**Name of Journal:** *World Journal of Clinical Cases*

**Manuscript NO:** 63277

**Manuscript Type:** MINIREVIEWS

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

Huang CT *et al*. Effect of statin on pancreatic cancer

Chung-Tsui Huang, Yao-Jen Liang

**Chung-Tsui Huang,** Department of Gastroenterology and Hepatology, Far Eastern Memorial Hospital, New Taipei 220, Taiwan

**Yao-Jen Liang,** Graduate Institute of Applied Science and Engineering, Department and Institute of Life Science, Fu-Jen University, New Taipei 242, Taiwan

**Author** **contributions:** Huang CT wrote the manuscript; Liang YJ contributed to teaching physician Huang CT regarding the idea, title and how to research papers for the review article.

**Corresponding author: Yao-Jen Liang, PhD, Professor,** Graduate Institute of Applied Science and Engineering, Department and Institute of Life Science, Fu-Jen University, No. 510 Zhongzheng Road, Xinzhuang District, New Taipei 242, Taiwan. 071558@mail.fju.edu.tw

**Received:** January 27, 2021

**Revised:** March 11, 2021

**Accepted:** March 31, 2021

**Published online:**

**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 chemoprevention 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

Huang CT, Liang YJ. Anti-tumor effect of statin on pancreatic adenocarcinoma: From concept to precision medicine. *World J Clin Cases* 2021; In press

**Core Tip: A s**tatin 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.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.

**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.

**REFERENCES**

1 **Siegel RL**, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 7-30 [PMID: 31912902 DOI: 10.3322/caac.21590]

2 **Miller KD**, Fidler-Benaoudia M, Keegan TH, Hipp HS, Jemal A, Siegel RL. Cancer statistics for adolescents and young adults, 2020. *CA Cancer J Clin* 2020; **70**: 443-459 [PMID: 32940362 DOI: 10.3322/caac.21637]

3 **McGuigan A**, Kelly P, Turkington RC, Jones C, Coleman HG, McCain RS. Pancreatic cancer: A review of clinical diagnosis, epidemiology, treatment and outcomes. *World J Gastroenterol* 2018; **24**: 4846-4861 [PMID: 30487695 DOI: 10.3748/wjg.v24.i43.4846]

4 **Rahib L**, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014; **74**: 2913-2921 [PMID: 24840647 DOI: 10.1158/0008-5472.CAN-14-0155]

5 **Plunkett W**, Huang P, Xu YZ, Heinemann V, Grunewald R, Gandhi V. Gemcitabine: metabolism, mechanisms of action, and self-potentiation. *Semin Oncol* 1995; **22**: 3-10 [PMID: 7481842]

6 **Mini E**, Nobili S, Caciagli B, Landini I, Mazzei T. Cellular pharmacology of gemcitabine. *Ann Oncol* 2006; **17 Suppl 5**: v7-12 [PMID: 16807468 DOI: 10.1093/annonc/mdj941]

7 **Thota R**, Pauff JM, Berlin JD. Treatment of metastatic pancreatic adenocarcinoma: a review. *Oncology (Williston Park)* 2014; **28**: 70-74 [PMID: 24683721]

8 **Heinemann V**. Gemcitabine: progress in the treatment of pancreatic cancer. *Oncology* 2001; **60**: 8-18 [PMID: 11150902 DOI: 10.1159/000055290]

9 **Endo A**. A historical perspective on the discovery of statins. *Proc Jpn Acad Ser B Phys Biol Sci* 2010; **86**: 484-493 [PMID: 20467214 DOI: 10.2183/pjab.86.484]

10 **Buchwald H**. Cholesterol inhibition, cancer, and chemotherapy. *Lancet* 1992; **339**: 1154-1156 [PMID: 1349377 DOI: 10.1016/0140-6736(92)90744-n]

11 **Sumi S**, Beauchamp RD, Townsend CM Jr, Uchida T, Murakami M, Rajaraman S, Ishizuka J, Thompson JC. Inhibition of pancreatic adenocarcinoma cell growth by lovastatin. *Gastroenterology* 1992; **103**: 982-989 [PMID: 1499946 DOI: 10.1016/0016-5085(92)90032-t]

12 **Dimster-Denk D**, Schafer WR, Rine J. Control of RAS mRNA level by the mevalonate pathway. *Mol Biol Cell* 1995; **6**: 59-70 [PMID: 7749195 DOI: 10.1091/mbc.6.1.59]

13 **Müller C**, Bockhorn AG, Klusmeier S, Kiehl M, Roeder C, Kalthoff H, Koch OM. Lovastatin inhibits proliferation of pancreatic cancer cell lines with mutant as well as with wild-type K-ras oncogene but has different effects on protein phosphorylation and induction of apoptosis. *Int J Oncol* 1998; **12**: 717-723 [PMID: 9472115 DOI: 10.3892/ijo.12.3.717]

14 **Kusama T**, Mukai M, Iwasaki T, Tatsuta M, Matsumoto Y, Akedo H, Nakamura H. Inhibition of epidermal growth factor-induced RhoA translocation and invasion of human pancreatic cancer cells by 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors. *Cancer Res* 2001; **61**: 4885-4891 [PMID: 11406567]

15 **Kusama T**, Mukai M, Iwasaki T, Tatsuta M, Matsumoto Y, Akedo H, Inoue M, Nakamura H. 3-hydroxy-3-methylglutaryl-coenzyme a reductase inhibitors reduce human pancreatic cancer cell invasion and metastasis. *Gastroenterology* 2002; **122**: 308-317 [PMID: 11832446 DOI: 10.1053/gast.2002.31093]

16 **Mistafa O**, Stenius U. Statins inhibit Akt/PKB signaling *via* P2X7 receptor in pancreatic cancer cells. *Biochem Pharmacol* 2009; **78**: 1115-1126 [PMID: 19540829 DOI: 10.1016/j.bcp.2009.06.016]

17 **Wong WW**, Dimitroulakos J, Minden MD, Penn LZ. HMG-CoA reductase inhibitors and the malignant cell: the statin family of drugs as triggers of tumor-specific apoptosis. *Leukemia* 2002; **16**: 508-519 [PMID: 11960327 DOI: 10.1038/sj.leu.2402476]

18 **Boudreau DM**, Yu O, Johnson J. Statin use and cancer risk: a comprehensive review. *Expert Opin Drug Saf* 2010; **9**: 603-621 [PMID: 20377474 DOI: 10.1517/14740331003662620]

19 **Demierre MF**, Higgins PD, Gruber SB, Hawk E, Lippman SM. Statins and cancer prevention. *Nat Rev Cancer* 2005; **5**: 930-942 [PMID: 16341084 DOI: 10.1038/nrc1751]

20 **Sleijfer S**, van der Gaast A, Planting AS, Stoter G, Verweij J. The potential of statins as part of anti-cancer treatment. *Eur J Cancer* 2005; **41**: 516-522 [PMID: 15737555 DOI: 10.1016/j.ejca.2004.12.009]

21 **Jakobisiak M**, Golab J. Potential antitumor effects of statins (Review). *Int J Oncol* 2003; **23**: 1055-1069 [PMID: 12963986]

22 **Lyu J**, Yang EJ, Shim JS. Cholesterol Trafficking: An Emerging Therapeutic Target for Angiogenesis and Cancer. *Cells* 2019; **8** [PMID: 31035320 DOI: 10.3390/cells8050389]

23 **Cerqueira NM**, Oliveira EF, Gesto DS, Santos-Martins D, Moreira C, Moorthy HN, Ramos MJ, Fernandes PA. Cholesterol Biosynthesis: A Mechanistic Overview. *Biochemistry* 2016; **55**: 5483-5506 [PMID: 27604037 DOI: 10.1021/acs.biochem.6b00342]

24 **Murugan AK**, Grieco M, Tsuchida N. RAS mutations in human cancers: Roles in precision medicine. *Semin Cancer Biol* 2019; **59**: 23-35 [PMID: 31255772 DOI: 10.1016/j.semcancer.2019.06.007]

25 **Prior IA**, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. *Cancer Res* 2012; **72**: 2457-2467 [PMID: 22589270 DOI: 10.1158/0008-5472.CAN-11-2612]

26 **Prior IA**, Hood FE, Hartley JL. The Frequency of Ras Mutations in Cancer. *Cancer Res* 2020; **80**: 2969-2974 [PMID: 32209560 DOI: 10.1158/0008-5472.CAN-19-3682]

27 **Waters AM**, Der CJ. KRAS: The Critical Driver and Therapeutic Target for Pancreatic Cancer. *Cold Spring Harb Perspect Med* 2018; **8** [PMID: 29229669 DOI: 10.1101/cshperspect.a031435]

28 **Mohammed A**, Qian L, Janakiram NB, Lightfoot S, Steele VE, Rao CV. Atorvastatin delays progression of pancreatic lesions to carcinoma by regulating PI3/AKT signaling in p48Cre/+ LSL-KrasG12D/+ mice. *Int J Cancer* 2012; **131**: 1951-1962 [PMID: 22287227 DOI: 10.1002/ijc.27456]

29 **Liao J**, Chung YT, Yang AL, Zhang M, Li H, Zhang W, Yan L, Yang GY. Atorvastatin inhibits pancreatic carcinogenesis and increases survival in LSL-KrasG12D-LSL-Trp53R172H-Pdx1-Cre mice. *Mol Carcinog* 2013; **52**: 739-750 [PMID: 22549877 DOI: 10.1002/mc.21916]

30 **Walker EJ**, Ko AH, Holly EA, Bracci PM. Statin use and risk of pancreatic cancer: results from a large, clinic-based case-control study. *Cancer* 2015; **121**: 1287-1294 [PMID: 25649483 DOI: 10.1002/cncr.29256]

31 **Wu BU**, Chang J, Jeon CY, Pandol SJ, Huang B, Ngor EW, Difronzo AL, Cooper RM. Impact of statin use on survival in patients undergoing resection for early-stage pancreatic cancer. *Am J Gastroenterol* 2015; **110**: 1233-1239 [PMID: 26195180 DOI: 10.1038/ajg.2015.217]

32 **Jeon CY**, Pandol SJ, Wu B, Cook-Wiens G, Gottlieb RA, Merz CN, Goodman MT. The association of statin use after cancer diagnosis with survival in pancreatic cancer patients: a SEER-medicare analysis. *PLoS One* 2015; **10**: e0121783 [PMID: 25830309 DOI: 10.1371/journal.pone.0121783]

33 **Nakai Y**, Isayama H, Sasaki T, Mizuno S, Sasahira N, Kogure H, Kawakubo K, Yamamoto N, Hirano K, Ijichi H, Tateishi K, Tada M, Koike K. Clinical outcomes of chemotherapy for diabetic and nondiabetic patients with pancreatic cancer: better prognosis with statin use in diabetic patients. *Pancreas* 2013; **42**: 202-208 [PMID: 23000889 DOI: 10.1097/MPA.0b013e31825de678]

34 **Iarrobino NA**, Gill B, Bernard ME, Mishra MV, Champ CE. Targeting Tumor Metabolism With Statins During Treatment for Advanced-stage Pancreatic Cancer. *Am J Clin Oncol* 2018; **41**: 1125-1131 [PMID: 29509593 DOI: 10.1097/COC.0000000000000433]

35 **Tamburrino D**, Crippa S, Partelli S, Archibugi L, Arcidiacono PG, Falconi M, Capurso G. Statin use improves survival in patients with pancreatic ductal adenocarcinoma: A meta-analysis. *Dig Liver Dis* 2020; **52**: 392-399 [PMID: 32113888 DOI: 10.1016/j.dld.2020.01.008]

36 **Abdel-Rahman O**. Statin treatment and outcomes of metastatic pancreatic cancer: a pooled analysis of two phase III studies. *Clin Transl Oncol* 2019; **21**: 810-816 [PMID: 30465184 DOI: 10.1007/s12094-018-1992-3]

37 **Hamada T**, Khalaf N, Yuan C, Morales-Oyarvide V, Babic A, Nowak JA, Qian ZR, Ng K, Rubinson DA, Kraft P, Giovannucci EL, Stampfer MJ, Fuchs CS, Ogino S, Wolpin BM. Prediagnosis Use of Statins Associates With Increased Survival Times of Patients With Pancreatic Cancer. *Clin Gastroenterol Hepatol* 2018; **16**: 1300-1306.e3 [PMID: 29474971 DOI: 10.1016/j.cgh.2018.02.022]

38 **Chen YH**, Chen YC, Lin CC, Hsieh YP, Hsu CS, Hsieh MC. Synergistic Anticancer Effects of Gemcitabine with Pitavastatin on Pancreatic Cancer Cell Line MIA PaCa-2 *in vitro* and in vivo. *Cancer Manag Res* 2020; **12**: 4645-4665 [PMID: 32606957 DOI: 10.2147/CMAR.S247876]

39 **Karavias D**, Thomas P, Koh A, Irving G, Navarro AP, Cameron IC, Gomez D; Nottingham HPB Surgery Group. Statin therapy does not influence the outcome of patients undergoing surgery for pancreatic cancer. *ANZ J Surg* 2020; **90**: 1671-1676 [PMID: 31845479 DOI: 10.1111/ans.15600]

40 **Longo J**, van Leeuwen JE, Elbaz M, Branchard E, Penn LZ. Statins as Anticancer Agents in the Era of Precision Medicine. *Clin Cancer Res* 2020; **26**: 5791-5800 [PMID: 32887721 DOI: 10.1158/1078-0432.CCR-20-1967]

41 **Zhang X**, Liu Q, Liao Q, Zhao Y. Pancreatic Cancer, Gut Microbiota, and Therapeutic Efficacy. *J Cancer* 2020; **11**: 2749-2758 [PMID: 32226493 DOI: 10.7150/jca.37445]

42 **Ammer-Herrmenau C**, Pfisterer N, Weingarten MF, Neesse A. The microbiome in pancreatic diseases: Recent advances and future perspectives. *United European Gastroenterol J* 2020; **8**: 878-885 [PMID: 32703080 DOI: 10.1177/2050640620944720]

43 **Wei X**, Mei C, Li X, Xie Y. The Unique Microbiome and Immunity in Pancreatic Cancer. *Pancreas* 2021; **50**: 119-129 [PMID: 33565788 DOI: 10.1097/MPA.0000000000001744]

44 **Akshintala VS**, Talukdar R, Singh VK, Goggins M. The Gut Microbiome in Pancreatic Disease. *Clin Gastroenterol Hepatol* 2019; **17**: 290-295 [PMID: 30144522 DOI: 10.1016/j.cgh.2018.08.045]

45 **Vieira-Silva S**, Falony G, Belda E, Nielsen T, Aron-Wisnewsky J, Chakaroun R, Forslund SK, Assmann K, Valles-Colomer M, Nguyen TTD, Proost S, Prifti E, Tremaroli V, Pons N, Le Chatelier E, Andreelli F, Bastard JP, Coelho LP, Galleron N, Hansen TH, Hulot JS, Lewinter C, Pedersen HK, Quinquis B, Rouault C, Roume H, Salem JE, Søndertoft NB, Touch S; MetaCardis Consortium, Dumas ME, Ehrlich SD, Galan P, Gøtze JP, Hansen T, Holst JJ, Køber L, Letunic I, Nielsen J, Oppert JM, Stumvoll M, Vestergaard H, Zucker JD, Bork P, Pedersen O, Bäckhed F, Clément K, Raes J. Statin therapy is associated with lower prevalence of gut microbiota dysbiosis. *Nature* 2020; **581**: 310-315 [PMID: 32433607 DOI: 10.1038/s41586-020-2269-x]

46 **McGregor GH**, Campbell AD, Fey SK, Tumanov S, Sumpton D, Blanco GR, Mackay G, Nixon C, Vazquez A, Sansom OJ, Kamphorst JJ. Targeting the Metabolic Response to Statin-Mediated Oxidative Stress Produces a Synergistic Antitumor Response. *Cancer Res* 2020; **80**: 175-188 [PMID: 31562248 DOI: 10.1158/0008-5472.CAN-19-0644]

47 **Chen X**, Kang R, Kroemer G, Tang D. Broadening horizons: the role of ferroptosis in cancer. *Nat Rev Clin Oncol* 2021 [PMID: 33514910 DOI: 10.1038/s41571-020-00462-0]

48 **Chen X**, Yu C, Kang R, Kroemer G, Tang D. Cellular degradation systems in ferroptosis. *Cell Death Differ* 2021 [PMID: 33462411 DOI: 10.1038/s41418-020-00728-1]

49 **Khan AA**, Liu X, Yan X, Tahir M, Ali S, Huang H. An overview of genetic mutations and epigenetic signatures in the course of pancreatic cancer progression. *Cancer Metastasis Rev* 2021; **40**: 245-272 [PMID: 33423164 DOI: 10.1007/s10555-020-09952-0]

50 **Bengtsson A**, Andersson R, Rahm J, Ganganna K, Andersson B, Ansari D. Organoid technology for personalized pancreatic cancer therapy. *Cell Oncol (Dordr)* 2021; **44**: 251-260 [PMID: 33492660 DOI: 10.1007/s13402-021-00585-1]

51 **Shiihara M**, Ishikawa T, Saiki Y, Omori Y, Hirose K, Fukushige S, Ikari N, Higuchi R, Yamamoto M, Morikawa T, Nakagawa K, Hayashi H, Mizuma M, Ohtsuka H, Motoi F, Unno M, Okamura Y, Kinoshita K, Furukawa T. Development of a system combining comprehensive genotyping and organoid cultures for identifying and testing genotype-oriented personalised medicine for pancreatobiliary cancers. *Eur J Cancer* 2021; **148**: 239-250 [PMID: 33752134 DOI: 10.1016/j.ejca.2021.01.047]

52 **Karamitopoulou E**. Tumour microenvironment of pancreatic cancer: immune landscape is dictated by molecular and histopathological features. *Br J Cancer* 2019; **121**: 5-14 [PMID: 31110329 DOI: 10.1038/s41416-019-0479-5]

53 **Hilmi M**, Cros J, Puleo F, Augustin J, Emile JF, Svrcek M, Hammel P, Arsenijevic T, Van Laethem JL, Bachet JB, Nicolle R. Tumour and stroma RNA signatures predict more accurately distant recurrence than clinicopathological factors in resected pancreatic adenocarcinoma. *Eur J Cancer* 2021; **148**: 171-180 [PMID: 33743485 DOI: 10.1016/j.ejca.2021.01.042]

**Footnotes**

**Conflict-of-interest statement:** There is no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/Licenses/by-nc/4.0/

**Manuscript source:** Unsolicited manuscript

**Peer-review started:** January 27, 2021

**First decision:** February 27, 2021

**Article in press:**

**Specialty type:** Medicine, research and experimental

**Country/Territory of origin:** Taiwan

**Peer-review report’s scientific quality classification**

Grade A (Excellent): 0

Grade B (Very good): B

Grade C (Good): 0

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Ogino S **S-Editor:** Gao CC **L-Editor:** Webster JR **P-Editor:**

**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 |