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Review

Aspirin in pancreatic cancer: chemopreventive effects and therapeutic potentials

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ABSTRACT

Pancreatic cancer is one of the most aggressive malignancies with dismal prognosis. Recently, aspirin has been found to be an effective chemopreventive agent for many solid tumors. However, the function of aspirin use in pancreatic cancer largely remains unknown. We herein argued that aspirin could also lower the risk of pancreatic cancer. Importantly, aspirin assumes pleiotropic effects by targeting multiple molecules. It could further target the unique tumor biology of pancreatic cancer and modify the cancer microenvironment, thus showing remarkable therapeutic potentials. Besides, aspirin could reverse the chemoradiation resistance by repressing tumor repopulation and exert synergistic potentials with metformin on pancreatic cancer chemoprevention. Moreover, aspirin secondarily benefits pancreatic cancer patients through modestly reducing cancer pain and the risk of venous thromboembolism. Furthermore, new aspirin derivatives and delivery systems might help to improve risk-to-benefit ratio. In brief, aspirin is a promising chemopreventive agent and exerts significant therapeutic potentials in pancreatic cancer.

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1. Introduction

Pancreatic cancer is one of the most aggressive malignancies, ranking as the 4th highest cancer-related mortality in America [1]. Particularly, the incidence of pancreatic cancer still keeps increasing meanwhile some other cancers' morbidity is decreasing conversely [1]. According to the Pancreatic Cancer Action Network, pancreatic cancer is projected to become the second leading cause of cancer-related death by 2030 [2]. Despite decades of efforts, the 5-year survival rate of pancreatic cancer remains only ~5% [3]. Even though surgery offers the only chance of cure, most patients miss the opportunity due to locally unresectable or distant metastasis. Even worse, the majority of patients who underwent resection will still recur locally or distantly soon [3]. Besides, pancreatic cancer is markedly resistant to chemo- or radiotherapy, although gemcitabine showed some marginally benefits. Due to difficulties in early diagnosis, poor response to treatments and high mortality, the prophylaxis of pancreatic cancer comes to the stage. Recently, several studies have revealed that chemotherapeutic agent combinations targeting variant hallmarks of pancreatic cancer enhanced the treatment efficacy [4,5], which expands our view to explore more suitable combinations of anti-cancer drugs, or to find out agents to target multiple hallmarks for targeting therapy of pancreatic cancer.

Aspirin (acetylsalicylic acid), a non-steroidal anti-inflammatory drug (NSAID), has been widely used for analgesia, antipyresis, anti-inflammation and anti-platelet. Recently, mounting experimental, epidemiological, and clinical evidences have revealed that aspirin is a promising chemopreventive agent for several cancers, including colorectal cancer [6], esophageal cancer [7], stomach cancer [8], lung cancer [9], and prostate cancer [10]. Further, aspirin could reduce the risk of distant metastasis and the long-term risk of death for adenocarcinoma after a latency period of at least 5 years [11–13]. Meanwhile, short-term of daily aspirin use (from 3 years onwards) was also revealed to reduce the cancer incidence and mortality [14]. Recently, a new recommendation around the use of aspirin for prevention of colorectal cancer has been released [15]. Regular aspirin use after the diagnosis of colorectal cancer is associated with lower risk of colorectal cancer-specific and overall mortality [16]. Besides, aspirin also assumes therapeutic potentials by targeting suppression of tumor growth and angiogenesis, induction of apoptosis, reversion of tumor promoting microenvironment, inhibition of metastasis, *etc.* [17–22].

However, less attention was paid to the role of aspirin use in pancreatic cancer. Hereinafter, we will systematically discuss its chemopreventive effects and therapeutic potentials in pancreatic cancer, reveal the underlying mechanisms, and distinguish its effect in reversing chemoradiation resistance and enhancing immunotherapy efficacy. Moreover, due to the fact that aspirin and metformin may target key molecules and risk factors of pancreatic cancer in different manners, we will quest their potential synergistic effect in pancreatic cancer. Further, we will explore its benefits of modestly reducing the pancreatic cancer pain and the risk of related venous thromboembolism more than the anti-tumor effect, and finally seek for the strategies to gain higher risk-to-benefit ratio.

2. The chemopreventive effects of aspirin in pancreatic cancer

Over two decades ago, it was first found that aspirin showed a tendency to decrease pancreatic tumor incidence in N-nitrosobis(2-oxopropyl)amine (BOP)-treated hamsters [23]. In the azaserine-treated rat model, aspirin was found to reduce the number, volume and diameter of pancreatic atypical acinar cell foci [24]. Moreover, Fendrich V *et al.* found that aspirin was able to significantly delay the development of mPanINs (murine pancreatic intraepithelial neoplasia) in LSL-Kras^{G12D}/Pdx1-Cre (KC) mice and partially inhibit the progression of invasive pancreatic cancer in LSL-Kras^{G12D}/LSL-Trp53^{R172H}/Pdx1-Cre (KPC) transgenic mice [25]. However, evidences from the clinical data were somewhat controversial (Table 1). Among the 15 clinical studies or analyses, five endorsed the protective effect of aspirin use in pancreatic cancer [11,26–29], one indicated the harmful effect [30], and the others deemed no significant correlation [31–39]. Noteworthily, the Nurse's Health Study that showed the harmful effect of aspirin use only followed up for 18 years [30]. But as the Nurses' Health Study combined with Health Professionals Follow-up Study and prolonged its follow-up to 32 years, it was found that there was no significant correlation between aspirin use and pancreatic cancer (relative risk (RR) = 0.95; 95% CI, 0.80–1.12) [39]. Nevertheless, the latest meta-analysis of the late 15 years' observational studies enrolling approximately 258,000 participants, revealed that the administration of aspirin rather than other NSAIDs significantly reduced the incidence of pancreatic cancer (odds ratio (OR) = 0.77; 95% CI, 0.62–0.96) [40]. Remarkably, Rothwell's analysis revealed that regular aspirin use resulted in a significant reduction of death rate in pancreatic cancer after a latency period of about 5 years (hazard ratio (HR) = 0.25; 95% CI, 0.07–0.92) [11].

As known, in particular to the pancreatic cancer biology, it usually takes at least a decade for pancreatic cells to initiate the mutation(s) for breeding the parental, non-metastatic founder cells, another five more years for the acquisition of metastatic ability, and an average of two more years for patient death [41]. Thus, aspirin use within the late 10 ~ 15 years might just slow down the tumorigenesis process rather than prevent it. Notably, most conclusions were drawn from the re-analysis of the researches that were initially supposed to testify the efficacy of aspirin as a cardiovascular prophylactic and/or analgesic agent, in which the dose of aspirin use and its intake frequency were relatively low. However, higher dose and more intensive frequency of aspirin use, which are essential for anti-inflammation and suppressing PTGS (prostaglandin-endoperoxide synthase, also known as COX (cyclooxgenase))-independent targets, were not studied in most researches. Apparently, it is necessary to evaluate the effect of relatively higher dose of aspirin use in pancreatic cancer. Recently, a meta-analysis revealed that the higher (OR = 0.88; 95% CI, 0.76–1.01) rather than the lower (OR = 0.99; 95% CI, 0.91–1.07) dose of aspirin intake was marginally associated with a decreased risk of pancreatic cancer [42]. Hence, further efforts should be made to explore the chemopreventive effects as well as the dose, frequency and duration of aspirin use for a better clinical practice.

Particularly recently, molecular pathological epidemiology, which has emerged as the transdisciplinary integration of molecular pathology and epidemiology, sheds light on the investigation of aspirin as an anti-cancer agent [43]. The efficacy of aspirin in colorectal cancer prevention differs along with the genetic variations, including *PTGS2 (COX2)* [44], *HPGD* (hydroxyprostaglandin dehydrogenase 15-(NAD)) [45] or HLA (major histocompatibility complex) class I antigen [46] overexpression, *PIK3CA* (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) mutation [47], and *BRAF* (B-Raf proto-oncogene, serine/