pro-tumorigenic factors (Ohio State University Medical Center, 2011).
Non-genetic factors that can increase the inflammation-cancer risk include free radicals, which are considered the hallmarks of tumor progression. Free radicals, molecules that are unstable due to extra outer shell electrons, have been shown to play a role in tumor initiation and development by increasing metastatic potential (the potential for cancer to spread from one organ to another), especially in tumors (Arrabal, Cordon , Leon, Román-Marinetto, Del Mar Salinas-Asensio, Calvente, Núñez, 2013).

Figure 4. (1) Acute inflammation (2) chronic inflammation with hyperplasia and dysplasia (3) and carcinoma (4) Hematoxylin and eosin



Everyday factors that have long-reaching effects in abnormally activating these inflammatory pathways, and increasing the risk of inflammation-induced cancer include tobacco, mental stress, diet, and alcohol. These factors are responsible for up to 95% of all cancers as a result of many mechanisms, including the inflammation-induced pathway (Aggarwal & Gehlot, 2009).

In conclusion, although the inflammatory pathway is vital for our survival as it repairs and restores the body's cells, it can also be turned against the body due to the negative influence of many everyday factors. Once the inflammatory pathway begins to produce regenerative cells, despite having fixed the necessary problem, this becomes a trademark site of tumor production. The further prolonging of this regeneration increases the metastatic potential of these tumors, and makes it more likely that the cancer will spread to organs throughout the body.

Many factors such as nuclear factor kappa B, reactive oxygen and nitrogen species, and anti-inflammatory cytokines have been shown to play having key roles in this mechanism. The direction of future cancer research is to better understand the activation pathways of these factors so that they can be manipulated to prevent or slow tumor growth. Although the stress that prolonged inflammation places on one's cells is deadly, there is still hope for a cure in the near future.

References:

Arrabal SR, Cordon FA, Leon J, et al. Involvement of free radicals in breast cancer. Springerplus. 2013; 2:404. doi: 10.1186/2193-1801-2-404.

Aggarwal BB, Gehlot P. Inflammation and Cancer: How friendly is the relationship for cancer patients. Curr Opin Pharmacol. 2009; 9(4): 351-369. doi: 10.1016/j.coph.2009.06.020.

Bharti AC, Aggarwal BB. Nuclear factor-kappa B and cancer: its role in prevention and therapy. Biochemical Pharmacology. 2002; 64(5-6): 883-888.

Coussens LM, Werb J. Inflammation and cancer. Nature. 2002 December 19; 420(6917): 860-867. doi: 10.1038/nature01322.

Demaria S., Pikarsky E., Karin M., Coussens L.M., Chen Y.C., El-Omar E.M., Trinchieri G., Dubinett S.M., Mao J.T., Szabo E., et al. Cancer and inflammation: Promise for biologic therapy. J. Immunotherapy. 2010;33:335–351. doi: 10.1097/CJI.0b013e3181d32e74.

Lu, Haitian, Weiming Ouyang, and Chuanshu Huang. Inflammation, a Key Event in Cancer Development. Molecular Cancer Research 4.221 (2006): 5-261. Web. 7 Oct. 2013. <http://mcr.aacrjournals.org/content/4/4/221.full#cited-by>.

Ohio State University Medical Center (2011, April 19). How inflammation can lead to cancer. ScienceDaily. Retrieved October 7, 2013, from http://www.sciencedaily.com¬ / releases/2011/04/110419091159.htm

Opal SM, DePalo VA. Anti-Inflammatory Cytokines. Chest Journal. 2000; 117(4): 1162 – 1172. Doi: 10.1378/chest.117.4.1162

Pribluda A, Elyada E, Wiener Z, et al. A senescence-inflammatory switch from cancer-inhibitory to cancer-promoting mechanism. Cancer Cell. 2013; 24(2): 242-256. doi: 10.1016/j.ccr.2013.06.005

Rakoff-Nahoum S. Why cancer and inflammation? Yale Journal of Biology and Medicine. 2006;79(3-4):123–130.

Ren JL, Pan JS, Lu YP, et al. Inflammatory Signaling and Cellular Senescence. Cell Signal. 2009; 21(3): 378-383. doi: 10.1016/j.cellsig.2008.10.011

Schetter AJ, Heegaard NH, Harris CC. Inflammation and cancer: interweaving microRNA, free radical, cytokine and p53 pathways. Carcinogenesis. 2010; 31(1): 37–49. doi: 10.1093/carcin/bgp272.

Image References:

http://web.mit.edu/newsoffice/2012/cancer-inflammation-h-pylori-0611.html

http://ajpgi.physiology.org/content/286/3/G361

http://www.33rdsquare.com/2012/06/prostate-cancer-drug-trial-stopped-so.html