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Mechanisms and effects of aspirin to cancer cells

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Abstract. Aspirin, everyone knows it is an anti-inflammatory drug, has great promise mostly for the prevention and treatment of cancer by using a number of methodologies. Its anti-cancer property come from its induction of apoptosis, inhibition of cell growth, and disruption of important signaling pathways. By exploring the mechanisms through which aspirin affects cancer cells, particularly having the impact on signaling pathways like non-coding RNAs (ncRNAs), and controlling the activity of platelets. It is also mentioned that the inhibition of cyclooxygenase (COX) enzymes is involved in aspirin's primary action, leading to lower rate of inflammatory mediators produced and changing cellular signaling networks. The modulation of ncRNAs, especially in connection to specific cancer pathways, concentrating its role in cancer treatment for many areas. However, although huge potential of the drug exhibits, the use of aspirin is not without risks. Common symptoms such as gastrointestinal discomfort and bleeding are in considering. As all mentioned below, numerous good results in improved treatment approaches for patients will come out, follow the continued investigation into the many ways that aspirin affects cancer cells.

Keywords: Aspirin; Cancer cell; Platelet; Effect.

1. Introduction

Aspirin, is a kind of anti-inflammatory drugs, which can also reduce fever and relieve pain. Its main part acetylsalicylic acid is widespread in plants and is highly active [1]. Willow bark contains salicylates, which Hippocrates employed as an analgesic and whose antipyretic properties have been known for more than 200 years [2]. Acetylsalicylic acid, or aspirin, was introduced in the late 1890s and has been used to treat a variety of inflammatory conditions; however, not until almost 70 years later, people discovered the antiplatelet activity of this agent [2]. Numerous studies on plants have demonstrated that salicylates are a strong hormone that controls different reactions to both biotic and abiotic stress [1]. Cancer cells' growth, spread, resource use and metabolite production, tissue disruption, and co-option of normal noncancerous cells disruption cause the cancer disease [3].

According to the current studies, aspirin is convinced as the effective drug which is worth doing more researches. Lowering the activation of platelets have been explored as anticancer therapies, while in long-term administration, which cumulatively increases the risk of bleeding [4]. Aspirin affects the signal transduction of some specific enzymes pathway like PI3K, and this greatly solves the problem of late-stage drug resistance of some chemotherapy drugs [5, 6]. Some studies also combine aspirin with enzyme inhibitors to achieve the effect of reducing cell proliferation [7]. It has been discovered that aspirin directly inhibits the growth of tumors, causes apoptosis in cancer cells, and may improve the effectiveness of traditional cancer treatments [8].

Through exploring the effect of aspirin to cancer cells, it might find the remarkable potential in many kinds of cancer diseases since it has been known well about the mechanisms of the cancer. The features of disease occurring helps us correspondingly take the prevention and treatment into action after the observation and experiments, and this can greatly realize the potential of aspirin and also discover the disadvantages of the drug to complement the blank of pharmacology theory. On the side of clinical aspect, personal treatment can inform through the research on aspirin's effects on cancer cells. As the difference among the types and subtypes of the cancer, the sensitivity of aspirin will vary throughout the individual change, so it can make aspirin-based therapies better for their object by understanding the genetic and molecular parts. In addition, the study of aspirin's mechanisms of

action against cancer cells can offer valuable insights into the fundamental pathways and development of cancer. By clarifying how cellular signaling networks, proliferation, angiogenesis, and immunological responses are impacted by aspirin's regulation of cyclooxygenase (COX)-dependent and COX-independent pathways, scientists can more easily deal with the complicated interplay among inflammation, oxidative stress and so on which are included in the specific nature of cancer disease. That because aspirin's primary mode of action is the inhibition of COX enzymes, which are essential for the synthesis of inflammatory mediators like prostaglandins [9].

For the future, it is meaningful to create the new types of drugs which are anti-tumor. The figures or the records could be used to find new target side of tumor curing and innovative therapeutic strategies. Based on the existing molecular structure and mechanisms of aspirin, it should be preserved the possibility of designing and synthesizing more targeted anti-cancer compounds. The invention of this drug will cater to an unmet need in cancer treatment at present. This research will analyze the mechanism of action of aspirin on cancer cells. All in all, numerous benefits and significance of doing researches on the effect of aspirin to cancer cells are mentioned and also there will be great promise in this area in the future. The study not only contribute to fighting against the cancer disease and cure current patients through clinical decision-making but also give much space to design and invent new types of anti-cancer drugs, improving pharmacological knowledge.

2. Mechanisms

2.1. NcRNAs and signaling pathways

The reason why aspirin has effects on cancer can be understood through the key of working mechanisms. The drug occurs acidification with phosphorylation in the mitochondria, resulting into lower signaling modulation under the condition of the preventing NF-κB in neoplastic cells [10]. At the same time, respiratory control ratio is declined and respiration is more frequent. When considering about the signal pathway, it is worth-thinking that non-coding RNAs (ncRNAs) play an important role in the process. Since the feature of mammal transcriptomes is noncoding, the aspirin may have effects on both genetic expression and the modifying of target site. MiRNAs and ncRNAs under the joint effect of aspirin with other drugs, will be altered. In different conditions, there are various final results due to the ncRNA effects, the condition may be like 100 μL aspirin or 1 mM Aspirin+0.1 mM lapatinib treated gastric cancer cell linkage and 10 mM aspirin worked on colorectal cancer cell linkage. For instance, transcription factor might take part into target genes regulation in the Wnt/β-catenin/TCF4 signaling pathway [10]. In a related study on colorectal cancer, 28 incRNAs were shown to have increased following treatment with aspirin (100 μM), with incRNA OLA1P2 showing the greatest alteration among them. Aspirin was discovered to upregulate FOXD3, which in turn enhances OLA1P2 transcription. OLA1P2 has the ability to suppress the proliferation and metastasis of colorectal cancer cells by activating the STAT3 signaling pathway and blocking the production of phosphorylated STAT3 homodimers [10].

2.2. Role of platelets

Platelets can release a kind of diverse group membrane-enclosed vesicles called EV of different sizes. And most enclosed vesicles derived from platelets are very small with another name microparticles (MPs) [11]. Platelet-derived MPs, which take the most proportion in the circulating EVs of almost 70-90% in the peripheral blood of healthy individuals, are also one common type of the EVs. Many situations like platelet activity, stress, apoptosis and necrosis may cause plasma membrane to release MPs. Cell communication involves membrane-derived EVs through different mechanisms. It should be known that the process equips the premise that EVs directly stimulate cells as a kind of signaling complex. In addition, membrane receptors, proteins, mRNA, and organelles are objects to transfer between cells. EVs deliver infectious agents into cells. Because platelets lack a nucleus, aspirin has a brief half-life (about 20 minutes), but its irreversible inhibition of platelet COX-1 lasts throughout the duration of the platelet (five to ten days). This means that the practically total reduction of platelet

COX-1 activity (>97%) by low-dose aspirin administered once daily can be explained by irreversible enzyme inactivation in a nucleated cell with a lengthy lifespan *in vivo*. Platelet-derived MPs can transfer specific microRNAs to cancer cells in vitro and *in vivo*, thus promoting phenotypic changes [11]. In contrast, the irreversible inhibition of aspirin will recover fast to effect on COX activity through protein synthesis in a nucleated cell, thus the result of this property is that it is essential to obtain an adequate inhibitory effect by daily dosing many times prostaglandins generation, translating into therapeutic effects. Existing experiments have shown that there wasn't any aspirin-inhibitory effect on colon cancer cells constitutively expressing COX-2 until the drug exposure lasted for 24 h to completely recovered the irreversible inhibition of activity of COX-2. This was followed by the regulation migration, cell division and death. Although once daily low-dose aspirin administration is unlikely to directly block COX-2-dependent prostaglandins generation in nucleated cells, it would be necessary for anticancer effects. From all above, by preventing platelet activation and the release of several chemicals, low-dose aspirin can influence COX-2 expression in stromal cells and cancer cells [11]. These lines of evidence provide a support of the function that platelets play in stimulating early carcinogenic signaling pathways that aspirin inhibits.

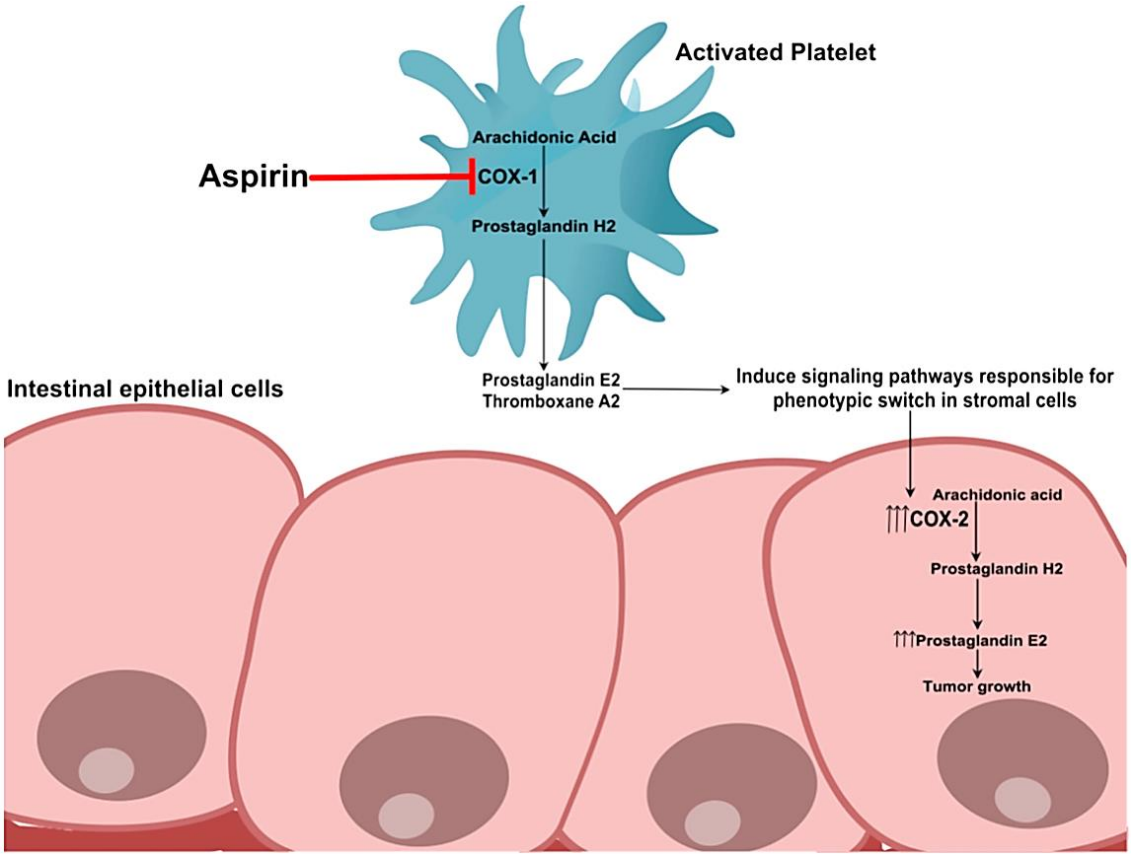

Figure 1. Platelet hypothesis [12].

2.3. Enzymes

A class of enzymes known as cyclooxygenases is involved in the manufacture of prostaglandins from arachidonic acid, which includes different prostaglandins (PGs) and thromboxane A2 (TXA2). PGE2 is a kind of prostaglandins play a part in inflammatory responses, although TXA2 mainly participates in aggregation of platelets. There is something distinct between the two COX enzymes, the overexpression of COX-2 overexpression is linked to the advancement of cancer and the biggest difference that COX-2 has with COX-1 is not normally in many cell types. However, COX-1 can be found in platelets, which is constitutively present in all cell types. But as it was already noted, COX-2 expression is upregulated in inflammatory and other pathological settings, such cancer. According to its involvement in cancer, it is possible that inhibition of COX-2 plays an important role in aspirin's anti-cancer actions. By associating the relationship between COX-1 and COX-2, various steps can be

taken to indirectly lower the overexpression of COX-2 due to the inhibition effect of COX-1 in platelets, given that low-dose aspirin is just as effective as higher doses in preventing colorectal cancer [12], as shown in Figure 1.

It is known that the aggregation and activation of platelets in the colorectal tissues cause the tumor advancement at the site of intestinal damage [12]. Activation of platelets can lead to the release prostaglandin (PGE2) and growth factors from platelets, in this way the growth of stromal cell growth may occur with the induction of expression in COX-2 in intestinal cells of the colonic mucosa. The final consequence is neoplastic phenotype development after the changes, higher prostaglandin generation may cause hyperplasia, the epithelial-mesenchymal transition. The capacity of aspirin to suppress platelet aggregation by inhibiting COX-1, which in turn inhibits TXA2, is thought to be essential to its ability to prevent colorectal cancer. The release of growth factors and lipid mediators from platelets, which would otherwise cause the production of COX-2 and be linked to carcinogenesis, is prevented when platelet aggregation is prevented. According to this theory, aspirin prevents cancer by first inhibiting the expression of COX-1 in platelets and then inhibiting the expression of COX-2 in nearby nucleated cells of the intestinal mucosa [12].

3. Effects

3.1. Positive effect

Whatever the clinical settings or research, aspirin has already been proved that there are many potential effects on cancer cells. It is worth paying attention that one significant impact is suppressing the tumor growth as its capacity. Through mechanisms such as inducing apoptosis and interfering with cell cycle progression, aspirin may reduce the proliferation of cancer cells. In addition, anti-inflammatory properties play a crucial role in decreasing the tumor-promoting environment. This will lead to a relatively lower risk of advancement of cancers. To prevent the cancer cell from spreading to the rest parts of the body by targeting pathways involved in cell migration and invasion. When combining with other therapies, aspirin will show the huge potential to enhance effect of the treatment and improve the patients' situations.

3.2. Side effect

It is essential to be aware of its potential side effects. It is so common that aspirin can cause gastrointestinal discomfort as its side effects, also include nausea, vomiting, and indigestion. More dangerously, when using large doses of aspirin, especially over prolonged periods of time, stomach bleeding or ulcers may occur. For some certain people, aspirin allergies can occur and present as rashes, swelling, or itching, and these allergies can develop into anaphylaxis, a potentially fatal reaction in extreme situation. As the description above, platelets aggregating can be prevented by aspirin, which raises the possibility of bleeding, particularly in patients who have bleeding disorders or during surgery. Long-term use may have an impact on renal function, especially in people who have the regarding diseases and it is danger to face blood pressure elevation and fluid retention. For other special groups, children or teenagers, they should never be given aspirin after recovering from viral infections, such as the flu or chickenpox due to the risk of Reye's syndrome, a rare but serious illness that could make people get liver and brain damage.

4. Conclusion

During cancer prevention and treatment, it is obvious that there is much potential of aspirin through multiple mechanisms. Its ability to cause anti- cancer effects exhibits in inducing apoptosis, suppressing cell proliferation, and interfering with critical signaling pathways. By modulating the expression of noncoding RNAs and influencing pathways such as Wnt/β-catenin and STAT3, gene expression can be altered in cancer cells by aspirin, thereby suppressing tumor growth and metastasis. Moreover, aspirin does well in inhibiting platelet aggregation, as the growth factors and some

mediators participate into the promotion of tumor progression importantly and in this way, it reduces the release of these two components successfully. Due to the indirect induction of COX-2 expression in epithelial cells, its anti-cancer properties will be further effective. While aspirin's therapeutic benefits are compelling, considering the possibility of side effects is still important, including gastrointestinal discomfort, bleeding risks and allergic reactions. Long-term use warrants caution, particularly in some case, such as children recovering from viral infections.

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