



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 79276

Title: Recent progress in molecular mechanisms of postoperative recurrence and metastasis of hepatocellular carcinoma.

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00724887

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Academic degree: MD

Professional title: Attending Doctor

Reviewer's Country/Territory: India

Author's Country/Territory: China

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

This review is written very well. It covers all relevant molecular mechanism involved in recurrence and metastasis of HCC.



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Comments to the authors: The manuscript is well organized. While the topic is timely, the manuscript would benefit from substantial revisions throughout to aid with clarity.

1) What do you mean by “intrahepatic distant metastasis”, as “HCC metastasis can be roughly divided into intrahepatic and extrahepatic (distant) metastasis.”, on Page 3. 2)

Page 4: “Of these processes, the activation of oncogenes and the inactivation of tumor suppressor genes can lead to uncontrolled growth of cancer cells and thus have the potential to metastasize.” This sentence is confusing as written, as the subject is

misused for “have the potential to metastasize”. 3) Page 5: “OPN is a glycoprotein with secretory calcium-binding phosphorylation”, and “OPN can secrete stromal cells and chemokines”, these sentences were confusing. 4) Page 6: “Therefore, S100A9

exhibits poor stability; is prone to deletion, translocation and other gene mutations; and is connected to the growth, differentiation and metastasis potential of various malignancies”, this sentence has grammar problems, as a subject is needed after each

semicolon. In addition, what do you mean by saying “S100A9 is prone to other gene mutations”? 5) Page 6: define “MDSCs” when it appears for the first time. 6) Page 10: confirm that reference 66 was correctly cited, as “tumor resection” was not

mentioned in this paper. 7) Page 20: “HSCs play important roles in promoting HCC invasion and metastasis by multiple mechanisms.” This paragraph clarifies the action of HSCs after activated. But it may be more important to focus on the molecular

mechanisms that activated HSCs, for possible intervention of HCC recurrence and metastasis. The authors should address these mechanisms in the manuscript. 8) Page 24: “TECs can be directly and selectively targeted to inhibit or kill TECs and inhibit or



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prevent HCC metastasis and recurrence.”, this sentence was confusing as written. 9)

Page 25: “Changes in adhesion in tumor cell-ECM and HCC metastasis”, do you mean “Adhesion enhancement in tumor cell-ECM promotes HCC metastasis”? 10)Page

30: UPA is the abbreviation for Urokinase-like Plasminogen Activator, but not “plasminogen activator”. In addition, if you mean “Urokinase-like Plasminogen Activator”, three abbreviations UPA, u-PA and uPA (page 31) are used in the text, choose one of them. 11) Page 30-31: “A prerequisite for HCC metastasis and

recurrence after surgery is the degradation of the ECM and BM by a series of proteolytic enzymes. During HCC aggressiveness and metastasis, only when HCC cells disrupt the dynamic balance of the ECM and penetrate the BM can they invade the surrounding tissues and cause HCC diffusion and metastasis. This process subsequently depends on two important enzymes. One is uPA secreted by tumor cells, which can promote HCC invasion and metastasis by degrading the ECM and penetrating the BM [307,308]. The other enzymes are MMPs that are correlated with HCC metastasis and recurrence, and the roles of MMP-2 and MMP-9 have been confirmed in many studies [309-311].”, this paragraph can be deleted, as the content has been expressed in the previous two paragraphs. 12) Page 31: “In short, specific inhibitors targeting MMP-2, MMP-9 and

uPA inhibit the activities of MMP-2, MMP-9 and uPA and further inhibit HCC growth, invasion and metastasis.”, this sentence is not appropriate, because there is no mention on the pharmacological inhibitors of these proteins before. 13) Page 32: “In addition,

IFN- γ can inhibit activated T helper type-1 (Th1) lymphocytes and the generation of IFN- γ and IL-2 by increasing the expression of Fc receptors on the membrane of macrophages. Thus, the levels of the inhibitory factor of macrophage factor synthesis are increased, which inhibits the immune response and is tightly associated with HCC development [315].”, these sentences are confusing. First, can IFN- γ inhibit the generation of itself in macrophage, and is it mentioned in ref 315? Second, is it



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dependent on the inhibition of activated T helper type-1 (Th1) lymphocytes by IFN- γ , and is it mentioned in ref 315? Third, ref 315 is negative on IFN- γ effect of inhibiting HCC occurrence, but ref 314 and 316 are positive. Discuss ref 315 at the end. Last, by saying “of macrophage factor synthesis”, is it better for “on synthesis of macrophage factors”, and what do you mean by “the inhibitory factor”? 14) Page 32: “One probable reason is that a low level of IFN- γ reduces the inhibitory effect on HCC cell proliferation and metastasis and the apoptosis-promoting effect on HCC cells and thereby promotes HCC occurrence and development.” There is no reference for this sentence. And the grammar needs revision for smooth reading. 15) Page 32: “Another reason is that T helper (Th) cells are important immunomodulatory cells. Th1 and Th2 cells are the main subsets of Th cells. Th1 cells mainly mediate the cellular immune response by secreting cytokines such as TNF- γ [317]. Th2 cells mainly mediate humoral immunity, which can inhibit the Th1 cellular immune response. Th1 cells are the main immune regulators of tumors. A Th1/Th2 imbalance (increase in Th2 cells and decrease in Th1 cells) occurs in the HCC microenvironment, the HCC microenvironment is in a state of immunosuppression [318], and tumor cells undergo immune evasion, which leads to HCC metastasis and recurrence.” These sentences are confusing and need revision too. 16) Page 33: “to break through the capsule and spread to the outside of the capsule.”, is it better for “to break through and eventually spread to the outside of the liver capsule.”? 17) Page 33: “The tumor is currently at the expansion stage”, “currently” is not suitable here. 18) Page 33-34: “Alternatively, most HCC cells synthesize and secrete IL-8, which may affect the biological behavior and metastasis of HCC through autocrine and paracrine signaling.”, There is no supporting reference for this sentence. 19) Page 37-38: “VEGF, as a crucial regulatory factor of angiogenesis, can reflect the level of proliferation, migration and vascular construction of HCC VECs and provides a pathway for HCC cells to metastasize along the blood vessels, which is also an important



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reason why HCC exhibits high vascular invasion, metastasis tendency and postoperative recurrence [382-384]." These sentences are confusing and need revision. 20) Page 48: "DNA methylation, DNA methylation, histone modifications, genomic imprinting", DNA methylation repeated, do you mean acetylation? 21) Page 50: define "ceRNA" 22) Page 51-52: "and HCC invasion and metastasis are complex processes", "and" is not appropriate here, use "but" or "while", etc.