Innate immune responses of natural killer cells and macrophages against bone sarcomas : towards cellular immunotherapy

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Innate Immune Responses of Natural Killer cells and Macrophages against Bone Sarcomas

Towards Cellular Immunotherapy

PhD Thesis

Jens Pahl

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CONTENTS OF THIS THESIS

OUTLINE AND SCOPE OF THIS THESIS

The research performed in this thesis demonstrates that human natural killer cells and macrophages are able to mediate anti-cancer immune responses against osteosarcoma and Ewing sarcoma. Implications for harnessing natural killer cells and macrophages for potential anti-cancer immunotherapy are described.

Osteosarcoma and Ewing sarcoma are the most common bone cancers in children and young adults. Despite advanced surgical techniques and multi-drug chemotherapy, one-third of the patients still succumb to recurrent disease with poor prognosis. Likewise, patients with metastatic and chemotherapy-resistant disease have a poor outcome. Thus, novel targeted therapies are needed that combine potent and specific anti-cancer activity with limited toxicity toward normal tissues. Previous research lines have provided evidence that natural killer (NK) cells and macrophages, both cell types of the innate immune system, are able to contribute to anti-cancer responses against osteosarcoma and Ewing sarcoma cells.

The research in this thesis is performed with the aim to characterize cellular interactions of NK cells and macrophages with osteosarcoma and Ewing sarcoma cells in order to achieve favorable effects on anti-cancer immune cell functions. It is explored in preclinical studies, how the anti-cancer potential of especially NK cells but also macrophages can be enhanced and directed to cancer cells. Modulation of tumor–immune cell interactions and the cytolytic activity of NK cells and macrophages may help to design novel immunotherapeutic approaches to harness anti-cancer functions of (innate) immune cells against osteosarcoma and Ewing sarcoma.

In the following introductory chapter 1, clinical and biological properties of osteosarcoma and Ewing sarcoma are described, followed by an overview of cancer immunology and immunotherapy with the primary focus on innate immunity of NK cells and macrophages. The chapters 2 to 6 compose the main body and are further outlined in section 3 of chapter 1. The thesis is concluded by chapter 7 with a general discussion of the key findings.