Mini Review

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.51.008156

Activated Translation of HIF-1α mRNA as a Key Mechanism in Oncogenesis of Pancreatic Ductal Adenocarcinoma and Other Malignant Diseases

Mitsuru Sakitani*

Director of the Institute CCC, Ibukidai-Higashimachi, Nishi ward, Kobe, Hyogo, Japan

***Corresponding author:** Mitsuru Sakitani, Director of the Institute CCC, Ibukidai-Higashimachi, Nishi ward, Kobe, Hyogo, Japan

ARTICLE INFO

Received: July 17, 2023

Published: July 25, 2023

Citation: Mitsuru Sakitani. Activated Translation of HIF-1α mRNA as a Key Mechanism in Oncogenesis of Pancreatic Ductal Adenocarcinoma and Other Malignant Diseases. Biomed J Sci & Tech Res 51(5)-2023. BJSTR. MS.ID.008156.

ABSTRACT

Molecular targeted therapies against KRAS mutant pancreatic ductal adenocarcinoma (PDAC) remain insufficient. The most serious causes are supposed to be bypass activation of the PI3K/AKT/mTOR signaling pathway and crosstalk between mTOR and hypoxia inducible factor (HIF). This short review is aimed at clarifying the involvement of activated translation of HIF-1α mRNA in oncogenesis of KRAS mutant PDAC in association with CA9 activation. Over 90% of PDAC harbors KRAS mutations, and it is supposed that activated translation of HIF-1α mRNA is induced by 1. mutant KRAS binding to PI3K, 2. translation activation of HIF-1α mRNA by mTORC1 in the activated PI3K/AKT/mTOR signaling or 3. by ERK1/2 in the activated KRAS/RAF/REK/ERK signaling. Activated HIF-1α finally activates CA9 via hypoxia responsive element (HRE). In this sense, activated translation of HIF-1α mRNA is a key mechanism in oncogenesis of KRAS mutant PDAC. In KRAS mutant intraductal papillary mucinous neoplasm of the pancreas (IPMN) and adult T-cell leukemia/lymphoma (ATL), the same mechanism is suggested to play a crucial role in oncogenesis. In addition, CA9 inhibitors can offer novel molecular targeted therapies against these therapy resistant PDAC, IPMN and ATL.

Keywords: KRAS; PDAC; IPMN; ATL; PI3K; Translation; HIF; CA9

Abbreviations: ATL: Adult T-cell Leukemia/lymphoma; ERK: Extracellular Signal-Regulated Kinase; HIF-1α: Hypoxia Inducible Factor-1α; HRE: Hypoxia Responsive Element; mTORC1: mechanistic Target of Rapamycin Complex 1; NF-κB: Nuclear Factor-κB; PI3K: PhosphatidylInositol 3-Kinase

Introduction

Therapy resistance is a serious problem in clinical oncology. Pancreatic ductal adenocarcinoma (PDAC) harbors genetic alterations of KRAS (93%), TP53 (72%), CDKN2A (32%), SMD4 (32%), RNF43 (7%), ARID1A (6%) or others [1]. Various mechanisms of therapy resistance in molecular targeted therapies against PDAC such as resistant mutations [2,3], bypass signaling activation [4,5] or phenotypic plasticity of endothelial-to-mesenchymal transition (EMT) [6,7] have been suggested [8-10]. For instance, insufficient results by inhibitors against effectors in the KRAS/RAF/ MEK/ extracellular signal-regulated kinase (ERK) signaling pathway [8,11] can be ascribed to bypass activation of the phosphatitylinositol 3-kinase (PI3K)/AKT/ mechanistic target of rapamycin (mTOR) signaling pathway [4,5,12]. In addition, it is indicated that translation of mRNA is activated by mTORC1 (mTOR complex 1) [13-15] or ERK1/2 [13,15]. Furthermore, it is suggested that hypoxia inducible factor (HIF)-1α is involved in oncogenesis of PDAC [16,17], while it is well known that HIF-1α activates transcription of carbon anhydrase IX (CA9) [18,19]. Finally, CA9 is supposed to be involved in oncogenesis of PDAD [20,21].

This short review is aimed at clarifying the involvement of activated translation of HIF-1α mRNA in oncogenesis of KRAS mutant PDAC in association with CA9 activation. First, we briefly summarize this complicated interaction in PDAC between the mutant KRAS signaling and the PI3K/ATK/mTOR signaling pathway around activated translation of mRNA HIF-1α, resulting in CA9 activation, because this is crucial in oncogenesis of PDAC. Second, activation of HIF-1α and CA9 in intraductal papillary mucinous meoplasm of the pancreas (IPMN) and adult T-cell leukemia/lymphoma (ATL) is concisely shown.

Translation of mRNA

Eukaryotic mRNA translation consists of four phases, initiation, elongation, termination, and ribosome recycling [13], and the first initiation is rate-limiting [22]. mRNA has two characteristic structures, 5′ 7-methylguanosine (m7G) cap [23] and 3′ poly(A) tail [24], and translation initiation of mRNA is processed in eight phases [13,15,25]: 1. Formation of the ternary complex of eukaryotic translation initiation factor 2 (eIF2), GTP and initiating methionyl tRNA (Met-tRNAi); 2. Formation of the 43S pre-initiation complex (PIC) that consists of the ternary complex (eIF2/GTP/Met-tRNAi), a 40S ribosomal subunit, eIF1, eIF1A, eIF3 and eIF5 [26]; 3. Activation of mRNA by the eIF4F complex, composed of eIF4E (a mRNA-cap binding component), eIF4G (a scaffolding protein) and eIF4A (an ATP-dependent RNA helicase) [14], with assistance of eIF4B and poly(A)-binding protein (PABP) [27]; 4. Attachment of the 43S PIC to the activated mRNA; 5. Scanning of the 5′ UTR of mRNA in 5′ to 3′ direction by 43S PIC; 6. Recognition of start codon (AUG) and formation of the 48S initiation complex; 7. Joining of 60S ribosomal subunit to the 48S initiation complex with assistance of eIF5B-GTP and concomitant release of eIF2-GDP and other factors such as eIF1, eIF3, eIF4B, eIF4F and eIF5; 8. Hydrolysis of eIF5B-GTP and release of eIF1A and eIF5B-GDP from the 80S initiation complex of ribosome. Then elongation phase starts.

Activated translation of mRNA by mTORC1

PI3K activated by its ligand successively activates AKT and mTORC1 [28]. Activated mTOR1 phosphorylates 4E-binding protein 1 (4E-BP1). Phosphorylated 4E-BP1 is released from eIF4E, leading to the association of eIF4E with eIF4G, and finally the assembly of the mRNA-cap binding eIF4F complex is induced [13-15]. The activated eIF4F complex activates translation of mRNA. mTOR1 also activates S6Ks, which then activates eIF4B. Activated eIF4B enhances the mRNA-unwinding activity of eIF4A as a component of the mRNA-cap binding eIF4F complex, leading to activation of mRNA translation [29].

Activated Translation of mRNA by ERK1/ERK2

In the KRAS/RAF/MEK/ERK signaling pathway, activated ERK1/2 phosphorylate RSKs [13,15], which then activate eIF4B, leading to activation of mRNA translation [29]. ERK1/2 also phosphorylate MNKs, and activated MNKs then phosphorylates eIF4E in the eIF4F complex [15], resulting in activation of mRNA translation.

Activated Translation of HIF mRNA and Activation of CA9 in PDAC

Mutant KRAS in PDAC activates its downstream effectors RAF, MEK1/2 and ERK1/2 [8,11]. Activated ERK1/2 phosphorylate various targeted molecules [30], but RSKs and MNKs are important because these finally activate translation of mRNA of numerous targeted genes. Of these, HIF-1α is the most important because HIF-1α is involved in oncogenesis of PDAC [16,17,31]. In addition, CA9 is activated by HIF-1α via hypoxia responsive element (HRE) in the promoter region of CA9 [18,19] (Table 1), and inhibitors of CA9 suppress cell proliferation of PDAC cells [16,17,20,21]. In this sense, CA9 is one of the final effectors in PDAC oncogenesis [20,21] and CA9 inhibitors are suggested to be promising molecular targeted therapies against PDAC [12,21]. In addition, mutant KRAS in PDAC activates the bypass PI3K/AKT/mTOR1 signaling pathway. Mutant KRAS activates PI3Kα by direct binding to a RAS-binding domain of p110α in PI3K [32] (Table 1). Activated PI3K then activates successively its downstream effectors AKT and mTORC1. As indicated above, mTORC1 activates translation of HIF-1α mRNA via 4E-BP1 and eIF4B, leading to activation of CA9 in PDAC.

IPMN

A precursor lesion pancreatic intraepithelial neoplasia (PanIN) progresses into PDAC [4], but there is another precursor IPMN [33]. IPMN harbors KRAS (up to 80%) and/or GNAS (about 70%) mutations, and coexistence of both KRAS and GNAS is found in over 30% [34-36]. Since poor prognosis of malignant IPMN is comparable to that of PDAC [33] and due to high mutation rate of KRAS in IPMN, involvement of HIF-1α and CA9 in malignant progression and oncogenesis of IPMN is quite possible [37] (Table 1), as in PDAC [16,17,20,21].

ATL

ATL is a hematological malignancy [38] caused by human T-cell leukemia virus type 1 (HTLV-1) [39,40]. In the multistep oncogenesis model of ATL [41], final oncogenic progression is completed by additional events in host cells, not by the HTLV-1-derived Tax [42,43] nor HBZ [44]. In this regard, constitutive activation of nuclear factor-κB (NF-κB) [45,46] is the most important among the additional events at the final stage of ATL oncogenesis, because NF-κB molecules directly activate transcription of HIF-1α [47,48], leading to activation of CA9 (Table 1). Furthermore, activated expression of AKT is observed in ATL cell lines [49,50] and primary ATL cells [49], while expression of HIF-1α is activated in ATL cell lines as well as primary ATL cells [49]. In addition, expression of CA9 is confirmed in primary ATL cells [51] and high expression of CA9 in ATL cell lines is correlated with tumorigenicity [51]. These data can support crosstalk between the PI3K/AKT/mTOR signaling pathway and HIF-1α/CA9 via activated translation of HIF-1α mRNA (Table 1).

Table 1: Activation of PI3K and HIF-1α/CA9 in KRAS mutant PDAC/IPMN and ATL.

Diseases	Activation of PI3K	Activated translation of HIF-1α mRNA	Activation of CA9
KRAS mutant PDAC/IPMN	Binding of KRAS to PI3K	by mTORC1 and/or ERK1/2	HRE of CA9 by HIF-1α
ATL	Activated transcription of PI3K by NF-κB	by mTORC1	HRE of CA9 by HIF-1α

Conclusion

Activated translation of HIF-1α mRNA is a key mechanism in oncogenesis of KRAS mutant PDAC in association with CA9 activation. In KRAS mutant IPMN and ATL, the same activated translation of HIF-1α mRNA is suggested to play a crucial role in oncogenesis. In ATL, another crosstalk between NF-κB and the HIF-1α/CA9 signaling is indicated to be significant in multistep oncogenesis of ATL. In addition, CA9 inhibitors can offer novel molecular targeted therapies against these therapy resistant PDAC, IPMN and ATL. To realize novel therapies, further studies are required.

Conflicts of Interests

The author declares that there is no conflict of interests.

References

1. Cancer Genome Atlas Research Network (2017) Integrated genomic characterization of pancreatic ductal adenocarcinoma. Cancer Cell 32(2): 185-203.
2. Bannoura SF, Uddin MH, Nagasaka M, Fazili F, Al-Hallak MN, et al. (2021) Targeting KRAS in pancreatic cancer: New drugs on the horizon. Cancer Metastasis Rev 40(3): 819-835.
3. Huang L, Guo Z, Wang F, Fu L (2021) KRAS mutation: From undruggable to druggable in cancer. Signal Transduct Target Ther. 6(1): 386.
4. Eser S, Schnieke A, Schneider G, Saur D (2014) Oncogenic KRAS signalling in pancreatic cancer. Br J Cancer 111(5): 817-822.
5. Hou P, Wang YA (2022) Conquering oncogenic KRAS and its bypass mechanisms. Theranostics 12(13): 5691-5709.
6. Dardare J, Witz A, Merlin JL, Bochnakian A, Toussaint P, et al. (2021) Epithelial to mesenchymal transition in patients with pancreatic ductal adenocarcinoma: State-of- the-art and therapeutic opportunities. Pharmaceuticals (Basel) 14(8): 740.
7. Malinova A, Veghini L, Real FX, Corbo V (2021) Cell lineage infidelity in PDAC progression and therapy resistance. Front Cell Dev Biol 9: 795251.
8. Waters AM, Der CJ (2018) KRAS: The critical driver and therapeutic target for pancreatic cancer. Cold Spring Harb Perspect Med 8(9): a031435.
9. Digiacomo G, Volta F, Garajova I, Balsano R, Cavazzoni A (2021) Biological hallmarks and new therapeutic approaches for the treatment of PDAC. Life (Basel) 11(8): 843.
10. Anderson EM, Thomassian S, Gong J, Hendifar A, Osipov A (2021) Advances in pancreatic ductal adenocarcinoma treatment. Cancers (Basel) 13(21): 5510.
11. Zeitouni D, Pylayeva-Gupta Y, Der CJ, Bryant KL (2016) KRAS mutant pancreatic cancer: No lone path to an effective treatment. Cancers (Basel) 8(4): 45.
12. Sakitani M (2022) Multifaceted roles of carbon anhydrase IX in cancer cell proliferation, survival, metastasis and therapy resistance and indication of promising novel therapies by its inhibitors. J Mol Genet Med 16(11): 582.
13. Ali MU, Ur Rahman MS, Jia Z, Jiang C (2017) Eukaryotic translation initiation factors and cancer. Tumour Biol 39(6): 1010428317709805.
14. Roux PP, Topisirovic I (2018) Signaling pathways involved in the regulation of mRNA translation. Mol Cell Biol 38(12): e00070-18.
15. Hao P, Yu J, Ward R, Liu Y, Hao Q, et al. (2020) Eukaryotic translation initiation factors as promising targets in cancer therapy. Cell Commun Signal 18(1): 175.
16. Logsdon DP, Grimard M, Luo M, Shahda S, Jiang Y, et al. (2016) Regulation of HIF1α under hypoxia by APE1/Ref-1 impacts CA9 expression: Dual targeting in patient-derived 3D pancreatic cancer models. Mol Cancer Ther 15(11): 2722-2732.
17. Logsdon DP, Shah F, Carta F, Supuran CT, Kamocka M, et al. (2018) Blocking HIF signaling via novel inhibitors of CA9 and APE1/Ref-1 dramatically affects pancreatic cancer cell survival. Sci Rep 8(1): 17359.
18. Wykoff CC, Beasley NJ, Watson PH, Turner KJ, Pastorek J, et al. (2000) Hypoxia-inducible expression of tumor-associated carbonic anhydrases. Cancer Res 60(24): 7075-7083.
19. Kaluz S, Kaluzová M, Liao SY, Lerman M, Stanbridge EJ (2009) Transcriptional control of the tumor- and hypoxia-marker carbonic anhydrase 9: A one transcription factor (HIF-1) show? Biochim Biophys Acta 1795(2): 162-172.
20. McDonald PC, Chafe SC, Brown WS, Saberi S, Swayampakula M, et al. (2019) Regulation of pH by carbonic anhydrase 9 mediates survival of pancreatic cancer cells with activated KRAS in response to hypoxia. Gastroenterology 157(3): 823-837.
21. McDonald PC, Chafe SC, Supuran CT, Dedhar S (2022) Cancer therapeutic targeting of hypoxia induced carbonic anhydrase IX: From bench to bedside. Cancers (Base) 14(14): 3297.
22. Verma M, Choi J, Cottrell KA, Lavagnino Z, Thomas EN, et al. (2019) A short translational ramp determines the efficiency of protein synthesis. Nat Commun 10(1): 5774.
23. Choe J, Oh N, Park S, Lee YK, Song OK, et al. (2021) Translation initiation on mRNAs bound by nuclear cap-binding protein complex CBP80/20 requires interaction between CBP80/20-dependent translation initiation factor and eukaryotic translation initiation factor 3g. J Biol Chem 287(22): 18500-18509.
24. Danckwardt S, Hentze MW, Kulozik AE (2008) 3′ end mRNA processing: Molecular mechanisms and implications for health and disease. EMBO J 27(3): 482-498.
25. Jackson RJ, Hellen CU, Pestova TV (2010) The mechanism of eukaryotic translation initiation and principles of its regulation. Nat Rev Mol Cell Biol 11(2): 113-127.
26. Passmore LA, Schmeing TM, Maag D, Applefield DJ, Acker MG, et al. (2007) The eukaryotic translation initiation factors eIF1 and eIF1A induce an open conformation of the 40S ribosome. Mol Cell 26(1): 41-50.
27. Sonenberg N, Hinnebusch AG (2009) Regulation of translation initiation in eukaryotes: Mechanisms and biological targets. Cell 136(40): 731-745.
28. Masoud GN, Li W (2015) HIF-1α pathway: Role, regulation and intervention for cancer therapy. Acta Pharm Sin B (5): 378-389.

29. Shahbazian D, Roux PP, Mieulet V, Cohen MS, Raught B, et al. (2006) The mTOR/PI3K and MAPK pathways converge on eIF4B to control its phosphorylation and activity. EMBO J 25(12): 2781-2791.
30. Furukawa T (2015) Impacts of activation of the mitogen-activated protein kinase pathway in pancreatic cancer. Front Oncolo 5: 23.
31. Shin S, Solorzano J, Liauzun M, Pyronnet S, Bousquet C, et al. (2022) Translational alterations in pancreatic cancer: A central role for the integrated stress response. NAR Cancer 4(4): acac031.
32. Rodriguez Viciana P, Warne PH, Vanhaesebroeck B, Waterfield MD, Downward J (1996) Activation of phosphoinositide 3-kinase by interaction with Ras and by point mutation. EMBO J 15(10): 2442-2451.
33. Tanaka M, Fernández del Castillo C, Adsay V, Chari S, Falconi M, et al. (2012) International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology 12(3): 183-197.
34. Amato E, Molin MD, Mafficini A, Yu J, Malleo G, et al. (2014) Targeted next-generation sequencing of cancer genes dissects the molecular profiles of intraductal papillary neoplasms of the pancreas. J Pathol 233(3): 217-227.
35. Paini M, Crippa S, Partelli S, Scopelliti F, Tamburrino D, et al. (2014) Molecular pathology of intraductal papillary mucinous neoplasms of the pancreas. World J Gastroenterol 20(29): 10008-10023.
36. Mas L, Lupinacci RM, Cros J, Bachet JB, Coulet F, et al. (2021) Intraductal papillary mucinous carcinoma versus conventional pancreatic ductal adenocarcinoma: A comprehensive review of clinical-pathological features, outcomes, and molecular insights. Int J Mol Sci 22(13): 6756.
37. Sakitani M (2023) Molecular oncogenesis of intraductal papillary mucinous neoplasm of the pancreas and its possible molecular targeted therapy. J Mol Genet Med 17(2): 602.
38. Uchiyama T, Yodoi J, Sagawa K, Takatsuki K, Uchino H (1977) Adult T-cell leukemia: Clinical and hematologic features of 16 cases. Blood 50(3): 481-492.
39. Hinuma Y, Nagata K, Hanaoka M, Nakai M, Matsumoto T, et al. (1981) Adult T-cell leukemia: Antigen in an ATL cell line and detection of antibodies to the antigen in human sera. Proc Natl Acad Sci U S A 78(10): 6476-6480.
40. Seiki M, Hattori S, Hirayama Y, Yoshida M (1983) Human adult T-cell leukemia virus: Complete nucleotide sequence of the provirus genome integrated in leukemia cell DNA. Proc Natl Acad Sci U S A 80(12): 3618-3622.
41. Sakitani M (2023) Essential role of carbon anhydrase IX, activated via the nuclear factor-κB and phosphatidylinositol 3-kinase signaling pathways, in multistep oncogenesis of adult T-cell leukemia/lymphoma caused by human T-cell leukemia virus type 1. J Microbiol Biotechnol 8(1): 000256.
42. Azran I, Schavinsky-Khrapunsky Y, Aboud M (2004) Role of Tax protein in human T-cell leukemia virus type-I leukemogenicity. Retrovirology 1: 20.
43. Boxus M, Twizere JC, Legros S, Dewulf JF, Kettmann R, et al. (2008) The HTLV-1 Tax interactome. Retrovirology 5: 76.
44. Matsuoka M, Mesnard JM (2020) HTLV-1 bZIP factor: The key viral gene for pathogenesis. Retrovirology 17(1): 2.
45. Arima N, Matsushita K, Obata H, Ohtsubo H, Fujiwara H, et al. (1999) NF-κB involvement in the activation of primary adult T-cell leukemia cells and its clinical implications. Exp Haematol 27(7): 1168-1175.
46. Mori N, Fujii M, Ikeda S, Yamada Y, Tomonaga M, et al. (1999) Constitutive activation of NF-κB in primary adult T-cell leukemia cells. Blood 93(7): 2360-2368.
47. BelAiba RS, Bonello S, Zähringer C, Schmidt S, Hess J, et al. (2007) Hypoxia up-regulates hypoxia-inducible factor-1α transcription by involving phosphatidylinositol 3-kinase and nuclear factor κB in pulmonary artery smooth muscle cells. Mol Biol Cell 18(12): 4691-4697.
48. Rius J, Guma M, Schachtrup C, Akassoglou K, Zinkernagel AS, et al. (2008) NF-κB links innate immunity to the hypoxic response through transcriptional regulation of HIF-1α. Nature 453(7196): 807-811.
49. Tomita M, Semenza GL, Michiels C, Matsuda T, Uchihara JN, et al. (2007) Activation of hypoxia-inducible factor 1 in human T- cell leukaemia virus type 1-infected cell lines and primary adult T-cell leukaemia cells. Biochem J 406(2): 317-323.
50. Yamaguchi K, Takanashi T, Nasu K, Tamai K, Mochizuki M, et al. (2016) Xenotransplantation elicits salient tumorigenicity of adult T-cell leukemia-derived cells via aberrant AKT activation. Cancer Sci 107(5): 638-643.
51. Nasu K, Yamaguchi K, Takanashi T, Tamai K, Sato I, et al. (2017) Crucial role of carbonic anhydrase IX in tumorigenicity of xeno transplanted adult T-cell leukemia-derived cells. Cancer Sci 108(3): 435-443.

ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.51.008156

Mitsuru Sakitani. Biomed J Sci & Tech Res