◎総　説

Oncogenes and tumor suppressor genes in pancreatic cancer

Koji Ochi, Naoki Matsumura, Mitsuko Ichimura, Takaaki Mizushima, Hideo Harada, Hideaki Hasuoka[1], Motohiro Yokoyama[2], Tetsuya Tsurumi[2], Fumihiro Mitsunobu[3], Yoshiro Tanizaki[3]

Dept Laboratory Medicine, Okayama University Medical School, Katsuyama Hospital[1], Okayama Red Cross Hospital[2], Misasa Medical Branch, Okayama University Medical School[3]

Abstract: Recent advances in molecular biology have revealed that a number of oncogenes (K-ras, erbB-2, and Met) and tumor suppressor genes (p53, p16, APC, and DCC) contribute to the development of pancreatic cancer. This paper reviewed the present knowledge of oncogenes and tumor suppressor genes relevant to pancreatic cancer. Further studies on molecular alterations in pancreatic cancer may lead to a better understanding of tumor biology, offering a possibility of development of new diagnostic and therapeutic approaches in the future.

Key Word: Pancreatic cancer, oncogene, tumor suppressor gene, genetic mutation

Introduction

Pancreatic cancer is an important cause of deaths from cancers in the developed countries including Japan. It has remained to elucidate its biological characteristics and also to establish the method for its early detection. Recent advances in molecular biology has revealed that a number of oncogenes and tumor suppressor genes contribute to the development of pancreatic cancer. Improvement in its prognosis may be enabled by early molecular diagnosis and gene-targeting treatment in the future. This paper reviews the present knowledge of oncogenes and tumor suppressor genes relevant to pancreatic cancer.

K-ras

Ras gene family consists of three kinds of genes: N-ras, H-ras, and K-ras. Each of the genes encode a 21-kDa protein with GTPase involved in cell growth and differentiation[1]. If K-ras was mutated, the protein seems to lose GTPase activity and thereby to affect the tumorigenic process by altering the signal transduction pathway across the membrane[2]. K-ras point mutation at codon 12 has been detected in 80-90% of pancreatic ductal adenocarcinoma[3-6].

In the model of colorectal carcinoma, ras mutations are considered to be associated with progression of the neoplastic process, because 10% of adnomas <1.0 cm in size have as compared with 50% of adenomas >1.0 cm in size have ras mutations[7]. In pancreatic cancer, K-ras mutation is not related to clinical course, metastasis, or prognosis[6,8]. K-ras point mutation is known to be often detected in the ductal cell hyperplasias adjacent to pancreatic cancer[9]. It is controversial whether these lesions are precancerous[9]. In animal models, weekly injection of nitrosamine induced K-ras mutations in 28% of hyperplastic lesions, 48% of papillary hyperplastic lesions, 78% of carcinomas-in-situ, and 80% of invasive cancers of the pancreas. These results suggested that K-ras mutation is an early event in the multi-step progression to pancreatic neoplasm[10].

K-ras mutations in pure pancreatic juice (PPJ) have been identified in attempts to diagnose pancreatic cancer in early stage[11-13]. Some investigators[14,15] reported that K-ras mutation in PPJ preceded the definitive diagnosis of pancreatic cancer. We also experienced a case of small pancreatic cancer diagnosed by serial follow-up studies promptly by a positive K-ras point mutation in PPJ[16]. However, K-ras mutation from PPJ was reported to be detected in 37-44% of patients with chronic pancreatitis[17,18], and long-term follow-up of patients with chronic pancreatitis revealed that no pancreatic cancer developed in mutation-positive patients[17]. Further studies are needed to explore the clinical implication of detection of K-ras mutations in the early diagnosis of pancreatic cancer.

erbB-2

The erbB-2 (Her-2/neu) oncogene encodes a transmembrane protein with homology to the epidermal growth factor receptor. The erbB-2 protein is overepressed in 25~58% of pancreatic cancers[19-23]. Frequency of erbB-2 protein overexpression depends on tumor differentiation. Lower expression of erbB-2 was observed in poorly differentiated adenocarcinoma than in moderate or well-differentiated adenocarcinoma[23,24]. As the erbB-2 protein is also overexpressed in mucinous hyperplasia of the pancreatic duct, the erbB-2 is suggested to be a potential mediator of growth factor-related signal transduction in pancreatic duct[24]. Overexpression of erbB-2 was reported to be inversely related to the survival of patients with pancreatic cancer[20].

The positive rate of serum c-erbB-2 protein was reported as from 25% to 35%[19,22]. Although Okada[22] reported that serum c-erbB-2 correlated with metastases and decreased survival rate in patients with pancreatic cancer, liver function influenced its serum levels[19].

Met

The c-Met oncogene encodes MET protein which is the receptor for hepatocyte growth factor (HGF)[25]. Although MET immunoreactiveity was mild in acinar, ductal, and islet cells of the normal pancreas was , it was intense in many of the duct-like cancer cell of human pancreatic adenocarcinoma was intense[26]. Since concomitant overexpreesion of HGF was observed in the pancreatic cancer, HGF is suggested to play a role in proliferation of pancreatic cancer as the autocrine or paracrine[26,27]. MET immunoreactivity leads to a significantly longer survival than negative/focal staining[28]. These data suggest that Met might have an important pathogenetic role during the early stages of development of pancreatic cancer[28].

p53

The p53 gene, which is localized on the short arm of chromosome 17, encodes p53 protein. The p53 protein is believed to play a prominent role in the regulation of cell cycles. After the identification of the p53, early observation suggested that p53 might function as an oncogene, because overexpression of p53 appeared to cause oncogenic transformation of cells. Several later studies, however, defined the normal function of the p53 to be anti-oncogenic because p53-null mice developed tumors much more[29,30]. The p53 gene is inactivated in diverse human cancers by allelic deletions, point mutations that result from amino-acid

substitutions, and rearrangement[31,32]. p53 gene mutations are observed in almost half of pancreatic adenocarcinomas[8].

Relationship between p53 mutations and survival in pancreatic carcinoma is controversia[8]. Redston et al.[33] found that there was no significant difference in overall survival between patients with and those without p53 mutations. In contrast, Nakamori et al.[34] found that the median survival (6.2 months) of the patients with p53 mutations was significantly shorter than that (15.0 months) of those without p53 mutations.

Immunohistochemical examination for p53 protein was known to be useful to detect p53 gene mutation, because mutated p53 protein had a considerably longer half-life than wild p53 protein. Further studies have revealed that p53 protein accumulation is not always dependent on p53 gene mutation[35]. Bourdon et al. reported that stabilization of the p53 protein depended also on mechanisms other than p53 gene mutation, such as binding other molecules of cellular origin[35]. In addition, Maacke et al[36]. reported that p53 protein overexpression in cytological specimens of PPJ samples was found in 59% of patients with pancreatitis and 67% of patients with pancreatic cancer: Overepressed p53 in pancreatitis appears to be wild-type p53 and may result from DNA damage occurring during chronic inflammation.

p16/CDKN2(MTS1)

The p16 in the chromosome 9p21 encodes a protein which inhibits the activity of the cyclin-dependent kinase 4 (cd4)[37]. p16 is called multiple tumor suppressor 1 (MTS1) because inactivation of p16 was observed in many cancers[38]. In pancreatic cancer, Caldas et al.[39] reported that p16 was deleted homozygously in 15 (41%) and mutated in 14 (38%) of 37 pancreatic carcinomas.

The p16 gene mutations were reported to be more frequent in culture cell line than in primary tumors[40,41]. The effect of p16 mutations on survival in pancreatic cancer has not been reported yet.

APC

APC, located on the chromosome 5q21, is the causative gene of non-polipotic familial adenoma of the colon. APC is known to participate in the early stage of multi-step carcinogesis of the colon cancer[42]. This gene was found to encode for a cytoplasmic protein with sequence homology to intermediate filament proteins such as myosin and keratin[43]. Although Horii et al.[44] found that APC mutaations was observed in 40% of pancreatic cancer, another two studies[45,46] showed frequencies below 3% of APC mutations was below 3%. Further studies are needed on APC gene in pancreatic cancer.

DCC

Approximately 70% of colon cancers have deletions in the region of 18q21, which was later found to be the locus of DCC (deleted in colorectal carcinoma gene)[42]. Hohne et al.[47] reported that 63.2% of pancreatic cancers had DCC mutations. They found that DCC mutations occurred more commonly in poorly differentiated pancreatic cancer47).

Conclusion

Further studies on molecular alteration in pancreatic cancer may lead to a better understanding of tumor biology, offering a possibility of develo0ing new diagnostic and therapeutic approaches in the future.

References

1. Smit VTHBM, Boot AJM, Smits AMM, Gleuren GJ, Cornelisse CJ, Bos JL: K-RAS codon 12 mutations occur very frequently in pancreatic carcinoma. Nucleic Acids Res 16:7773-7782,1988.
2. Lemoine NR: ras oncogenes in human cancers. In Sluyser M, ed, Molecular biology of cancer genes. Horwood, Chichester, p 82-118, 1990.
3. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N, Perucho M: Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 53:549-554,1988.
4. Grunewald K, Lyons J, Frohlich A:High frequency of Ki-ras codon mutations in pancreatic adeno-

carcinoma. Int J Cancer. 43 :1037-1041,1989.

5. Bos JL: The ras gene family and human carcinogenesis. Mutat Res 195:255-271,1988.

6. Hruban RH, van Mansfeld AOM, Offerhaus GJA, van Weering DHJ, Allison DC, Goodman SN, Kensler TW, Bose KK, Cameron JI, Bos JLK: K-ras oncogene activation in adenocarcinoma of the human pancreas: a study of 62 carcinomas using a combination of muttant-enriched polymerase chain reaction analysis and allele-specific oligonucleotide hybridization. Am J Pathol 143:545-554,1993.

7. Vogelstein B, Fearon ER, Hamilton SR, Kern SE; Preisinger AC; Leppert M; Nakamura Y; White R; Smits AM; Bos JL: Genetic alterations during colorectal tumor development. New Engl J Med 319:525-532,1988.

8. Howe JR, Conlon KC: The molecular genetic of pancreatic cancer. Surg Oncol 6:1-18,1997.

9. Pellegata NS, Sessa F, Renault B, Bonato M, Leone BE, Solcia E, Ranzani GN: K-ras and p53 gene mutations in pancreatic ductal and nonductal tumors progress through different genetic lesions. Cancer Research 54:1556-1560,1994.

10. Cerny W, Mangold KA, Scarpelli DG: K-ras mutation is an early event in pancreatic duct carcinogenesis in the Syrian golden hamstar. Cancer Research 52:4507-4513,1992.

11. Miki H, Matsumoto S, Harada H, Mori S, Haba R, Ochi K, Kobayashi S, Ohmori M: Detection of c-Ki-ras point mutation from pancreatic juice. Int J Pancreatol 14:145-148,1993.

12. Kondo H, Sugano K, Fukayama N, Kyogoku A; Nose H; Shimada K; Ohkura H; Ohtsu A; Yoshida S; Shimosato Y: Detection of point mutations in the Ki-ras oncogene at codon 12 in pure pancreatic juice for the diagnosis of pancreatic carcinoma. Cancer 73:1589-1594,1994.

13. Watanabe H; Sawabu N; Ohta H; Satomura Y; Yamakawa O; Motoo Y; Okai T; Takahashi H; Wakabayashi T: Identification of K-ras oncogene mutations in the pure pancreatic juice of patients with ductal pancreatic cancers. Jpn J Cancer Res, 84:961-965, 1993.

14. Berthelemy P, Bouisson M, Escourrou J, Vaysse N, Rumeau JL, Pradayrol L: Identification of K-ras mutations in pancreatic juice in the early diagnosis of pancreatic cancer. An Intern Med 123:188-191,1995.

15. Wakabayashi T ; Sawabu N ; Watanabe H ; Morimoto H; Sugioka G; Takita Y: Detection of K-ras point mutation at codon 12 in pure pancreatic juice collected 3 years and 6 months before the clinical diagnosis of pancreatic cancer. Am J Gastroenterol 91:1848-1851,1996.

16. Ochi K, Hasuoka H, Mizushima T, Matsumura N, Harada H: A case of small pancreatic cancer diagnosed by serial follow-up studies promptly by a positive K-ras point mutation in pure pancreatic juice. Am J Gastroenterol 93:1366-1368, 1998.

17. Furuya N, Kawa S, Akamatsu T, Furihata K: Long-term follow-up of patients with chronic pancreatitis and K-ras gene mutation detected in pancreatic juice. Gastroenterology 113:593-598,1997.

18. Uehara H, Nakaizumi A, Baba M, Iishi H, Tatsuta M, Kitamura T, Ohigashi H, Ishikawa O, Takenaka A, Ishiguro S: Diagnosis of pancreatic cancer by K-ras point mutation and cytology of pancreatic juice. Am J Gastroenterol 91:1616-1621,1996.

19. Motoo Y, Sawabu N, Yamaguchi Y, Mouri I, Yamakawa O, Watanabe H, Ohta H, Okai T, Makino H: Serum levels of c-erbB-2 protein in digestive diseases.

20. Lei S, Appert J, Nakata B, Domenico D, Kim K, Howard J: Overexpression of HER2/neu oncogene in pancreatic cancer correlates with shortened survival. Int J Pancreatol 17:1521,1995.

21. Yamanaka Y, Friess H, Kobrin MS, Büchler M, Kunz J, Beger HG, Korc M: Overexpression of HER/2neu oncogene in human pancreatic carcinoma. Hum Pathol 24:1127-1134,1993.

22. Okada N, Ohshio G, Yamaki K, Imamura T, Imamura M: Elevated serum c-erbB-2 protein levels

in patients with pancreatic cancer: correlation to metastasis and shorter survival. Oncology 52:392-396, 1995.

23. Dugan MC, Dergham ST, Kucway R, Singh K, Biernat L, Du W, Vaitkevicius VK, Crissman JD, Sarkar FH: HER-2/neu expression in pancreatic adenocarcinoma: relation to tumor differentiation and survival. Pancreas 14:229-236,1997.
24. Day JD, Digiuseppe JA, Yeo C, Lai Goldman M, Anderson SM, Goodman SN, Kern SE, Hruban RH: Immunohistochemical evaluation of HER-2/neu expression in pancreatic adenocarcinoma.
25. Di Renzo MF, Poulsom R, Olivero M, Comoglio PM, Lemoine NR: Expression of the Met/hepatocyte growth factor receptor in human pancreatic cancer. Cancer Res 55:1129-1138,1995.
26. Ebert M, Yokoyama M, Friess H, Büchler MW, Korc M: Coexpression of the c-met proto-oncogene and hepatocyte growth factor in human pancreatic cancer. Cancer Res 54:5775-5778,1994.
27. Kiehne K, Herzig KH, Fölsch UR: c-met expression in pancreatic cancer and effects of hepatocyte growth factor on pancreatic cancer cell growth. Pancreas 15:35-40,1997.
28. Furukawa T, Duguid WP, Kobari M, Matsuno S, Tsal MS: Heptaocyte growth factor and Met receptor expression in human pancreatic carcinogenesis. Am J Pathol 147:889-895,1995.
29. Donehower LA: The p53-deficient mouse: a model for basic and applied cancer studies. Semin Cancer Biol, 7: 269-278,1996.
30. Kemp CJ; Wheldon T; Balmain A: p53-deficient mice are extremely susceptible to radiation-induced tumorigenesis. Nat Genet, 8:66-69,1994.
31. Levine AJ, Momand J, Finlay CA: The p53 tumour suppressor gene. Nature 351:453-456,1991.
32. Nigro JM, Baker SJ, Preisinger AC, Jessup JM; Hostetter R; Cleary K; Bigner SH; Davidson N; Baylin S; Devilee P: Mutation in the p53 gene occur in diverse human tumour types. Nature 342:705-508,1989.
33. Redston MS, Caldas C, Seymour AB, Hruban RH, Costa L, Yeo CJ, Kern SE: p53 mutations in pancreatic carcinoma and evidence of common involvement of homocopolymer tracts in DNA microdeletions. Cancer Res 54:3025-3033,1994.
34. Nakamori S, Yashima K, Murakami Y, Ishikawa O; Ohigashi H; Imaoka S; Yaegashi S; Konishi Y; Sekiya T: Association of p53 gene mutations with short survival in pancreatic adenocarcinoma. Jp J Cancer Reserch 86:174-181,1995.
35. Bourdon JC, D'errico A, Paterlini P, Grigioni W; May E; Debuire B: p53 protein and accumulation in European hepatocellular carcinoma is not always dependent on p53 gene mutation. Gastroenterology 108:1503-1511,1995.
36. Maccke H, Kessler A, Schmiegel W, Roeder C, Vogel I, Deppert W, Kalthoff H: Overexpression p53 protein during pancreatitis. Br J Cancer 45:1501-1504,1997.
37. Serrano M, Hannon GJ, Beach D: A new regulatory motif in cell-cycle control causing specific inhibition of cyclin D/CDK4. Nature 366:704-707,1993.
38. Bartsch D, Shevlin DW, Tungs WS, Kisker O, Wells Jr SA, Goodfellow PJ: Frequent mutations of CDKN2 in primary pancreatic adnocarcinomas. Genes, Chromosom Cancer 14:189-195,1995.
39. Caldas C, Hahn SA, da Costa LT, Redston MS; Schutte M; Seymour AB; Weinstein CL; Hruban RH; Yeo CJ; Kern SE: Frequent somatic mutations and homozygous deletions of the p16 (MTS1) gene in pancreatic adenocarcinoma. Nat Genet 8:27-32,1994 .
40. Cairns P; Mao L; Merlo A; Lee DJ; Schwab D; Eby Y; Tokino K; van der Riet P; Blaugrund JE; Sidransky D : Rates of p16 (MTS1) mutations in primary tumors with 9p loss. Science 265:415-416,1995.
41. Spruck CH 3rd; Gonzalez Zulueta M; Shibata A; Simoneau AR; Lin MF; Gonzales F; Tsai YC; Jones PA: p16 gene in uncultured tumours. Nature

370:183-184,1994.
42. Ferron ER, Vogelsterin B: A genetic model for colorectal tumorigenesis. Cell 61:759-767,1990.
43. Kinzler KW; Nilbert MC; Su LK; Vogelstein B; Bryan TM; Levy DB; Smith KJ; Preisinger AC; Hedge P; McKechnie D: Identification of FAP locus genes from chromosome 5q21. Science 253:661-665,1991.
44. Horii A, Nakatsuru S, Miyoshi Y, Ichii S, Nagase H, Ando H, Yanagisawa A, Tsuchiya E, Kato Y, Nakamura Y: Frequent somatic mutations of the APC gene in human pancreatic cancer. Cancer Rese. 52:6696-6698,1992.
45. McKie AB, Filipe MI, Lemoine NR: Abnormalities affecting the APC and MCC tumour suppressor gene loci on chromosome 5q occur frequently in gastric cancer but not in pancreatic cancer. Int J Cancer 55:598-603,1993.
46. Yashima K; Nakamori S; Murakami Y; Yamaguchi A; Hayashi K; Ishikawa O; Konishi Y; Sekiya T: Mutations in the adenomatous polyposis coli gene in the mutation cluster region: Comparison of human pancreatic and colorectal cancer. Int J Cancer 59:43-47,1994.
47. Hohne MW, Halatsch ME, Kahl GF, Weinel RJ: Frequent loss of expression of the potential tumor suppressor gene DCC in ductal pancreatic adenocarcinoma. Cancer Res 52:2616-2619,1992.

膵癌における癌遺伝子および癌抑制遺伝子

越智浩二，松村直樹，一村光子，水島孝明，原田英雄，蓮岡英明[1)]，横山元浩[2)]，鶴見哲也[2)]，光延文裕[3)]，谷崎勝朗[3)]

岡山大学臨床検査医学，勝山病院[1)]，岡山赤十字病院[2)]，岡山大学三朝分院[3)]

要旨：膵癌の予後は惨澹たるものである。一方で，最近の分子生物学の分野での研究の進歩により，遺伝子レベルでの異常が膵癌では数多く存在することも明らかになってきた。膵癌の予後を改善するために，発展が期待される膵癌における遺伝子診断や遺伝子治療に向けて現在までの膵癌で明らかになった癌遺伝子 (k-ras, erbB-2, Met)，癌抑制遺伝子 (p53, p16, APC,DDC) について，概説した。