

HODGKIN'S LYMPHOMA

Pathoprofile

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INTRODUCTION

Hodgkin's lymphoma (HL) is a type of cancer that affects the lymphatic system. It is one of the most common lymphomas in the Western world, with an annual incidence of about 3 cases per 100,000 persons.¹ In 2017, 990 Canadians were diagnosed with HL, of which 140 died.² The age groups most affected by HL are individuals 20-40 years old and those 55 or older. In general, cancerous tumours are the result of transformed cells that proliferate uncontrollably and invade healthy tissues.³ While HL usually starts in peripheral lymph nodes, it can also affect organs such as the liver, lung, and the bone marrow.² The tumour cells causing the malignancy can take on different phenotypes, and as a result the disease is divided into two major types: classical HL and nodular lymphocyte-predominant HL. This Pathoprofile will focus specifically on the classical form of HL, which accounts for 95% of HL cases.¹

CELLS IN CLASSICAL HL

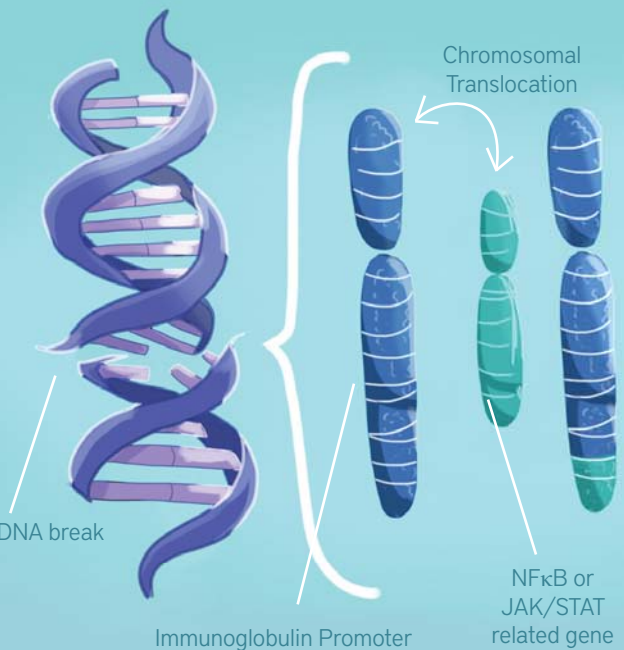
HL is diagnosed by the presence of transformed B cells known as Hodgkin and Reed-Sternberg (HRS) cells, which drive tumorigenesis.⁴ Although HRS cells are critical to HL pathogenesis, they only comprise 1 - 10% of the tumour tissue, which is otherwise dominated by normal fibroblasts, endothelial cells and infiltrating immune cells.⁵



Lymph node



Pro-B Cell



Double-stranded DNA break

Immunoglobulin Promoter

Chromosomal Translocation

NFκB or JAK/STAT related gene

B CELL DEVELOPMENT

B cells are an integral component of the adaptive immune system responsible for the production of antibodies that recognize foreign or self molecules known as antigens.⁶ Antibodies contain a variable region which can bind the antigen, and a constant region which can activate the immune response. The immune system must recognize a diverse repertoire of antigens to protect the host from the extensive number of pathogens encountered during their lifetime. This diversity is generated by genetic recombination which involves the introduction of double-stranded breaks in the DNA. This produces B cells that express a unique B cell receptor. After a naïve B cell encounters its corresponding antigen for the first time, it will undergo additional recombination events termed somatic hypermutation as well as class switching before becoming a mature B cell.⁶

TRANSFORMATION INTO HRS

HRS cells, the tumour cells responsible for HL, originate from clonally related mature B cells as evidenced by their identical gene recombinations at the antibody locus.⁷ The properties of cancerous cells are acquired, in part, from mutations affecting proto-oncogenes, which are typically genes that promote proliferation and cell survival. Proto-oncogenes can become cancer-causing oncogenes if mutated or upregulated.⁸ HRS cells acquire transforming mutations from chromosomal translocations that result from inappropriate resolution of double-stranded DNA breaks elicited by antibody gene recombination.⁴ Typically, proto-oncogene expression is tightly regulated to prevent unwanted cellular proliferation and survival. The translocation of the proto-oncogene downstream of the antibody transcription promoter results in constitutive expression, thus causing continuous unregulated oncogene activation.^{9,10} Typically, B cells with deleterious B cell receptors undergo apoptosis; however, HRS cells escape apoptosis and do not mature further.¹¹ HRS cells resemble pre-apoptotic germinal centre B cells that have undergone somatic hypermutation.¹⁰

CELL SIGNALING PATHWAYS IN HL

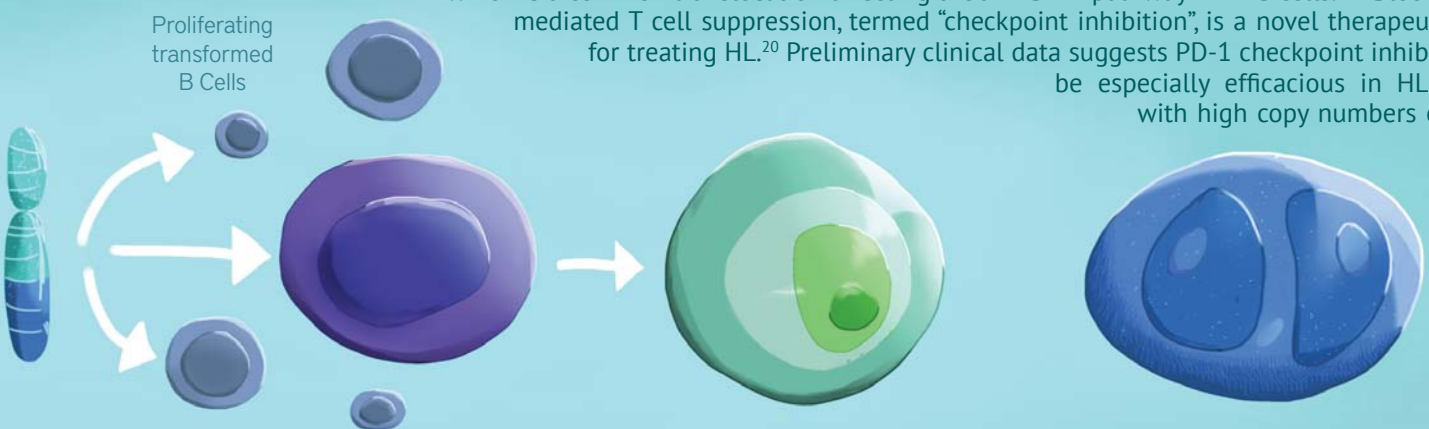
NF-κB and JAK-STAT cell signalling pathways are commonly affected by oncogenes expressed in HRS cells.^{7,9,12-15} While both of these pathways are normally activated in B cells and other immune cells, they are not constitutively active as in the malignant cells of classical HL.¹⁶ NF-κB is a transcription factor important for lymphocyte proliferation and survival, thereby endowing

it with oncogenic potential.¹⁷ Deregulated activation of the NF- κ B pathway due to constitutively expressed NF- κ B-related oncogenes can contribute to a cancerous phenotype in HRS cells. This is achieved by inducing unregulated proliferation, increasing the likelihood of cell survival and tissue invasion, and producing cytokines that contribute to the tumour microenvironment.¹⁸ The JAK-STAT pathway, normally activated by cytokines, regulates cell proliferation, differentiation, and survival, thereby also endowing it with oncogenic potential.¹⁵ JAK-STAT pathway mutations in HL can lead to constitutive activation of STAT transcription factors regardless of cytokine binding, resulting in uncontrolled cell proliferation and survival.⁹ Dysregulation of both the JAK-STAT and NF- κ B pathways is mechanistically diverse and can be caused by oncogenes affecting proteins at any step that either increase pathway activation or decrease activity of pathway inhibitors.¹⁵

TUMOUR MICROENVIRONMENT

In HL, only a small proportion of the tumour tissue is composed of the malignant HRS cells.⁹ Immune cells including T and B cells, eosinophils, neutrophils, plasma cells, and mast cells infiltrate the lymphoma and substantially contribute to tumour mass. Despite immune infiltration, the tumour is not destroyed because of a highly immunosuppressive environment.¹⁹ HRS cells can produce anti-inflammatory cytokine TGF- β and induce T regulatory cell differentiation, which can prevent T cell activation.¹⁹ There are also intrinsic changes to HRS cells that aid in immune evasion. They often carry a mutated β 2-microglobulin, a component of MHC class I, resulting in reduced antigen presentation to cytotoxic T cells.⁴ In some cases, the patient's HRS cells will directly inhibit T cell activation by upregulating programmed death-ligand 1 (PD-L1).⁴ Activated T cells express the PD-1 receptor and binding of HRS cell PD-L1 to T cell PD-1 inhibits the T cell response. PD-L1 is often upregulated following JAK2 copy number amplification,

which is a common translocation affecting the JAK-STAT pathway in HRS cells.^{4,20} Blocking PD-1 mediated T cell suppression, termed "checkpoint inhibition", is a novel therapeutic target for treating HL.²⁰ Preliminary clinical data suggests PD-1 checkpoint inhibition may be especially efficacious in HL patients with high copy numbers of JAK2.²⁰



Hodgkin's and Reed-Sternberg Cells

CLINICAL PRESENTATION

Patients with HL present with enlarged lymph nodes at the site of disease resulting from tumour tissue composed of HRS cells and tumour-infiltrating immune cells. If the enlargement of mediastinal nodes is significant, the mass effect can produce chest pain and shortness of breath. Around 40% of patients will present with a series of symptoms known as "B symptoms," which include unexplained profound weight loss, high fevers, and drenching night sweats. These symptoms are generally more common in severe forms of the disease.¹ In addition, each subtype of HL has distinct clinical features. Definitive diagnosis for HL is achieved through biopsy from a lymph node or suspected organ, and the histology will determine the type of HL that the patient has. From this, the appropriate treatment can be decided.

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Dr. Jonathan Bramson is a Professor in the Department of Pathology and Molecular Medicine and the Vice Dean of Research in the Faculty of Health Sciences. He holds a Tier I Canada Research Chair in Translational Cancer Immunology and the John Bienenstock Chair in Molecular Medicine. The Bramson lab is focused on developing methods to direct cancer patients' immune systems to attack their tumours. Currently, the lab is using synthetic biology methods to direct T cells against discrete tumour targets.

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