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Erratum

The following was originally published in Volume 28, Number 5, pages 467–481 (doi: https://doi.org/10.3727/096504020X15925659763817). In the original article there was misuse of Figure 3C. Because of this error the corrected figure is provided here and the figure has been replaced with the correct version in the original article in the online site (https://www.ingentaconnect.com/contentone/cog/or/2020/00000028/00000005/art00002). We apologize for our carelessness and inconvenience to readers.

Programmed Death Ligand-1 (PD-L1) Regulated by NRF-2/MicroRNA-1 Regulatory Axis Enhances Drug Resistance and Promotes Tumorigenic Properties in Sorafenib-Resistant Hepatoma Cells

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Sorafenib, a multityrosine kinase inhibitor, is a standard treatment for advanced hepatocellular carcinoma (HCC), but the clinical response to sorafenib is seriously limited by drug resistance. Programmed death ligand-1 (PD-L1) is one of the most important inhibitory molecules involved in tumor immune evasion. Recently, it has been reported that PD-L1 could play crucial roles in drug resistance of many kinds of cancers. However, the expression, function, and regulation of PD-L1 in sorafenib-resistant hepatoma cells remain unclear. In this study, we reported that PD-L1 was overexpressed in sorafenib-resistant hepatoma cells, and shRNA-mediated PD-L1 depletion attenuated drug resistance and suppressed the migration, invasion, colony formation, and tumorigenesis in sorafenib-resistant hepatoma cells in vitro and in vivo. Mechanistic investigations indicated that loss of microRNA-1 (miR-1), a tumor-suppressive microRNA, contributed to the PD-L1 upregulation in sorafenib-resistant hepatoma cells, and PD-L1 was a direct regulatory target of miR-1. Further study revealed that an oncogenic transcriptional factor, nuclear factor E2-related factor 2 (NRF-2), was induced in sorafenib-resistant hepatoma cells and inhibited expression of miR-1 in vitro. From molecular mechanism insight back to the functional verification, we eventually demonstrated that miR-1 executed its tumor-suppressive effects on drug resistance and other malignant properties in sorafenib-resistant hepatoma cells partially by PD-L1 inhibition in vitro and in vivo. In conclusion, our data suggested that a NRF-2/miR-1/PD-L1 regulatory axis contributed to the development and maintenance of drug resistance and other tumorigenic properties in sorafenib-resistant hepatoma cells and provided a potential therapeutic target for overcoming sorafenib resistance in HCC.

Key words: Sorafenib; Drug resistance; PD-L1; Hepatoma cells; MicroRNA-1 (miR-1); Nuclear factor E2-related factor 2 (NRF-2)

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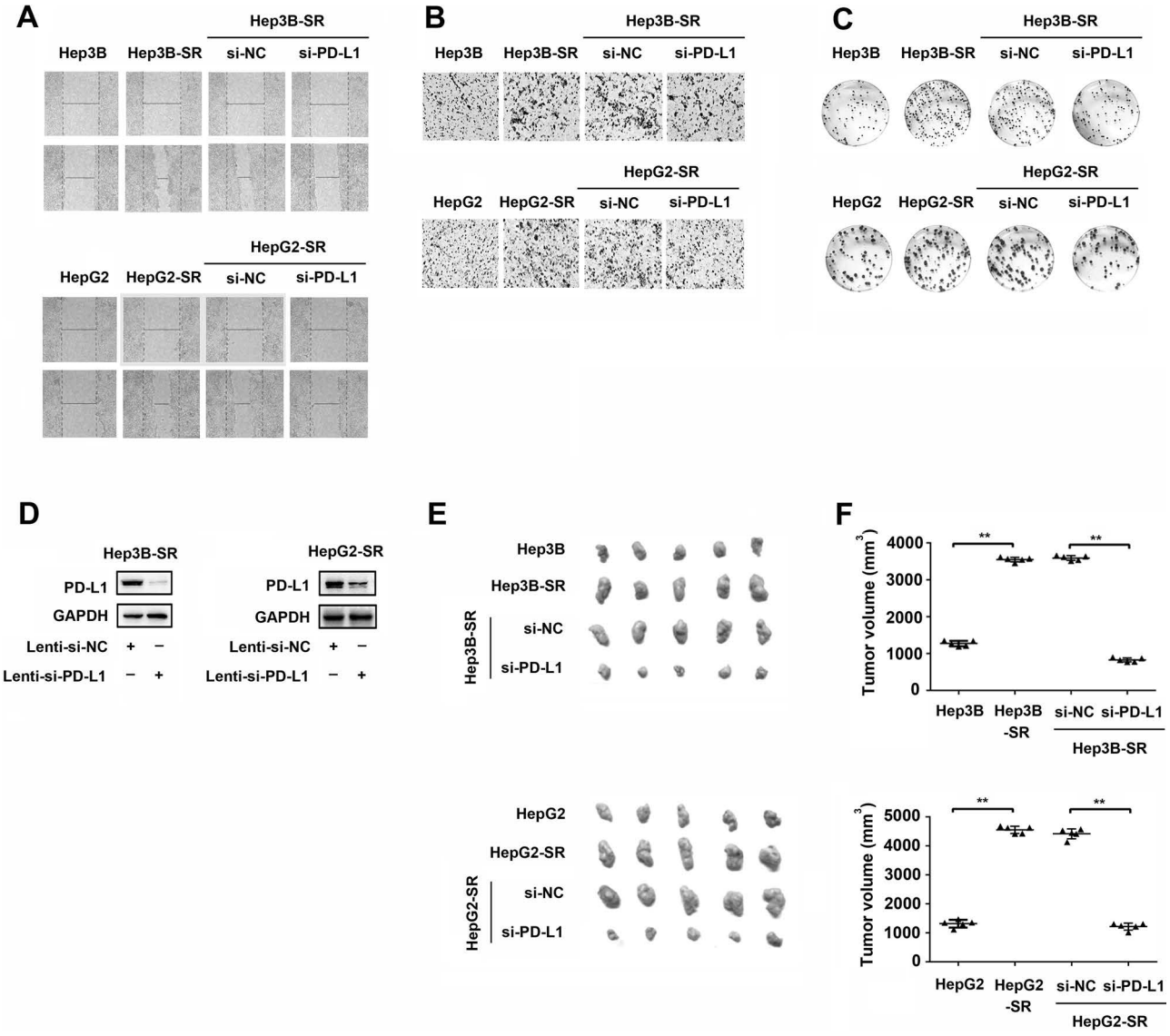

Figure 3. PD-L1 knockdown suppresses tumorigenic properties of sorafenib-resistant hepatoma cells. (A) Representative images of wound healing assay in sorafenib-resistant hepatoma cells and their parental cells. (B) Representative images of Matrigel invasion assay in sorafenib-resistant hepatoma cells and their parental cells. (C) Representative images of colony formation assay in sorafenib-resistant hepatoma cells and their parental cells. (D) Efficiency of PD-L1 knockdown by infection of PD-L1 siRNA-expressing recombinant lentivirus (Lenti-si-PD-L1) in sorafenib-resistant hepatoma cells was confirmed by Western blotting. $n = 3$. $^{**}p < 0.01$. (E, F) Representative images and data quantification of subcutaneous tumor sizes in BALB/c nude mice. $n = 5$. $^{**}p < 0.01$.