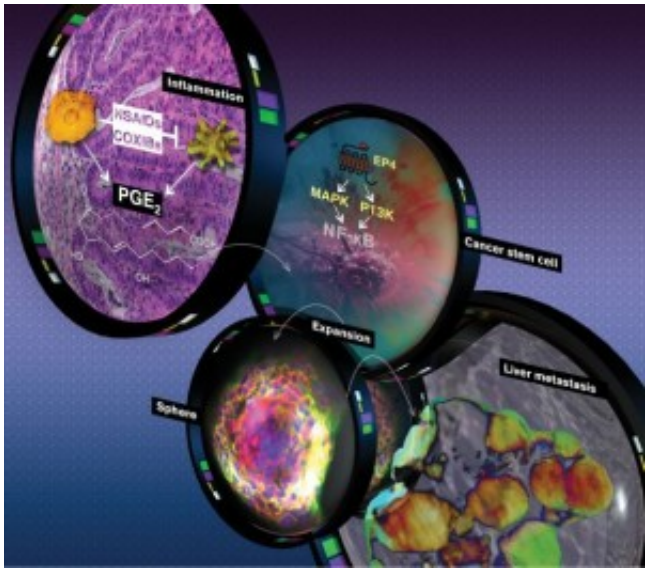
Cancer connection: study of inflammation offers tantalizing clues

The body displays a remarkable capacity for healing wounds— a process we often take for granted. Within a day, a finger we've carelessly nicked returns to normal.

Behind the scenes, a crucial mediator of the body's inflammatory response, a bioactive fat known as prostaglandin E_2 or PGE_2 swings into action, attracting the body's immune cells and stimulating pathways that heal the wound site.

Over a few days, depending on wound severity, levels of PGE_2 rise and ebb, returning to their baseline levels, as healing is completed.



Prostaglandin E2 is the most abundant pro-inflammatory bioactive fat, or lipid, found in colon, lung, breast, head and neck cancers. High levels of PGE2 found in cancer patients often indicate a poor prognosis. During cancer development, cells keep making PGE2 chronically. The condition resembles a wound that never finishes healing. In the process, heightened PGE2 stimulates cancer stem cells that promote cancer progression and metastatic spread.
Illustration by Michael Northrop: Biodesign Institute

Recently, our group has learned that the inflammatory response, an essential immune component safeguarding health, may also have a dark side. In diseases like colorectal cancer, the PGE_2 system gets hijacked. In this case, rather than switching off PGE_2 at the appropriate time, cells continue to manufacture it. The pathological condition may be compared with a wound that never

heals.

The effects of chronic PGE_2 overproduction include the development of cancer stem cells (CSCs), which promote cancer progression and metastasis—the spread of the disease to other parts of the body.

Our investigations have shown that the use of nonsteroidal anti-inflammatory drugs, or NSAIDs like ibuprofen and Aleve can act to reduce the risk of colorectal cancer, through their inflammation-retarding activity. Unfortunately, prolonged use of non-aspirin NSAIDs is increasingly associated with serious cardiovascular side effects.

Novel insights into inflammatory pathways and PGE_2 overproduction in cancer offer hope for new, more effective drug targets and screening methods for colorectal cancer.

Currently, the prognosis for advanced colorectal cancer is poor, with nearly half of all patients dying within five years following treatment. The reasons for colorectal cancer's high lethality are complex and include heightened resistance over time to treatments like chemotherapy. Increasingly, however, the role of inflammatory mediators in tumor metastasis has come to occupy center stage.

Cancers are highly complex entities, typically composed of a wide variety of cell types. Among these, one cell group's insidious nature is of particular relevance for colorectal cancer: so-called cancer stem cells. Such cells have the capacity for self-renewal, differentiation, and resistance to cytotoxic agents.

Our research demonstrates that the pro-inflammatory mediator PGE_2 is linked with an increased production of colorectal cancer stem cells in mice. PGE_2 accomplishes this by binding to its receptor on the surface of the cancer cell, PGE receptor 4, or EP4, triggering a cascade that signals cancer stem cells to renew, differentiate and eventually become resistant to chemotherapy.

Further, we found a correlation between levels of PGE_2 and 4 CSC markers in human colorectal cancer specimens, (CD133, CD44, LRG5, and SOX2 messenger RNAs). Cancer patients showing high levels of PGE_2 are often treatment resistant and are known to have a poor disease prognosis.

It appears that when cancer stem cells become depleted of oxygen in the colon, they fool the body into making more PGE_2, causing stem cells to multiply and migrate to other parts of the body. The addition of PGE_2 in mice increased the number of CSCs, which frequently migrated to the liver, a prime organ for initial metastasis. CSCs treated with PGE_2 showed a 1000-fold increase in their ability to spread.

Our studies also showed—for the first time—that blocking PGE_2 signaling by adding a drug inhibiting its binding to the EP4 receptor, reduced polyps and CSCs, and halted liver metastasis. Targeting and eliminating stem cells in patients with colorectal cancer offers a promising new

approach to the successful treatment of this leading killer.

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Publication

Prostaglandin E2 Promotes Colorectal Cancer Stem Cell Expansion and Metastasis in Mice.
Wang D, Fu L, Sun H, Guo L, DuBois RN
Gastroenterology. 2015 Aug 7