Immuno-Oncology Research Approaches in Hodgkin Lymphoma

TABLE OF CONTENTS

Introduction to Immuno-Oncology (I-O) in Hodgkin lymphoma

Hodgkin lymphoma epidemiology

Lymphoma is a cancer of the lymphatic system. There are two types of lymphoma: Hodgkin lymphoma and non-Hodgkin lymphoma.[1] Hodgkin lymphoma affects around 9,000 new patients annually in the US.[2]

Hodgkin lymphoma is unique compared to other malignancies in that it has a bimodal age distribution, peaking first in early adulthood, followed by another peak in late adulthood.[1,3,4] There is a higher prevalence of Hodgkin lymphoma in males and it is more common in Western countries.[1,4]

Treatment modalities

Current treatment modalities for Hodgkin lymphoma include **chemotherapy** and **radiation, stem cell transplantation**, **targeted therapy** and **immunotherapy**.[1] Traditional treatment approaches with chemotherapy and/or radiation therapy lead to responses in approximately 80% of all Hodgkin lymphoma cases.[5]

Despite this, about 10% of early-stage patients and 20%–30% of advanced-stage patients relapse or become refractory to initial lines of treatment,[6] which often include chemotherapy and radiation. In later lines of therapy, autologous stem cell transplantation and other therapies are used.[7,8,9]

The **emerging modality of immuno-oncology** seeks to harness the immune system's ability to detect and destroy tumor cells. Ongoing research is investigating immune-based cancer treatments as a potential option for patients.

Treatment modalities in Hodgkin lymphoma

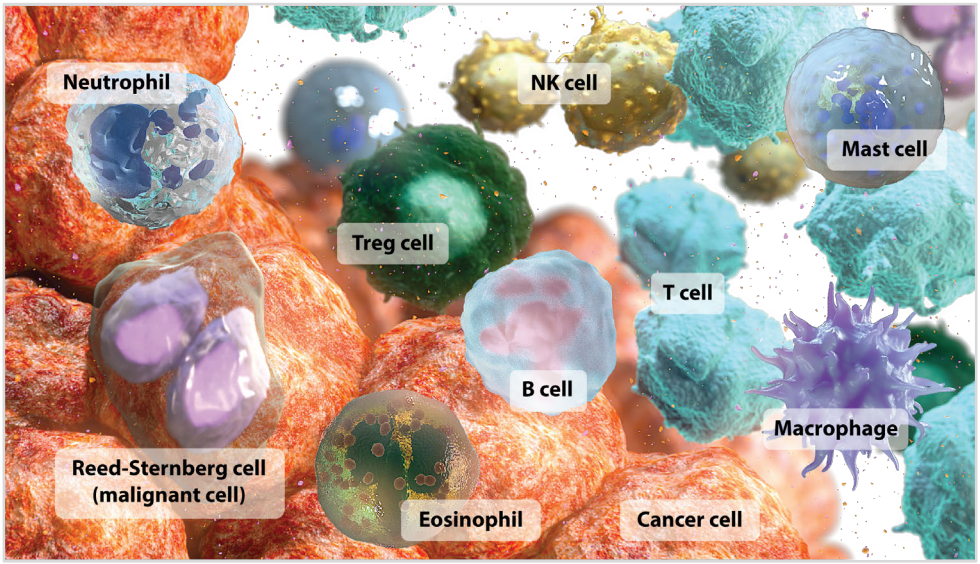
Role of the immune system in Hodgkin lymphoma

The immune system has natural anti-tumor activity

The immune system can recognize tumor cells and initiate an anti-tumor response to eliminate cancer. This is also known as tumor immune surveillance.[10]

Hodgkin lymphoma leads to a unique tumor microenvironment

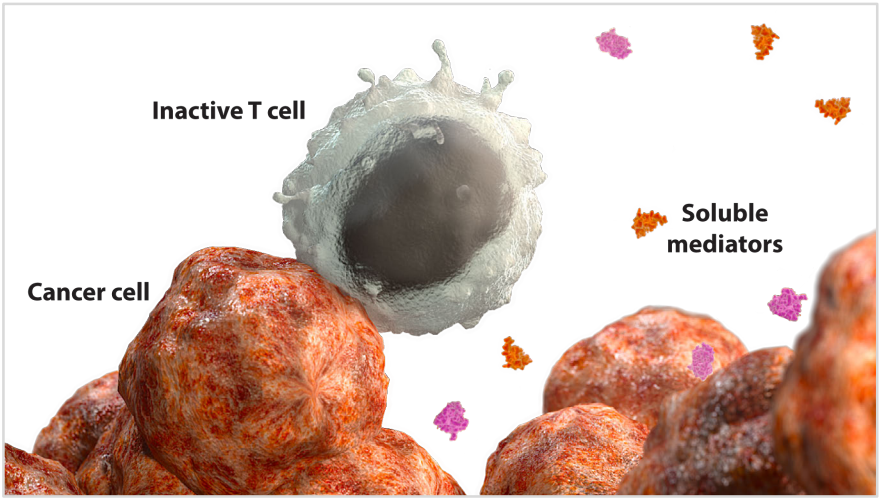
The development of disease starts within lymphocytes in the lymphatic system and eventually leads to the growth of a tumor, characterized by malignant cells that are surrounded by immune cells.[15] The hallmark of Hodgkin lymphoma is the presence of malignant Hodgkin Reed-Sternberg cells, which are derived from crippled B cells.[1,2,5,11] These malignant cells only make up a small minority of the total tumor mass. The rest of the tumor mass is dominated by a mixture of immune cells, including B cells, T cells, natural killer cells, mast cells, eosinophils, neutrophils and macrophages.[5]



In the Hodgkin lymphoma tumor microenvironment, malignant cells are surrounded by immune cells

Tumor evasion of the immune system

This unique tumor microenvironment actively suppresses immune responses, promotes tumor growth, and disease progression. Here, malignant Reed-Sternberg cells can interact with the immune cells in their environment through **direct cellular interactions** and through **the release of soluble mediators** which attract additional immune cells to the site.[5] By manipulating their environment, Reed-Sternberg cells can avoid attack by cytotoxic T cells or natural killer cells by attracting suppressive immune cells that can dampen the immune response. For example, malignant cells can attract regulatory T cells, also called Tregs, which inhibit cytotoxic T cell activity, making T cells less able to recognize and kill malignant cells.[5]



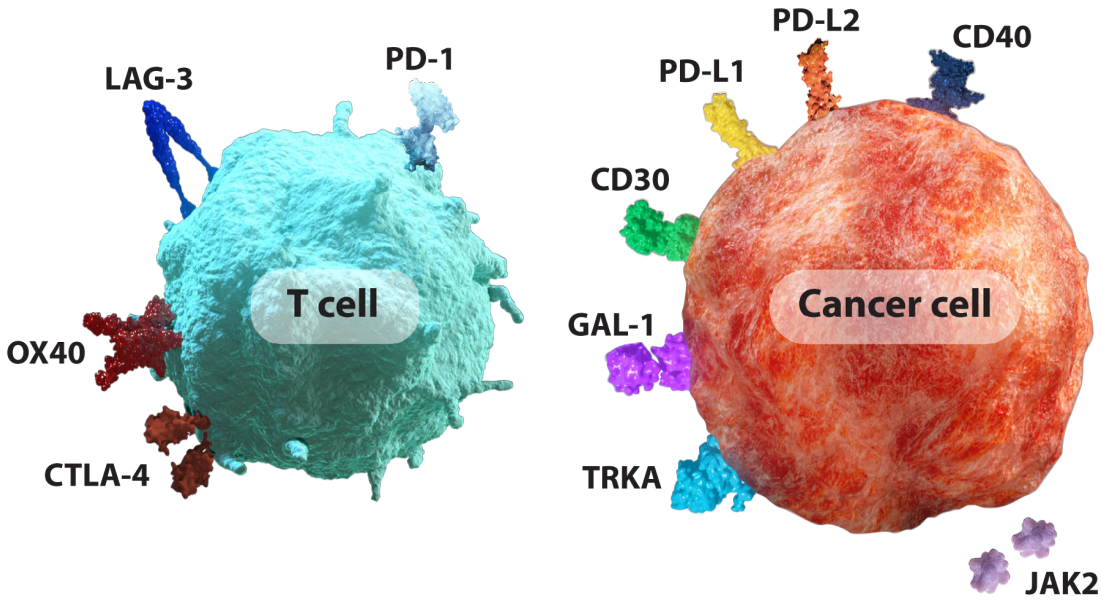
Tumor cells manipulate their environment through release of soluble mediators and direct cellular interactions

Immune system pathways of interest

Tumors can exploit specific molecular interactions to inactivate T cells

There is evidence that many immune system pathways are affected in Hodgkin lymphoma. For example, chromosome 9p24.1 amplifications in Reed-Sternberg cells have been shown to increase **PD-L1**, **PD-L2** and **JAK2** expression.[12] The overexpression of PD-1 ligands suggests a genetically determined capacity for immune evasion in these cells. Overexpression of immune checkpoint proteins, such as PD-L1, suppresses anti-tumor immune responses through T-cell exhaustion.[9,13]

Reed-Sternberg cells also express surface molecules, such as **GAL-1**, **CD30**, **CD40** and **TRKA,** which are thought to facilitate tumor growth and immune evasion.[5,14-17] Additionally, **LAG-3** expression on CD4+ T cells and NK cells in Hodgkin lymphoma is thought to suppress antitumor immunity through its effects on T cells, Tregs and NK cells.[18] Similarly, T cells expressing **OX40,** which is involved in immune tolerance, and **CTLA-4,** which negatively regulates T cell activation, are seen in Hodgkin lymphoma.[19,20]



Immune pathways that are exploited by tumors in Hodgkin lymphoma

Ongoing investigation into immune pathways

These key regulatory pathways represent advances in understanding the tumor microenvironment which has led to the investigation of various immuno-oncology strategies in Hodgkin lymphoma.

There is a strong biological and scientific rationale for investigating immuno-oncology approaches in Hodgkin Lymphoma, as Reed-Sternberg cells use checkpoint pathways to evade immune responses. Various strategies are under investigation which seek to interrupt the crosstalk between the tumor cells and the immune cells in the tumor microenvironment. Pathways under investigation include **PD-1**, **CTLA-4**, **LAG-3**, **CD27** and **OX40**.[21,22,23] Modulating these immune pathways either alone or in combination may enhance immune activity in the treatment of Hodgkin lymphoma.

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