UMEÅ UNIVERSITET

Umeå University Medical Dissertations, New Series No 2342

Neutrophils in cancer and cancer treatment

Anna Thunström Salzer

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av medicine doktorsexamen framläggs till offentligt försvar i Hörsal D, by 1D, plan 9, Umeå Universitetssjukhus, fredagen den 14:e februari, kl. 09:00.

Avhandlingen kommer att försvaras på engelska.

Fakultetsopponent: Adjungerad professor, Mikael Uhlin,

Institutionen för medicin, Karolinska Institutet, Stockholm, Sverige

Department of Clinical microbiology

Organization
Umeå University
Department of Clinical microbiology

Document type
Doctoral thesis

Date of publication
23 January 2025

Author
Anna Thunström Salzer

Title
Neutrophils in cancer and cancer treatment

Abstract
As part of innate immunity, neutrophils constitute the first line of defense against microbial infections. A low neutrophil count is a considerable risk factor for acquiring severe infections and is a common side effect for patients undergoing chemotherapy. Whether or not neutrophil function is affected by chemotherapy is still largely unknown. We evaluated the functions of neutrophils derived from the newly generated bone marrow of patients who underwent allogeneic stem cell transplantation. We sought to understand whether extended neutrophil dysfunction could add to the risk of infection. For this purpose, we assessed chemotaxis, phagocytosis, and oxidative burst using fluorescence- and luminol-based methods in neutrophils from transplanted patients. We found a decrease in chemotactic ability two weeks after neutrophil engraftment, and the lowered response only normalized at later time points. Interestingly, we observed a similar reduction in chemotactic ability in neutrophils isolated from healthy stem cell donors undergoing treatment with granulocyte-colony-stimulating factor (G-CSF) to prepare for stem cell donation, suggesting that this effect might be transferred to the newly generated neutrophils by an unknown mechanism.
Chemotherapy-free treatment against acute promyelocytic leukemia (APL) using arsenic in combination with retinoic acid has proven to be effective. One of the additional benefits is a decreased risk of neutropenia; however, to what extent the treatment affects neutrophil function remains unknown. We found that neutrophil function was altered in a compensatory manner, with increased chemotaxis at time points with decreased numbers of neutrophils.
In solid cancers, a high number of neutrophils in peripheral blood is often linked to a worse prognosis. In these instances, neutrophils frequently accumulate in the tumor microenvironment. We used a co-culture model with breast cancer cells and stromal cells to investigate the interaction between neutrophils and the tumor microenvironment. Culturing the cells together created a proinflammatory environment, much like the scenario seen in cancerous tissue. The supernatant was chemoattractive to neutrophils from healthy donors and activated them to produce reactive oxygen species. When neutrophils were added to the co-culture model, using Seahorse analysis, we observed a shift in the metabolic pattern of the co-culture, creating an increase in mitochondrial function. We conclude that the increased mitochondrial activity indicates a protumorigenic effect exerted by neutrophils.
In summary, neutrophil function in patients with hematological diseases is altered due to treatment and could contribute to patients' susceptibility to infection. Neutrophils alter the metabolism of cells in a cancer fibroblast co-culture, favoring the tumor cells, suggesting that neutrophils might be a promising target for future anticancer treatment.

Keywords
neutrophil, cancer, G-CSF, allogeneic transplantation, acute promyelocytic leukemia, chemotaxis, tumor microenvironment, tumor cell metabolism

Language
English

ISBN
print: 978-91-8070-592-9
PDF: 978-91-8070-593-6

ISSN
0346-6612

Number of pages
64 + 3 papers