EBioMedicine 54 (2020) 102709

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

MAP9/ERCC3 signaling cascade: A new insight on understanding the chromosomal instability in hepatocellular carcinoma

Etienne Ho Kit Mok[a], Carmen Oi Ning Leung[a], Terence Kin Wah Lee[a,b,*]

[a] Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University
[b] State Key Laboratory of Chemical Biology and Drug Discovery, The Hong Kong Polytechnic University, Hong Kong

ARTICLE INFO

Article History:
Received 24 February 2020
Accepted 24 February 2020
Available online xxx

In this article of *EBioMedicine*, Zhang and colleagues [1] showed that microtubule associated protein 9 (MAP9), a gene critical for spindle assembly and cytokinesis, was frequently downregulated in patients with hepatocellular carcinoma (HCC), and associated with poorer survival of patients. Mechanistically, they found that loss of MAP9 expression in HCC may lead to chromosomal instability (CIN) via regulation of nucleotide repair (NER) pathway.

HCC is one of the deadliest diseases, being the 6th most commonly diagnosed cancer and the 4th leading cause of cancer mortality in the world [2]. Hepatitis B and C viruses, alcohol abuse and diabetes are the major risk factors for HCC development [3]. Continuous destruction and repair process results in liver cirrhosis, which subsequently progresses to dysplastic nodules and ultimately HCC. CIN is the common feature of dysplastic nodules and HCC, which impedes prognosis and therapy. There are number of factors contributing to occurrence of CIN, among which elevated formation of inappropriate chromosome spindle attachment caused by abnormal spindle microtubule dynamics and/or spindle geometry defects attracts increasing attention [4]. Gene expression profiling analyses have recently shown that microtubule-related cellular assembly and organization is the most critical event in HCC development [5], suggesting microtubules to be an important target for therapeutic intervention in HCC. Despite the importance of spindle microtubule induced CIN to liver tumorigenesis is established, its underlying mechanisms that drive CIN and its precise roles in cancer initiation and progression remain poorly understood.

MAP9 belongs to MAP family, which regulates microtubule dynamics [6]. Thus far, few reports have shown a role for MAP9 in CIN, and its clinical relevance and functional role in HCC are largely unknown. In this study, Zhang and colleagues first found that MAP9 was frequently downregulated in HCC at both mRNA and protein levels due to promoter hypermethylation. MAP9 downregulation or promoter hypermethylation is an independent prognostic factor of tumor recurrence and poor survival in HCC patients. Through various *in vitro* functional assays, they found that ectopic introduction of MAP9 suppressed HCC cell proliferation and invasiveness through inducing cell cycle arrest and apoptosis. The role of MAP9 as tumor-suppressor was further confirmed *in vivo* in a liver-specific MAP9 knockout mice. $MAP9^{\Delta/\Delta hep}$ mice exhibited spontaneous liver hyperplastic nodule and accelerated diethylnitrosamine (DEN)-induced HCC formation. By comparing the gene expression profiles of livers between MAP9 knockout and WT mice, they have identified NER pathway to be most significantly altered in which excision repair cross-complementation group 3 (ERCC3), a nucleotide excision repair gene, was found to be most downregulated. *In vitro* and *in vivo* functional analyses demonstrated that ERCC3 counteracted the tumor suppressive effects of MAP9 in HCC cells. Clinically, ERCC3 was significantly upregulated in HCC, and may potentially be an independent prognostic marker for HCC patients. Collectively, they have identified NER pathway as the critical effector mediating the functions of MAP9 in HCC.

Although ERCC3 related NER pathway was identified as the downstream effector of MAP9, some questions remain unanswered. As a core player in NER pathway, ERCC3 may regulate the aggressive phenotypes of HCC cells upon DNA damage. However, this study did not provide any evidence showing how MAP9 regulates nucleotide repair during the process of DNA damage. In addition, although MAP9 was found to play role in the control of microtubule dynamics, there is no conclusive data demonstrating the direct functional role of MAP9 in regulation of CIN in this study. Having said that, Wang et al. from the same group have provided some clues in this area of research. They found that loss of MAP9 caused shortened spindles in metaphase that were extremely unstable, leading to CIN in colorectal cancer [7]. Further, they found that MAP9 loss caused CIN especially in $MAP9^{\Delta/\Delta}p53^{\Delta/+}$ mice [7]. Consistent to this finding, Basbous et al. reported

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2020.102701.
* Corresponding author at: Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Lee Shau Kee Building, Room 805, Block Y, Hong Kong.
E-mail address: terence.kw.lee@polyu.edu.hk (T.K.W. Lee).

https://doi.org/10.1016/j.ebiom.2020.102709

that MAP9 directly interacts and stabilizes p53 by regulating NER pathway [8]. The interaction between ERCC3 and p53 was further confirmed in hepatitis C virus infected cells [9]. Based on these findings, MAP9 may regulate ERCC3 in NER pathway through stabilizing p53. Further functional analyses are needed to confirm how MAP9 regulates CIN via ERCC3 regulation.

CIN contributes to HCC development and a potential therapeutic target for intervention [10]. However, the underlying mechanisms are not well characterized. The findings presented in this article provide a mechanistic insight of how CIN contributes to liver carcinogenesis. Zhang and colleagues have demonstrated that MAP9 loss may contribute to CIN possibly through inhibition of ERCC3. Strikingly, they have demonstrated an unprecedented tumor suppressive role of MAP9 in HCC. The findings can also be translated to clinical application. Methylated MAP9 may serve as a new biomarker for the prognosis of HCC patients. All in all, targeting MAP/ERCC3 signaling cascade may be a potential therapeutic strategy for treatment of advanced HCC patients.

Declaration of Competing Interest

None.

CRediT authorship contribution statement

Etienne Ho Kit Mok: Writing - review & editing. **Carmen Oi Ning Leung:** Writing - review & editing. **Terence Kin Wah Lee:** Supervision.

References

[1] Zhang J, Huang JZ, Zhang YQ, et al. Microtubule associated protein 9 inhibits liver tumorigenesis by suppressing ERCC3. EBioMedicine 2020. doi: 10.1016/j.ebiom.2020.102701.
[2] Bray F, Ferlay J, Soeriomataram I, Siegel RL, Torre LA, Jermal A. Global cancer statistics 2018: globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countires. CA Cancer J Clin 2018;68(6):394–424.
[3] Farazi PA, DePinho RA. Hepatocellular carcinoma pathogenesis: from genes to environment. Nat Rev Cancer 2006;6(9):674–87.
[4] Burrell RA, McGranahan N, Bartek J, Swanton C. The causes and consequences of genetic heterogeneity in cancer evolution. Nature 2013;501(7467):338–45.
[5] Patil MA, Chua MS, Pan KH, et al. An integrated data analysis approach to characterize genes highly expressed in hepatocellular carcinoma. Oncogene 2005;24(23):3737–47.
[6] Saffin J-M, Venoux M, Prigent C, et al. ASAP, a human microtubule-associated protein required for bipolar spindle assembly and cytokinesis. Proc Natl Acad Sci USA 2005;102(32):11302–7.
[7] Wang S, Huang J, Li C, et al. MAP9 loss triggers chromosomal instability, initiates colorectal tumorigenesis, and is associated with poor survival of colorectal cancer patients. Clin Cancer Res 2020;26(3):746–57. doi: 10.1158/1078-0432.CCR-19-1611.
[8] Basbous J, Knani D, Bonneaud N, Giorgi D, Brondello JM, Rouquier S. Induction of ASAP (MAP9) contributes to p53 stabilization in response to DNA damage. Cell Cycle 2012;11(12):2380–90.
[9] Qadri I, Iwahashi M, Simon F. Hepatitis c virus NS5A protein binds tbp and p53, inhibiting their DNA binding and p53 interactions with TBP and ERCC3. Biochim Biophys Acta 2002;1592(2):193–204.
[10] Rao CV, Asch AS, Yamada HY. Frequent mutated genes/pathways and genomic instability as prevention targets in liver cancer. Carcinogenesis 2017;38(1):2–11. doi: 10.1093/carcin/bgw118.