The Biology of Aspirin

There is newfound excitement in the world of cancer over the role of aspirin, thanks to a recent study in the journal *Lancet* on the chemopreventive effects of aspirin. This article was published on the heels of a media frenzy surrounding the invention of a new “super aspirin” called NOSH-aspirin. Because of all the renewed interest in a century old drug, we thought it would be a good time to revisit the biology of aspirin for those of you who may be interested.

Aspirin is one member of a drug class called non-steroidal anti-inflammatory drugs, or NSAIDs. Aspirin is primarily used as an analgesic (pain-reliever) and an anti-inflammatory drug. The effects of aspirin in combatting pain and inflammation arise through the ability of aspirin to inhibit the formation of a molecule called prostaglandin 2, PGE2.

PGE2 is an important signaling molecule in your body that can cause all sorts of physiological effects from muscle contraction to pain and blood clotting. Aspirin blocks PGE2 to relieve pain and prevent inflammation by thinning your blood, among other things. Aspirin blocks PGE2 by directly inhibiting cells from making PGE2, a function which is normally carried out by the enzyme cyclooxygenase (COX). There are two main forms of cycooxygenase in the body, COX-1 and COX-2. Aspirin is capable of inhibiting both COX-1 and COX-2, depending on the dose, and it can exert a great effect in cells like blood cells because platelets can’t regenerate COX once it is rendered dysfunctional by aspirin. This is helpful for the blood thinning functions of aspirin such as preventing stroke, but this is also where the serious bleeding side effects of aspirin are derived. Further, PGE2 has known protective effects in the gastrointestinal tract which is why many people suffer gastrointestinal irritations with frequent aspirin use.

So what exactly does aspirin have to do with cancer? COX-2 and PGE2 levels are increased in many solid tumor types, so I would refer you to Dr. West’s post on COX-2 inhibitors for more information on the rationale behind targeting COX-2 in the treatment of cancer. Aspirin will inhibit COX-2 at high doses and the most active metabolite of aspirin (salicylate) is preferentially a COX-2 inhibitor. While aspirin and other COX-2 inhibitors can reduce PGE2
levels through COX-2 inhibition, aspirin inhibits COX-2 in such a way that it drives the formation of an anti-tumor molecule called aspirin-triggered lipoxin, or ATL. Forcing the generation of ATL by COX-2 is a unique function of aspirin compared to other NSAIDs based on the unique way that aspirin switches the function of COX-2 rather than inhibiting it completely. The formation of ATL may also account for some of the antitumor effects of aspirin.

Aspirin exerts special anti-tumor effects specifically in the gastrointestinal tract, making it ideal for chemoprevention in people who are susceptible to colon cancer. For example, many colon cancers arise through mutation of the adenomatous polyposis coli (APC) tumor suppressor gene. This gene, when mutated, can activate an oncogenic signaling pathway called b-catenin/Wnt. Inhibiting PGE2 can work to suppress the b-catenin/Wnt pathway and provide an extra benefit in colon cells with mutated APC. Aspirin can also activate a protein involved in the regulation of the cell cycle, NFkB. Interestingly, aspirin can only activate NFkB in certain cell types including colorectal cancer cells.

Aside from these functions, aspirin can also activate other anti-tumor signaling molecules such as NSAID-activated gene 1, NAG-1. The exact role of NAG-1 in the cell is still unknown, but it is thought that NAG-1 may suppress COX-2 expression thereby contributing to the chemopreventive effects of aspirin. Additionally, aspirin can inhibit the affect of some carcinogens by reducing the peroxidase activity of certain enzymes in the cell which can reduce the amount of damaging free radicals in the cell. Aspirin can also indirectly inhibit other signaling molecules such as sphingosine-1-phosphate, which is known to have many cellular functions like metastasis, angiogenesis, and promoting drug resistance. Aspirin has still other effects that are known to us in the cell that are simply too numerous to list here.

Aspirin is clearly working on many known pathways in the cell and has some very definite anti-cancer properties. However, I hope to have disseminated that the effects of aspirin are highly complex, and likely some still eluding doctors and scientists somewhat. Therefore, it is always best to consult with your doctor before you consider starting an aspirin-containing regimen to be sure that it will not put you at risk for any complications based on your current health situation.

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