Photodynamic therapy-based combinations with immunotherapy in colon cancer treatment

Hao, Y.

APPENDICES

English summary

This PhD thesis starts with a general introduction (**Chapter 1**), which briefly describes the state of the art in oncology, nanotechnology and immunology research. Photodynamic therapy (PDT) is an established approach for the treatment of superficial cancers, with the advantage of low damage to normal tissues and being modestly invasive. My PhD research work has aimed to improve the therapeutic response of PDT in solid tumors by combining it with other therapeutic approaches and using nanotechnology to achieve tumor specific delivery.

In **Chapter 2**, the anti-cancer effects of the combination therapy of PDT with a novel immune activator adjuvant, STING agonist, are reported. STING agonist is an emerging and promising immunotherapeutic approach. This chapter describes the effects of single and combined treatments on primary colorectal cancer tumors. Immunological analyses of primary tumors, draining lymph nodes, and blood were performed. The combination of PDT with ADU-S100 transforms the tumor microenvironment and promotes adaptive immune responses in colon cancer of mice. Finally, we investigated the potential of treatment alone or combined to resist tumor recurrence and growth of distal tumors (simulated metastasis model). We discovered that combined therapy mediated local and systemic anticancer immunity and $CD4^+$ and $CD8^+$ T cell-mediated immune memory. This immune memory leads to rejection of syngeneic tumor rechallenge in cured mice and reduces untreated distant tumor growth.

In **Chapter 3**, we investigated whether the anti-cancer effect of PDT could be improved by combining it with a pharmacological vaccine that stimulates the systemic immune response. MC38 murine colorectal cancer model was used to examine the effects of single and combined treatments. Although hepatitis B core virus-like particles (HBc VLPs) induce APC activation and antibody responses, it cannot induce tumor growth arrest. Nevertheless, compared to individual therapies, an increased overall survival percentage is observed after PDT in combination with HBc VLPs. In addition, the levels of circulating lymphocytes and total IgG in the blood after the combination treatment were analyzed, as well as the response of different immune memory T cells upon reinfection. We observed a "reappearance" of amplified immune responses upon combination treatment and a recurrence protection in combined therapy.

In **Chapter 4**, the existing literature on nanoparticle-based PDT combination therapies is summarized. In particular, the combination of PDT with chemotherapy or immunotherapy in combination with nanoparticles is reviewed. In addition, the advantages and disadvantages of different types of nanoparticles and their important role in combination therapy are described. The possibilities of more effective PDT combination strategies, which are supported by nanoparticles for complex tumor settings and difficult-to-treat recurrent and metastatic tumors, are discussed.

In **Chapter 5**, we determined whether Poloxamer 407 (P407) hydrogel-supported photoimmunotherapy is suitable for treatment of colorectal cancer. The hydrogel as delivery vehicle was chosen because of its wide clinical use and its good biocompatibility

and biosafety. In this chapter, the anti-cancer effects of polymeric P407 hydrogel, which is co-loaded with photosensitizer (for PDT) and immune checkpoint inhibitors, were investigated. We found that a single dose of hydrogel, resulting less cumbersome treatment schemes, which potentially mitigates side effects and enhance antitumor efficiency by appropriate ICI administration time points after PDT.

In conclusion, my PhD research has provided a better understanding of PDT-based combination therapy in colorectal cancer. My research results may contribute to developing of new therapeutic regimens by overcoming the shortcomings of current single treatments and integrating the benefits of individual treatments. I hope it will allow for the clinical translation of PDT in colorectal cancer.