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MINIREVIEWS

Anti-tumor effect of statin on pancreatic adenocarcinoma: From concept to precision medicine

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Abstract

A statin is a cholesterol-lowering agent, which inhibits HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase and subsequently reduces the cholesterol precursor, and was first used commercially in 1987. The concept of cholesterol restriction leading to cancer cell dysfunction was proposed in 1992. The interruption of different signaling pathways has been proved in preclinical experiments to elucidate the anti-tumor mechanism of statins in pancreatic adenocarcinoma. Observational studies have shown that the clinical use of statins is beneficial in patients with pancreatic adenocarcinoma, including a chemo-prevention effect, post-surgical resection follow-up and therapeutic prognosis of advanced cancer stage. Arrest of the cancer cell cycle by the combined use of gemcitabine and statin was observed in a cell line study. The effect of microbiota on the tumor microenvironment of pancreatic adenocarcinoma is a new therapeutic approach as statins can modulate the gut microbiota. Hence, further randomized trials of statins in pancreatic adenocarcinoma treatment will be warranted with application of precision medicine from microbiota-derived, cell cycle-based and signaling pathway-targeted research.

Key Words: Statin; Pancreatic cancer; Precision medicine; Anti-tumor; Pancreatic adenocarcinoma

Core Tip: A statin is a cholesterol-lowering agent, which inhibits HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase and subsequently reduces the

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cholesterol precursor, and was first used commercially in 1987. This is a mini-review of statin use in pancreatic adenocarcinoma, focusing on the therapeutic effect. A search of relevant literature from 1992 to 2021 was conducted. The effect of microbiota on the tumor microenvironment of pancreatic adenocarcinoma is a new therapeutic approach as statins can modulate the gut microbiota.

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INTRODUCTION

The most common type of pancreatic cancer is adenocarcinoma, an extremely lethal cancer, with a 5-year survival rate of less than 10%[1,2]. With its incidence rising, pancreatic adenocarcinoma is currently the third leading cause of cancer-related death in the United States and estimated to become the second leading cause of cancer-related death by 2030[2-4]. The predominant causes of its lethality include it is rarely diagnosed in the early stage, aggressive nature of cancer cells, metastasis-prone anatomic location with rich surrounding vessels, non-capsulated organ structure, and lack of effective chemo-pharmacological interventions for advanced-stage cancer. At present, the predominant chemotherapy for pancreatic adenocarcinoma is gemcitabine, an analog of deoxycytidine, which shows cytotoxic effects by blocking cellular DNA synthesis[5,6]. For several decades, gemcitabine monotherapy has been used as the first-line treatment for patients with metastatic pancreatic cancer[7]. However, the clinical beneficial response to gemcitabine in pancreatic adenocarcinoma patients is only 20% to 30%[8]. Thus, to increase the therapeutic success rate, new anti-tumor approaches for pancreatic adenocarcinoma have been widely studied and a statin is a potential agent. Statins are used to lower cholesterol level by inhibiting HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase, which is a rate-limiting enzyme in the synthesis of mevalonate, a precursor of cholesterol. The first commercial statin, lovastatin, was approved by the US Food and Drug Administration in 1987[9].

This article is a review of related literature from the PubMed database, owned by the US National Library of Medicine. The search was made using two key words, statin and pancreatic cancer. In May 1992, an article entitled "Cholesterol inhibition, cancer, and chemotherapy" published in the *Lancet*[10] proposed the novel concept of cancer cell growth inhibited by cholesterol restriction. This hypothesis was raised according to a finding that cell malignant transformation requires cholesterol or its precursor. In September of the same year, a basic study using a pancreatic cancer cell line model found that statin hinders growth of cancer cells[11]. In 1995, another basic study using the yeast, *Saccharomyces cerevisiae*, was conducted to prove that the RAS mRNA level could be controlled through the mevalonate pathway[12]. This yeast study found that depletion of intracellular mevalonate would result in decreased levels of Ras1p and Ras2p, an effect mediated by mRNA accumulation. This finding can account for the possible anti-tumor mechanism of statin because overactive RAS protein signaling is associated with the growth of cancers, including pancreatic adenocarcinoma. Subsequently, the results of several cell-line studies all supported inhibition of pancreatic adenocarcinoma cell growth by statin[13-16]. A milestone study published in 2001 reported epidermal growth factor-induced pancreatic cancer cell invasion in humans inhibited by fluvastatin or lovastatin in a dose-dependent manner[14]. In 2002, a review article summarized that apoptosis of leukemia cells triggered by statin is related to down-regulation of bcl-2 expression in transformed cells and partially due to depletion of the downstream product geranylgeranyl pyrophosphate, not farnesyl pyrophosphate or other products of the mevalonate pathway including cholesterol[17]. Between 2000 and 2010, several review articles examined the anti-tumor effect of statin on various types of malignancies, including melanoma, breast cancer, gynecologic cancer, prostate cancer, lung cancer and colon cancer[18-21]. However, these observational studies only concluded that statin use is associated with a lower incidence of malignancy, especially the cancers mentioned above[18].

From the pathophysiological viewpoint, cholesterol plays the connecting role between statin and pancreatic adenocarcinoma. Cholesterol and its precursors are essential for cellular signaling and cell membrane stability[22,23]. Mevalonate, a precursor of cholesterol, is required for the stable synthesis of Ras protein[12]. Ras is a prototypical member of the Ras superfamily of proteins which regulate cellular function and behavior such as growth, differentiation or survival. There are three Ras oncogenes, HRas, KRas, and NRas, commonly found in human cancers[24,25]. Approximately 19% of cancer patients harbor Ras mutations[26]. In pancreatic duct adenocarcinoma, the frequency of Ras mutation is extremely high, generally exceeding 90%[27]. Hence, it is reasonable to postulate that statin, which blocks the synthesis of mevalonate, would hinder the production of Ras protein, including mutated Ras. Decreased Ras protein will lead to delayed growth of pancreatic adenocarcinoma cells.

The first large-scale clinical retrospective case-control study of statin and the incidence of pancreatic adenocarcinoma was conducted in the United States. The results published in 2007 concluded that statins seem to be protective against the development of pancreatic cancer. These valuable results need to be further clarified by basic research. In 2012, a milestone animal study found that statin significantly delayed the progression of pancreatic intra-epithelial neoplasm to adenocarcinoma by modulating phosphatidylinositol 3-kinase (PI3/AKT) signaling molecules[28]. Another study in 2013 reported similar findings of statin inhibiting pancreatic carcinogenesis and increasing survival in a mouse model. Statins can inhibit the prenylation of KRas protein, and modulate many other genes[29]. According to these animal models, it is reasonable to presume that statin benefits early-stage pancreatic adenocarcinoma or has a chemoprevention effect. In 2015, a clinical case-control study showed a correlation between the use of statin and a lower incidence of pancreatic adenocarcinoma[30]. In the same year, a retrospective cohort study involving 206 patients found that baseline use of moderate- and high-dose simvastatin was associated with improved overall and disease-free survival among patients undergoing resection of pancreatic cancer[31]. Another large-scale clinical study in 2015 reported that statin use benefited only early-stage pancreatic cancer[32]. For inoperable advanced pancreatic adenocarcinoma, statin is also related to favorable disease prognosis[33-37]. A recent pancreatic cancer cell line study showed that gemcitabine and pitavastatin synergistically suppressed the proliferation of cancer cells by causing sub-G1 and S-phase cell cycle arrest[38]. However, there was still uncertainty regarding the optimal timing of use and which stage of pancreatic cancer would benefit most from the anti-tumor effect of statin[39]. Hence, further precise studies are needed to define the characteristics of pancreatic cancer patients who would benefit from statin therapy[40].

Microbiota can provide a useful lead for precise selection of pancreatic adenocarcinoma patients suitable for statin treatment. Accumulated evidence showed involvement of the gut microbiota in the metabolism of chemotherapeutic agents and the tumor microenvironment in pancreatic cancer[41-43]. The association between gut microbial dysbiosis and pancreatic cancer was postulated by the pathogenesis of chronic pancreatitis[44]. The rationale is gut dysbiosis contributing to chronic pancreatitis, which increases the risk for developing pancreatic cancer. There is evidence of statin therapy associated with a lower prevalence of gut microbiota dysbiosis, like the Bact2 dysbiotic microbiome constellation[45]. The tumor microenvironment is a new target for treatment of pancreatic adenocarcinoma[46]. The anti-tumor effect of statin on pancreatic cancer is probably through the mechanism of ferroptosis which involves the iron-dependent form of regulated cell death[47,48]. The treatment of pancreatic adenocarcinoma can be approached by the molecular subtypes of cancer tissue as well as the genotype-oriented intervention. The application of molecular pathology can be used to predict treatment response, and the risk of distant metastasis[34,49-53].

CONCLUSION

In conclusion, statin treatment for pancreatic adenocarcinoma works through various anti-tumor mechanisms and experiments have progressed from pre-clinical to clinical studies in the past three decades since 1992 (Table 1). More large-scale clinical randomized trials with the precise application of statin for the treatment of pancreatic adenocarcinoma are required.

Table 1 Timeline for the anti-tumor effect of statin on pancreatic adenocarcinoma

Year	Event	Significance for the anti-tumor effect of statin
1987	First commercial use of statin[9]	
1992	First study article of statin and pancreatic adenocarcinoma cells[11]	Anti-tumor effect of statin proved
1995	Association between ras protein and the mevalonate pathway[12]	Mechanism
2001	Association between epidermal growth factor and statin[14]	Mechanism
2000-2010	Review articles for statin and cancers[18-21]	Widely accepted for anti-tumor effect of statin
2020	Association between statin and cell cycle of pancreatic adenocarcinoma[38]	Mechanism
2011-2020	Statin modulates gut microbiota which affects the tumor microenvironment[40-48]	Big data, precision medicine

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