Short-term exposure to a chemotherapeutic drug, Oxaliplatin increases metastatic potential of well-differentiated hepatocellular carcinoma cells

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Introduction

Metastasis, which account for 90% of cause of cancer death, are a main problem in treatments. Metastasis associates with several cellular processes including invasion, migration, and extracellular matrix (ECM) remodeling (Fig. 1). Matrix metalloproteinases (MMPs) are a group of enzyme responsible for ECM degradation (1). MMP-2 is a dominant enzyme related with cancer cell invasion and poor prognosis in many cancer types (2).

Hepatocellular carcinoma (HCC) is a major type of primary liver cancer with high rank of mortality and incidence worldwide (3).

Mounting evidences have been indicated the adverse effect of chemotherapeutic drugs on acceleration of invasion and metastasis in several cancer types (4-6).

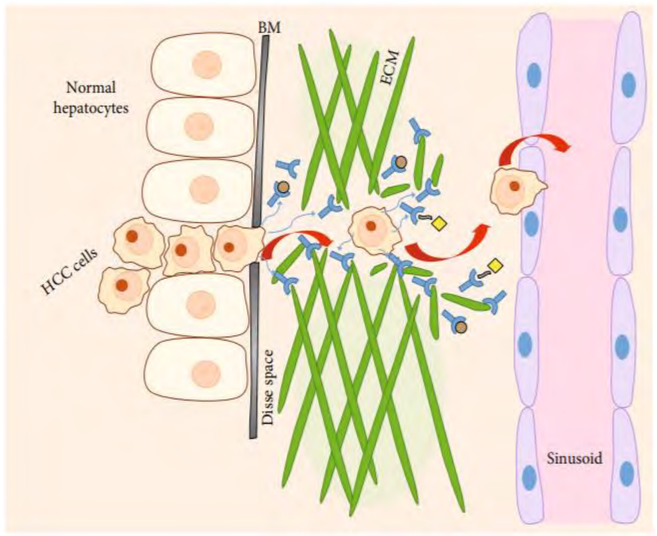

Figure 1) Invasion process of hepatocellular carcinoma cells (2)

Aim

To investigate the influence of a short-term treatment of chemotherapeutic drug oxaliplatin on invasiveness of HepG2 cells

Methodology

Cell viability was determined by MTT assay.
Migration and Invasion assays were evaluated by using Transwell chambers. Matrigel was applied to coat Transwell chamber for Invasion assay. Migration assay uses uncoated Transwell chamber. The cells were treated with oxaliplatin (1 μM) at 24 h, then they were subjected to the assays.
MMPs secretion and activity were detected by means of gelatin zymography. The cells were treated with oxaliplatin at 24 h then, replaced with serum-free media for 24 h. Conditioned media were collected and subjected to gelatin zymography.

Acknowledgement

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References

1.Leber MF, Efferth T. Molecular principles of cancer invasion and metastasis. International journal of oncology. 2009;34(4):881-95.
2.Scheau C, Badarau IA, Costache R, Caruntu C, Mihai GL, Didilescu AC, Constantin C, Neagu M. The role of matrix metalloproteinases in the epithelial-mesenchymal transition of hepatocellular carcinoma. Analytical Cellular Pathology. 2019 Oct;2019.
4.Karagiannis GS, Condeelis JS, Oktay MH. Chemotherapy-induced metastasis: mechanisms and translational opportunities. Clinical & experimental metastasis. 2018;35(4):269-84.
5. Gingis-Velitski S, Loven D, Benayoun L, Munster M, Bril R, Voloshin T, Alishekevitz D, Bertolini F, Shaked Y. Host response to short-term, single-agent chemotherapy induces matrix metalloproteinase-9 expression and accelerates metastasis in mice. Cancer research. 2011 Nov 15;71(22):6986-96.
6. Liu CL, Chen MJ, Lin JC, Lin CH, Huang WC, Cheng SP, Chen SN, Chang YC. Doxorubicin promotes migration and invasion of breast cancer cells through the upregulation of the RhoA/MLC pathway. Journal of breast cancer. 2019 Jun 1;22(2):185-95.

Results

Oxaliplatin treatment expressed cytotoxic effect on HepG2 in concentration- and time-dependent manners (Fig. 2). A concentration of 1 μM was selected as a sub-lethal dose of oxaliplatin for further exploring the impact on invasion process.

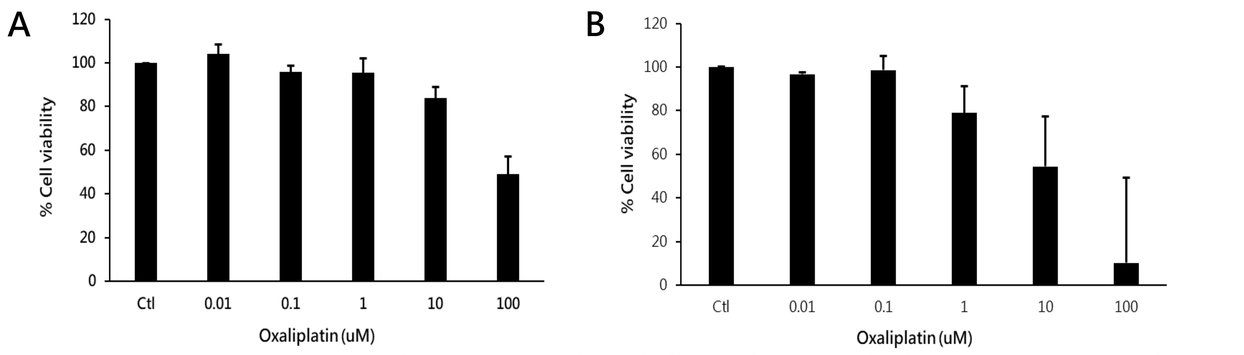


Figure 2) Percentage of HepG2 cell viability after oxaliplatin treatment for 24 h (A) and 72 h (B). Data are presented as mean ± S.D. in three independent experiments. * $p<0.05$, ** $p< 0.01$ (Student's t-test compared with control group)

Invasion is a critical step of metastasis. Pretreatment of oxaliplatin on HepG2 cells were significantly indicated increasing invasion rate at 24 h compared with control groups (Fig. 3A).

Invasion process involves cell migration and ECM-remodeling enzymes. Cell migration rate of HepG2 cells after oxaliplatin treatment was significantly increased (Fig. 3B).

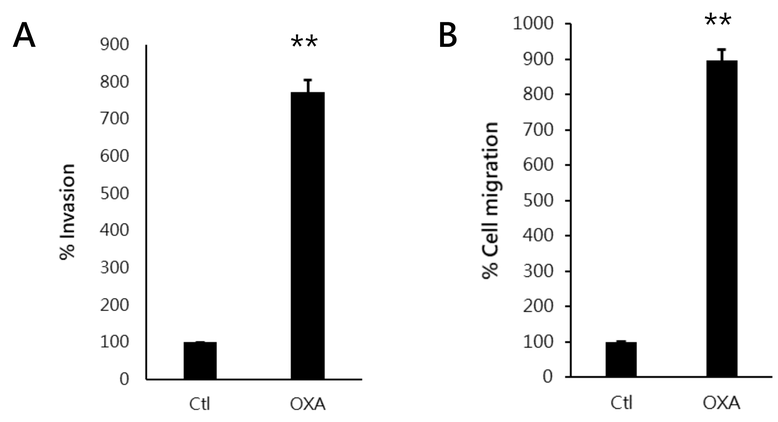
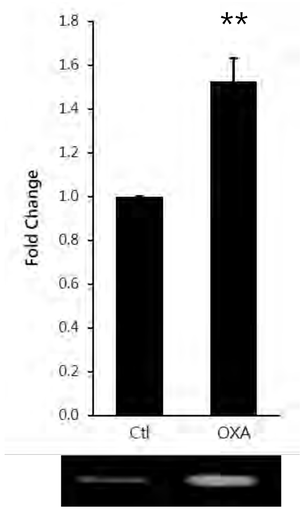


Figure 3) Percentage of invasion (A) and migration (B) of HepG2 cells after oxaliplatin treatment for 24 h. ** $p< 0.01$ (Student's t-test compared with control group)



MMP-2 facilitates cell invasion by degrading ECM. Gelatin zymography demonstrated the significant increase in level and activity of MMP-2 secreted by HepG2 cells after oxaliplatin treatment, compared with control group (Fig. 4).

Figure 4) Fold change of level and activity of MMP-2 secreted from HepG2 cells after 24 h oxaliplatin treatment. ** $p< 0.01$ (Student's t-test compared with control group)

- Cancer invasion is influenced by several processes including cell migration and ECM-remodeling enzymes. Here, we demonstrated that a short-term treatment (24 h) of oxaliplatin increased invasiveness of HepG2 cells by enhancing cell migration rate and MMP-2 secretion.

There are numerous evidences that indicate the effect of chemotherapeutic drugs on acceleration of invasion process (4). For example, Doxorubicin induced cell migration in breast cancer cells (5). Paclitaxel gained metastatic potential of cancer cells by modulation of MMPs enzymes in breast cancer model (6). In conclusion, the invasion-promoting effect of oxaliplatin could be observed in HepG2 cells after short-term exposure to the drug, and the underlying mechanism of this effect is the enhancement of cell migration capacity and MMP-2 production induced by oxaliplatin.