Plasmodium immunotherapy combined with gemcitabine has a synergistic inhibitory effect on tumor growth and metastasis in murine Lewis lung cancer models

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Abstract

Objective: Our previous studies have demonstrated that Plasmodium immunotherapy (infection) has antitumor effects in mice. However, as a new form of immunotherapy, this therapy has a weakness: its specific killing effect on tumor cells is relatively weak. Therefore, we tested whether Plasmodium immunotherapy combined with gemcitabine (Gem), a representative chemotherapy drug, has synergistic antitumor effects.

Methods: We designed subcutaneously and intravenously implanted murine Lewis lung cancer (LLC) models to test the antitumor effect of Plasmodium chabaudi ASS (Pc) infection in combination with Gem treatment and explored its underlying mechanisms.

Results: We found that both Pc infection alone and Gem treatment alone significantly inhibited tumor growth in the subcutaneous model, and combination therapy was more effective than either monotherapy. Monotherapy only tended to prolong the survival of tumor-bearing mice, while the combination therapy significantly extended the survival of mice, indicating a significant synergistic effect of the combination. In the mechanistic experiments, we found that the combination therapy significantly upregulated E-cadherin and downregulated Snail protein expression levels, thus inhibiting epithelial-mesenchymal transition (EMT) of tumor cells, which may be due to the blockade of CXCR2/TGF-β-mediated PI3K/Akt/GSK-3β signaling pathway.

Conclusion: The combination of Pc and Gem plays a synergistic role in inhibiting tumor growth and metastasis, and prolonging mice survival in murine lung cancer models. These effects are partially attributed to the inhibition of EMT of tumor cells, which is potentially due to the blockade of CXCR2/TGF-β-mediated PI3K/Akt/GSK-3β/Snail signaling pathway. The clinical transformation of Plasmodium immunotherapy combined with Gem for lung cancer is worthy of expectation.

Keywords: Plasmodium immunotherapy, Plasmodium chabaudi ASS, gemcitabine, anticancer effect, synergism, mouse lung cancer model