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„ Zbadanie roli komórek erytroidalnych wykazujących ekspresję cząsteczki CD71 (CECs) w regulacji odpowiedzi układu odpornościowego”

Streszczenie w języku angielskim

Elucidating the role of CD71+ erythroid cells (CECs) in the regulation of immune response

CD71+ erythroid cells (CECs) are progenitors and precursors of erythrocytes that have been recently identified as the regulators of the immune response. Anemia is the main factor that induces their expansion. However, the immunoregulatory role of anemia-induced CECs remained unknown. The aim of this dissertation that includes three publications was to describe the role of CECs in the regulation of immune response and to elucidate the immunoregulatory properties of anemia-induced CECs.

The first article included in the publication series is a review article “The role of CD71+ erythroid cells in the regulation of the immune response” published in Pharmacology & Therapeutics. This article discusses the mechanisms of erythropoiesis regulation and describes the role of CECs in the regulation of immune response in physiological and pathological processes in mice and humans. The role of CECs in neonates, in pregnant women, during the development of maternal-fetal tolerance, in cancer, in patients with infectious diseases, inflammatory diseases, and anemia is described. Next, we described the mechanisms of immune response regulation by CECs, including hydrolysis of L-arginine by arginase (ARG), production of transforming growth factor β (TGF-β), expression of immune checkpoints, production of immunomodulatory cytokines, and production of reactive oxygen species (ROS). This article presents potential therapeutic strategies to regulate the formation and maturation of CECs as well as methods to modulate their immunoregulatory properties. Additionally, it indicates what elements in the knowledge about CECs require further investigation and what are the prospects for further research on the role of these cells.

In the article "Tumor Immune Evasion Induced by Dysregulation of Erythroid Progenitor Cells Development", published in the Cancers journal, changes in erythropoiesis induced by cancer were described. Based on literature data, the dysregulation in the process of formation and differentiation of CECs in different types of cancer is presented. Next, the role of CECs as immunoregulatory cells is described and their functions are compared with well-described immune cells that play a role in the regulation of anti-tumor response, including myeloid-derived suppressor cells (MDSCs) and regulatory T cells. Next, the role of CECs in regulating antitumor and systemic immune responses in patients with cancer is presented. In addition, the effects of CECs on tumor cell proliferation and invasiveness and disease progression, depending on the differentiation stage of CECs, are described. Furthermore, the mechanisms leading to the expansion of CECs that are involved in increasing the risk of cancer progression and potential therapeutic strategies to promote the maturation of CECs and reduce their expansion are discussed. Finally, the clinical significance of CECs as regulators of disease progression and prognostic markers is presented.

The third publication is the original article "Potent but transient immunosuppression of T-cells is a general feature of CD71+ erythroid cells" published in the journal Communications Biology. The article describes the expansion of CECs at early stages of maturation in murine models of acute anemia. In this work, it was shown that expansion of CECs does not affect the production of IgG class anti-ovalbumin (OVA) antibodies in response to immunization in anemic mice or the production of tumor necrosis factor α (TNF-α) by cells expressing the CD11b molecule in the spleen, while it leads to the

impairment of the proliferation of cytotoxic T lymphocytes that recognize the OVA-derived peptide. Subsequently, anemia-induced CECs were shown to be responsible for impaired T-cell proliferation in ex vivo experiments. High expression of the mitochondrial ARG isoform, ARG2, and high levels of ROS in mouse CECs were described. Subsequently, ARG2 and ROS were shown to be crucial mechanisms of T-cell regulation by CECs in anemia. Furthermore, it was confirmed that CECs at the early stages of maturation, before enucleation, are responsible for the inhibition of T-cell proliferation. We further described the expansion of CECs in the peripheral blood of anemic patients and their effect on the inhibition of interferon γ (IFN-γ) production by T-cells. We observed the expression of both ARG isoforms and their role in regulating T-cell proliferation by CECs in the bone marrow of healthy donors. Using CECs differentiated from peripheral blood mononuclear cells (PBMCs) of healthy blood donors and model human erythroid cell lines, the role of ARG and ROS in the regulation of T-cell responses by human CECs was confirmed. It was demonstrated that CECs at the early stages of maturation possess the strongest immunoregulatory properties, which disappear with further differentiation of CECs.

In summary, the results presented in this dissertation indicate that CECs have important immunoregulatory functions in a variety of physiological and pathophysiological conditions. The role of CECs in the regulation of the immune response in anemia and the dependence of this regulation on ARGs and ROS were demonstrated. The immunoregulatory functions of CECs have been shown to be significantly altered during their differentiation and found to be the strongest at the earliest stages of erythroid cell maturation. Modulation of the differentiation of CECs and the mechanisms they use to regulate the immune response are promising therapeutic targets in many diseases.