The Duality of the JAK/STAT & the NFκB Pathway Malfunctioning to Create the Detrimental Consequences of Hodgkin's Lymphoma

Sadia Rahat

Abstract: Hodgkin's Lymphoma (HL) is a type of blood cancer that primarily affects white blood cells. It is divided into two different subcategories, such as classic Hodgkin Lymphoma (cHL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL). Both types are affected by mutations in two pathways: the JAK/STAT Pathway and the NFκB Pathway. The JAK/STAT Pathway focuses on a fast membrane-to-nucleus signaling pathway that can trigger the expression of many mediators within cancer and inflammation. NFκB is a transcription factor that can monitor and check parts of the immune system and can be helpful for inflammatory responses. Hence, mutations in either pathway can result in the proliferation of tumor cells, as the checkpoints and regulators in the pathway are dysregulated. In this review, the specific transcription of certain genes is discussed, and the differences between a normal pathway and its mutational effects are emphasized. The implications of the mutations and the spread of the lesions through molecular pathways are explained. Specific treatments focused on inhibitors within the pathways, which have resulted in either positive or negative effects are also considered. Both pathways mentioned, contribute to the development of Hodgkin's Lymphoma. Which is why understanding the mutations that are created within the pathways are key to comprehending the specific inhibitors that can eradicate the cancer. The data supporting treatment plans for both cHL and NLPHL are included in this review to elaborate on other potential treatments for HL patients. The mutations in the pathways and the inhibitors of the genes within the pathways, further emphasizes what happens when they are dysregulated. Dysregulation results in the vast proliferation of the cancerous cells, turning into malignant tumors that are then capable of taking over the whole body. The targeted drugs and immunotherapies relate the importance of ensuring that patients receive treatments specific to the genes that need to be inhibited. Pathways such as JAK/STAT and NFκB have been linked to various cancers, such as Hodgkin's Lymphoma, understanding the full scope of mutations possible in these pathways, allows us to become one step closer to assisting patients suffering from such cancers.

Background & Understanding of Hodgkin's Lymphoma

Hodgkin's Lymphoma (HL) is a type of cancer that primarily affects the lymphatic system. The lymphatic system is composed of organs, glands, tubelike vessels, and small clusters of cells that are referred to as lymph nodes. The lymphatic system plays a significant role in the immune system. There are two types of lymphomas: Hodgkin's lymphoma and non-Hodgkin lymphoma (NHL).[1]

NHL occurs more commonly in the patient population than HL.[1] The difference between the two is the specific lymphocyte (white blood cell) that is affected. HL typically originates from B lymphocytes, which are germ-fighting white blood cells.[2] Whereas NHL can stem from either B lymphocytes, T lymphocytes, or natural killer cells.[3] Another key difference is that HL will always contain a cell called a Hodgkin's Reed-Sternberg cell (HRS).[4] These cells are abnormal lymphocytes that have more than one nucleus. It has been proven that as the cancer progresses, the patient's cell count of HRS will also increase.[4]

However, this review will focus on HL, and the mutations present within that pathway. It is important to note that there are also two subcategories of HL: classical Hodgkin lymphoma (cHL) and Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL).[5] NLPHL is rare in comparison to cHL and are called "popcorn cells" due to the way they look and the way they grow. cHL has cells that grow from Hodgkin & Reed-Sternberg tumor cells and NLPHL cells tend to grow lymphocyte-predominant (LP) cells. Even though HL is very common and can be treated, there are also relapses that occur within the patients, as the treatment may not be as effective for some.[5]

It has been found that genetic lesions within both cHL and NLPHL cause constant activation of a certain pathway called the JAK/STAT (Janus kinase-signal transducer and activator of transcription) pathway. The mutations within this pathway have targeted proteins STAT6 and SOCS1. These abnormalities are also found in the pathway called NFκB (nuclear factor kappa-B) pathway.[2] Both pathways, notoriously create overactive survival signaling. The JAK/STAT pathway is necessary for a fast membrane-to-nucleus signaling path that can trigger the expression of many mediators within cancer and inflammation.[6] NFκB is a transcription factor

that can monitor and check parts of the immune system and can be helpful for inflammatory responses.[7]

In this paper, both pathways will be discussed in depth, as well as emphasizing which mutations cause HL to form. Targeted drugs and immunotherapies will be analyzed to emphasize how the mutations arise. How the mutations are suppressed from causing relapse to patients and triggering the spread of the cancer to other vital organs, will also be discussed.

To fully comprehend how HL arises, the mutational effects of the diseases must be understood. Which is why both mechanisms are explained below. JAK/STAT is explained first and then the NFκB is followed.

JAK/STAT Pathway

JAK/STAT Pathway Mechanism:

The JAK/STAT oversees various cell responses. These include cell activation, proliferation, and inflammation. Which is why inhibiting the activity of the pathway leads to immunosuppressive consequences on target cells and immune reactions.[6] Considering this, having an error within this system could start to trigger cancers and ultimately stop the checks necessary to allow proper regulation. The dysregulation of the pathway is supported by ongoing research evidence.[6] There have been 50 cytokine growth factors linked to the JAK/STAT signaling pathway that are significant for the following disease: hematopoiesis, immune fitness, tissue repair, inflammation, apoptosis, and adipogenesis.[6] The JAKS are noncovalently linked to cytokine receptors, mediate tyrosine phosphorylation of specific receptors, and can recruit one or more STAT proteins.

This is further explained in experimental studies to test the mutations within this pathway. It is key to understand how the disease functions in order to find a suitable treatment plan, which is why the mechanism is discussed next.

JAK/STAT Pathway Mutation Mechanism:

Just like any other disease, especially cancers, the underlying cause is most likely due to a mutation in the pathway. It has been proven that the mutations in the JAK/STAT mechanism disturbs the functionality of the process and can result in Hodgkin's Lymphatic Cancer. Defects can result from the activation of certain receptors within JAK/STAT, which can then function like a kinase to phosphorylate tyrosines that are specific to recruiter proteins. The proteins then recruit STAT proteins. However, this process can undergo hyperphosphorylation of a cascade of STAT proteins, as seen in ***Figure 1***.[2,6] This ends up triggering carcinogenesis by activating other targets like proto-oncogene MYC. Due to potential upregulation of the pathway, it can induce stress and create tumor cells of cytokines within the microenvironment.

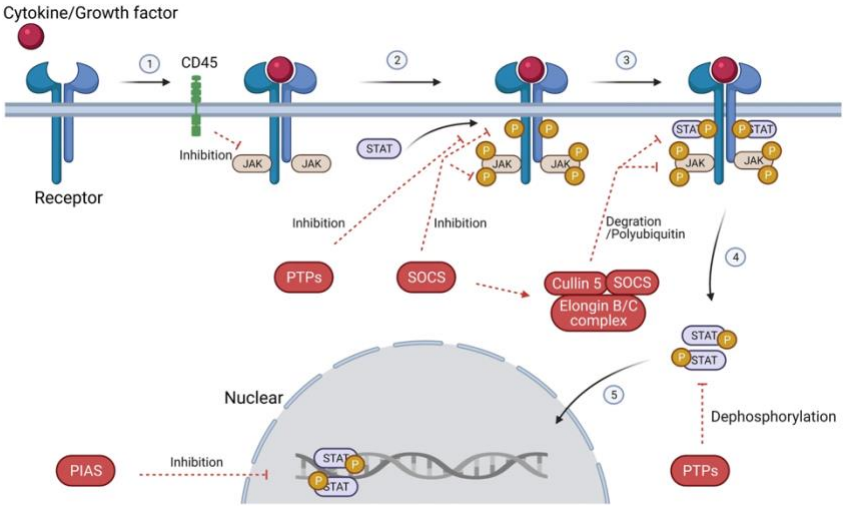


Figure 1: The JAK/STAT signaling pathways. The pathway follows 5 steps. 1st: cytokines and growth factors binding to the specific receptors and recruiting JAKs. 2nd: The JAK activation triggers tyrosine phosphorylation of the receptors. 3rd: The STATs are phosphorylated via tyrosine. 4th: The STATS detach from the receptors and create homodimers or heterodimers. 5th: Dimers go into the nucleus, can bind to the DNA and can control transcription.[6]

Commonly, the cytokine receptors within the cell surface go through conformational changes and then bind and phosphorylate other JAK proteins. There are many activation pathways for JAK/STAT in HL that may be common, however, it is very rare to have mutations within the JAK gene. It was found that genes such as SOCS and PTPN function like negative regulators of

the JAK/STAT pathway. This would occur in step 5, of ***Figure 1***, and can cause inhibition of the reaction via dephosphorylation of JAKs. There have been multitudes of studies that indicate a strong correlation between abnormalities within these genes and HL.[2,6]

The discussion of various JAK/STAT inhibitors leading to drug treatments approved for treatment for HL are discussed further in this paper.[6]

STAT6 & SOCS1

A specific study from *Blood*, tried to determine the significance of the two genes STAT6 and SOCS1 in the JAK/STAT pathway.[8] To determine this, mutations were created and one of the genes were silenced per cell line sample. The cell viability was first determined. It was confirmed that when the STAT6 gene is downregulated, this results in the death of cHL cells that are STAT6 mutated. When analyzing the SOCS1 gene, overexpression ends up suppressing the STAT6 phosphorylation, assisting in cell death of cHL cells.

Proving that the STAT6 and SOCS1 gene are vital in suppressing cHL cell and apoptosis of the cells. If not correctly functioning, this results in overgrowth of the cells and turns into malignant tumor cells.[8]

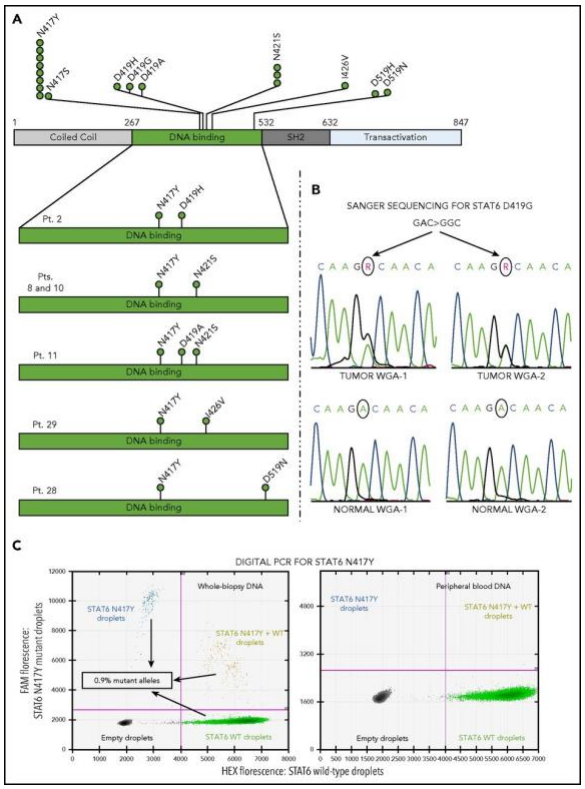


Figure 2. Understanding STAT6 mutations in cHL. 2A: Indicates the secondary structure of the STAT6 protein. It also shows mutations in cHL (depicted by the green circles), clustered in the DNA binding domain. 2B: Sanger-sequencing used as validation, proving heterozygous STAT6 in tumor WGA-DNA. C: PCR tracking a somatic mutation on the left, serves as a positive control as it contains tumor DNA of whole-tissue sections of a lymph node biopsy. However, the right, the peripheral blood sample serves as a negative control.[8]

As seen in ***Figure 2A***, there is a high mutational rate within the DNA binding domain. The alleles that are mutated within the binding site are not at random, but rather are specific to the binding site. The alleles that continuously show up are N417Y, which is a somatic mutation. This panel shows, exactly where the mutations are and in what genes. In ***Figure 2B,*** whole gene amplification (WGA) proved that the STAT6 protein is heterozygous mutation and has a tendency in tumor WGA-DNA duplicates. This means that when the gene was amplified, the STAT6 protein was showing up in the mutant sample and in the normal sample, only when there was overlapping regions. This meant that the mutant was heterozygous. The mutant was not seen in the normal sample alone.[8] Sanger sequencing was used to determine the specific nucleotides

and determine the mutational change between the base pairs. This proves that the STAT mutants can only occur in tumor containing cells.

In ***Figure 2C:*** The polymerase chain reaction (PCR) proves that the HRS cells have a very low frequency, which proves that even though there is not a lot of HRS cells, those cells can control the entire microenvironment.

The NFκB Pathway

The NFκB Pathway Mechanism:

NFκB is a transcription factor that functions by inducing the expression of certain pro-inflammatory genes, such as those specific for cytokines and chemokines, which also function in inflammasome regulation.[9] The factor is also pivotal in regulating the survival, activation, and the speciation of innate cells and inflammatory T cells. However, when there is dysregulation of the NFκB activation, this creates various forms of inflammatory diseases. There are various transcription factors that are involved in regulating the genes in the pathway. There are two signaling pathways. The canonical and the nonconical pathway. The canonical process is able to detect various stimuli such as cytokine receptors, pattern-recognition receptors, Tumor Necrosis Factor Receptor (TNFR) superfamily members, and the T-cell and B-cell receptor.[9] The noncanonical process only specifically responds to a certain group of stimuli such as ligands of the TNFR superfamily members. Hence, why having damage to this cascading process would result in pro-inflammation and cell proliferation.[9]

Understanding the NFκB pathway under Mutational Tendencies

As explained, constant activation of the NFκB of the transcription factors usually indicate HL, in most cases of all malignant HL, NFκB is detected. There are two categories mentioned earlier, canonical and nonconical are also present when the scheme is mutated. The canonical version of

the pathway uses 2 clusters of differentiation (CD), CD40 and CD30, to activate a specific complex. Classical HL (cHL) is also a B-cell created lymphoid malignancy that is defined by a clonal proliferation of Hodgkin and Reed-Sternberg (HRS) cells.[10] This complex, the IKK complex, promotes the degradation of the NFκB factors. As seen in ***Figure 3,*** the noncanonical and the canonical paths are activated, however, the inhibitors are ubiquitinated, so there is not proper functionality of the process when there are HRS cells present.

This is because of the constant survival of HRS cells, also control the NFκB pathway. Which can create the upregulation of proteins that can block intrinsic and extrinsic parts within the pathway.[7] It has been proven that the inhibition of the pathway results in spontaneous and apoptosis without tumor suppressor gene p53. At certain checkpoints, the cell can be rescued by the expression of gene BCL-XL. The activation of the pathway is also capable of various genes such as chemokines, cytokines, receptors, apoptotic regulators, and transcription factors.[7]

The alterations that occur in the pathway are mostly due to dysregulation of HRS cells which have dysregulation within the NFκB pathway. Deregulations create mutations in the ability of the pathway to create amplifications of activators or inactivating negative regulators.[7]

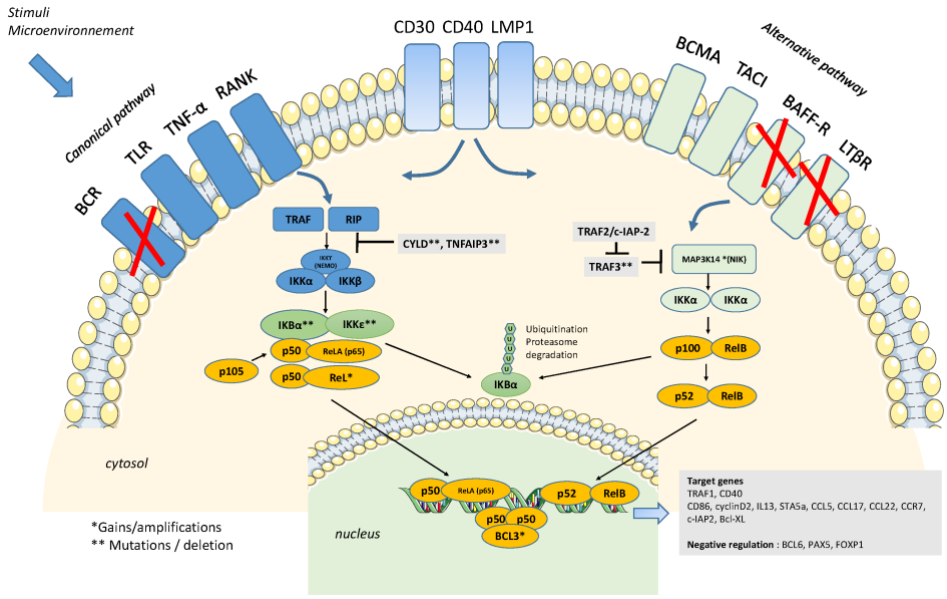


***Figure 3: Functionality of* the mutated NFκB pathway:** The figure represents the canonical and the noncanonical paths that are represented in the mutated pathway. The activation of TNF receptors activates both paths and the TNF receptor-associated factors (TRAFs) can engage with the IKK complex, activating ubiquitination of inhibitors and destruction of the proteasome.[7] Transcription factors are released and forced to regulate the NFκB genes.

The Various Cell Types of HL

cHL & Reed-Sternberg (HRS) Cells

HRS cells were very tricky to determine and fully understand because they have a specific immunophenotype that does not fit the normal immune cells that are commonly seen. The HRS cells have a lot of co-expression of marker of many cell types within the hematopoietic system.[11] The odd characterization of the cells is that that they express B-cell transcription factor PAX5, however, they lack the B-cell receptor expression as well as other B-cell markers.

The HRS cells were only fully understood until they were isolated and genetically analyzed. This process clarified that the cells portrays that the HRS cells were transformed B cells. They carry immunoglobulin (Ig) heavy and light chain shifts of the V gene, which are very specific to B cells.

Understanding cHL is rather difficult purely due to how make up of the HRS cells. The HRS cells on average only account for <5% of the total cell type and tend to be embedded in immune suppressive inflammatory background. This background has been found to be recruited by the cells themselves. This then helps them to grow faster and move past the antitumor response that a normal signaling pathway would determine.[8] As mentioned before, there has been many ways to understanding how the HRS cells function, but once the origins were discovered, this pointed to the fact that the various genetic lesions that would be found through cHL patients, were due to the pro-inflammatory NF-κB and JAK/STAT signaling pathways.[8]

A key feature of HRS cells is that they can control the microenvironment of the immune cells which is why they are even more dangerous**.** As seen in ***figure 4,*** the cytokines that interact with the HRS cells continue proliferating the cells that cause them to lose control from within the anti-tumor immune control.[11] These cells being mostly present within outside of lymph nodes, instead of the peripheral blood, is exactly what causes the danger of cHL.

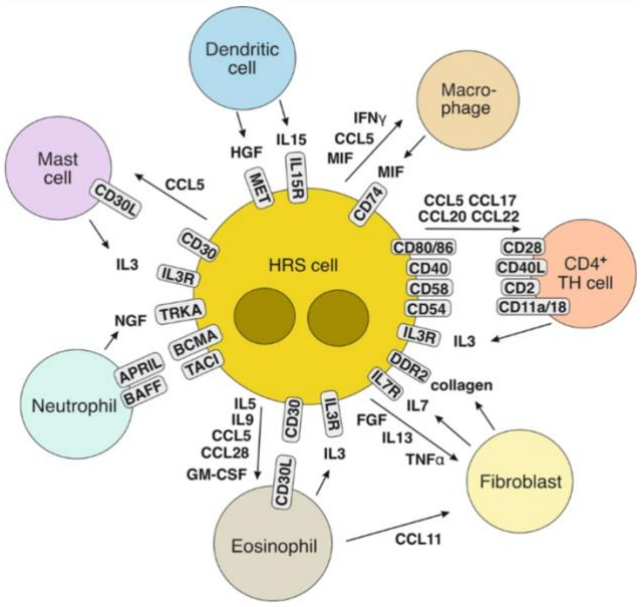


Figure 4. **Classic Hodgkin's Lymphatic (cHL) creating a self-perpetuating microenvironment causing Hodgkin and Reed-Sternberg (HRS) cells to proliferate & survive.** The HRS cells that actively take up the immune cells and fibroblasts are then picked up within the microenvironment via many cytokines.[11]

As mentioned previously, HRS cells are atypical in the sense that they are from B cells, but do not express the typical B-cell gene expression program system. They are incredibly significant in understanding the unwanted activation of signaling pathways. HRS cells change the environment that they are in quite abusively. They tend to downregulate the control cytokines as seen in **figure 4** and then upregulate activation. This allows them to start to take over the lymph node and become a metastatic tumor as seen in cHL.

Nodular Lymphocyte-Predominant Hodgkin's Lymphoma (NLPHL)

Unlike cHL, NLPHL is classified as lymphocyte-predominant (LP) cells also referred to "popcorn cells" because of how slowly they grow.[9] The phenotype of the LP in NLPHL cells represent their GC B-cell origins. They express B-cell markers such as Cluster of Differentiation 19 (CD19), CD20, and CD79, as well as GC B cell molecules such as BCL6, HGAL. LP cells generally indicate somatic mutated IgV genes. CD19 refers to being a marker for B-cell pathways. CD20 is only in B-cell markers that can express the early B cells into the mature B cells. CD79 is a heterodimer and are also very specific markers for B-cells. They tend to express B-cell receptors and their mutations to create a pattern that builds the expression of the functionality of the B-cell receptors.[11]

The LP cells have various derivations from B cells. The regulators of this cell are BCL6, which is the most important control for the GC B cell system. GC B cells are antigens that are activated through mature B cells. The histology of NLPL indicates that there is a huge relevance of LP cell growth with these GC structures. The detection of the LP cells within the NLPL were detected through their monoclonal properties. This was proven through the recognition of the clonal IG heavy and light chain gene arrangement within the cells.[12]

LP cells contain Ig V genes that carry somatic mutations. These mutations are presented through the GC reaction, making them a key characteristic of GC and post-GC B cells.[12]

The Duality of the JAK/STAT Pathway & the NFκB pathway

Comparing & Contrasting of the two pathways

Overall, both of the pathways lose control when they are in the presence of HRS cells. The functionality of any inhibitors within the pathways no longer functions accurately. The HRS cells downregulate the cytokines and do not allow proper receptor to be activated. This is true for both pathways. They are also very important pathways to regulate inflammation. However, the NFκB

pathway is mainly a pro-inflammatory pathway. The JAK/STAT pathway was connected to cell activation, proliferation, and inflammation. It also seemed to have a stronger correlation to the HL diagnosis. This was seen as true when the HRS cells had taken full control of the microenvironment and the and the tumor DNA was positive for a mutated STAT protein.[8] Even though this is the case, both pathways are still extremely affected by HRS cells, resulting in HL.

Treatment Methods of HL

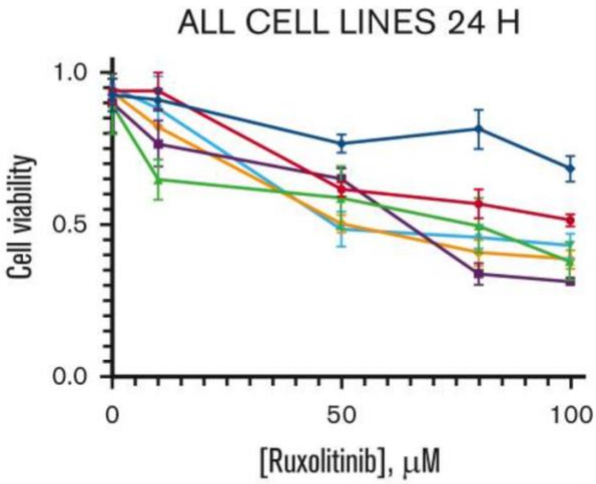
Ruxolitinib

There are various therapeutics that have been proposed to focus on cHL through the JAK/STAT pathway.[10] The drug Ruxolitinib, has been to treat high risk myelofibrosis. This drug is now being used through preliminary clinical trials for patients that a very advanced stage of cHL.[10] Whole-transcriptome studies were conducted to understand the molecular mechanisms of the Ruxolitinib and how it is able to inhibit the JAK/STAT pathway.

Through the studies, it was proven that there are specific expressions such as the anti-GCSF receptor that acts like biomarker for the JAK/STAT overactivation.[10] The study suggests that there are drugs that can act as biomarkers for JAK/STAT blockade. To test whether this drug was safe for a patient study, various cell lines were used. Various cells line of large B-cell Lymphoma cells were used as positive controls, and HeLa, epithelial, cell lines were used as the negative controls. There were also lymph node samples from 140 patients that were also collected and studied. The cells were incubated with or without the ruxolitinib to determine whether the drug could be toxic. The cell viability was also measured. Protein concentrations of the cells were also measured and then ran through SDS (sodium dodecyl sulfate-polyacrylamide) gel electrophoresis, and the proteins were determined through immunoblotting via various antibodies, such as STAT3, STAT6, and P-STAT5, all of which are a subcategory of cell

signaling indicators. To quantify the amount of anti-GCSF receptors available in the cells, quantitative RT-PCR was conducted.[10]

Apoptosis of the cells were also analyzed by analyzing the IC_{50} values of the cells treated with the drug or without, once stained, they were analyzed through a flow cytometer. There was also expression of the anti-CSF3R cells.



Cell line	IC_{50} at 24 hours (μM)
L-1236	14.78
L-540	29.55
L-428	30.64
L-591	36.28
KM-H2	54.09

Figure 5. The toxicity of the cell lines determined from the treatment of Ruxolitinib. This figure shows the growth curves of cHL cell lines when treated with ruxolitinib. The table under the graph shows the IC_{50} values after the 24 hour point.[10]

As seen in ***figure 5***, the viability of the cells significantly dropped and continued to drop with the addition of the Ruxolitinib. The high negative control viability also indicated how there it is not as toxic to the cells.

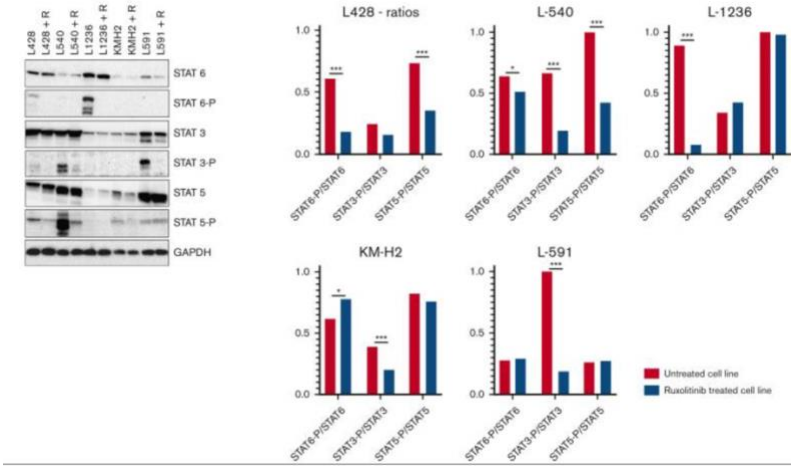


Figure 6. ***Western blotting analysis of various STATs phosphorylation levels.*** The western blot confirms that there is significant reduction in the STAT phosphorylation levels after the treatment of ruxolitinib.[10]

As seen in ***figure 6,*** the Western blot, provides high evidence for direct effect of phosphorylation levels within the JAK/STAT Pathway. There are high reductions within specific p-Stat6 antibodies. With all the results determined, it was proven that Ruxolitinib was a safe drug that has promising life changing affects to cure patients that are suffering through advanced stages of cHL.

A specific study done by Weniger and Küppers, investigated the treatment of ruxolitnib, which is a JAK/STAT inhibitor. They had conducted the study with mice models that had chronic infections and could secrete compounds which save cytotoxic T cells from fatigue. It was thought that the drugs for treatment could be combined with immune checkpoint inhibitors (ICIs). This would increase the chances of reactivation of the cells and stop the inhibition and fatigue of antitumor cells. When the most effective drug hits of the screening were various JAK inhibitors such as ruxolitinib.[10]

When combining ruxolitinib and the ICIs, it was proved to increase B, T, and NK cells, which all are vital for the antitumor mechanism. The drug was used in a clinical trial but was combined with the drug nivolumab. Nivolumab is a type of ICI which attack specifically HRS cells and

their technique of immune evasion. The treatment was conducted in the peripheral blood on a few patients and showed various promising results. The dilemma that the drug trial faces is that they have only been done within the peripheral blood. Which brings the question of whether the treatment is successfully attacking the HRS within the lymph nodes, or if it is only attacking the cells within the peripheral blood.[13] If the drug is not specific enough to attack the cells within the lymph node, this would result unsuccessfully stopping the spread of the disease.

With other cancers, reactivating the fatigued cytotoxic CD8 T cells results in a positive outcome for the patient. However, with HL patients, this does seem to be true. In most cases, the HRS cells lose the expression of MHC class I, as mentioned in the STAT section. This in turn, destroys the ability of HRS cells to detect CD8 T cells.

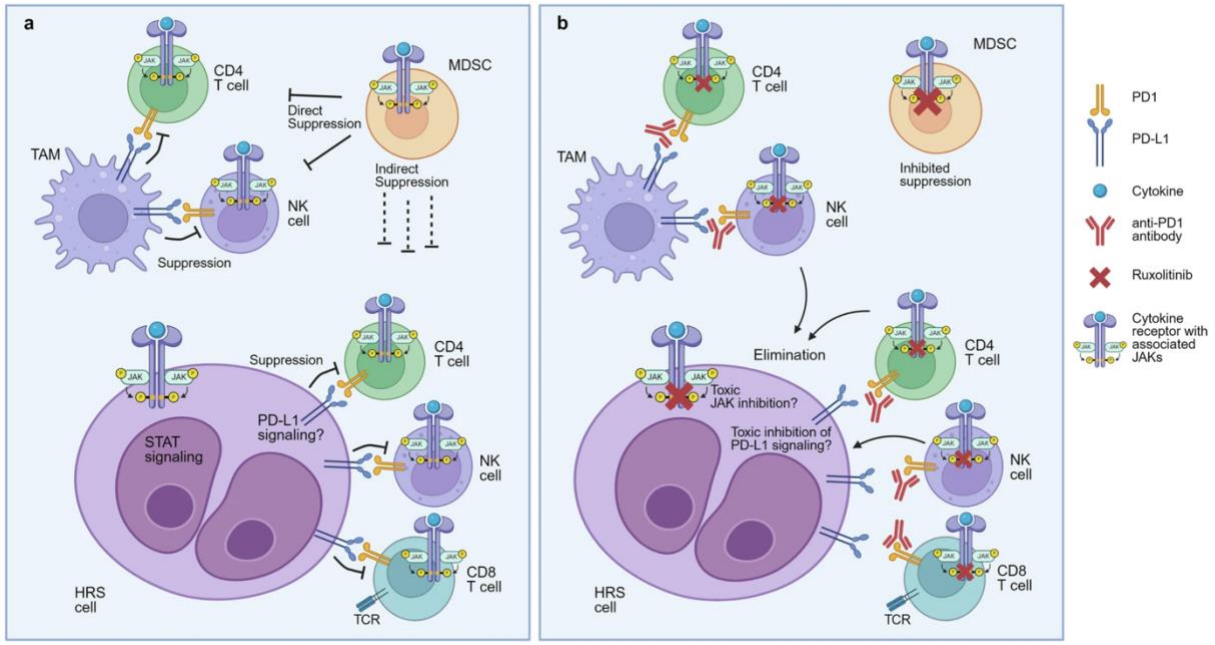


Figure 7. A representation of how HRS cells interact when inhibited. On side A, the HL microenvironment is represented. On the left side, on side B, the combined JAK ½ and PD1/PD-L1 inhibition is showen.[13]

As seen in ***figure 7A***, HRS cells tend to attach immune cells into the tumor tissue. This creates the problem of CD8 T cells being unable of going after HRS cells which no longer can detect the T cell targets. ***The figure 7B*** provide a proposed mechanism as to what JAK1/2 and PD1/PD-L1

inhibition creates for HRS cells. It is hypothesized that the JAK inhibition of the cells can immediately eliminate the HRS cells. As of now, it is still not truly clear as to which effector cells are able to fully kill HRS cells.

Fedratinib

Fedratinib is a JAK2 inhibitor, and a study was done to determine whether the apoptosis induction created on genetic silencing of the JAK/STAT pathway would result in less viability of the cHL cells.

Through this study, there was western blot analysis used to determine whether the gene mentioned earlier, SOCS1, would be expressed to trigger the phosphorylation of the STAT transcription factors, that proceed to inhibit the JAK2 genes.[14] The study had treated a panel of cells of cHL and Primary Mediastinal Large B-cell Lymphoma (MLBCL) with increased dosages of fedratinib. When looking at ***Figure 8A***, there was positive indication of decreased phosphorylation of the mutated JAK2 copy number. This proved that fedratinib shows promising treatment against JAK/STAT inhibition.[14]

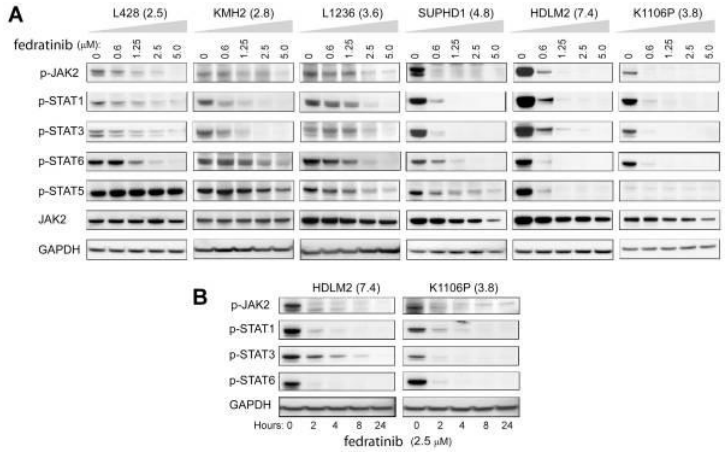


Figure 8. Western blot analysis of JAK2 and STAT treated with fedratinib. Overtime, the decreased JAK2 phosphorylation over time in A. In B, different cell lines and copy numbers were tested.[14]

Conclusion & Summary

Hodgkin's Lymphoma is white blood cancer that is primarily influenced by the microenvironment of HRS cells. These mutations arise within pathways such as the JAK/STAT and NF-κB signaling pathways result in either cHL or NLPHL disease subcategories. These pathways can become out of control when they can no longer have access to the checkpoints within the process. Which is why the mutations need to be followed with targeted therapies that can focus directly on the reaction types and the specific gene that is being mutated. These mutations, however, can be treated with various drugs that are specific to certain genes that are mutated within either pathway. Understanding the mechanistic flow of pathways allow for a deeper understanding of how to approach new treatments for HL patients, based on which gene in the pathway to inhibit. This also leaves room for other cancer pathways to be further investigated, and find potential drugs that can inhibit genes to stop cancerous cells from proliferating.

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