HCK-Mediated gp130/STAT3 Signaling in Multiple Myeloma: Mechanisms, Inhibitors, and Therapeutic Opportunities

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Abstract

Hematopoietic Cell Kinase (HCK) belongs to the Src-family of non-receptor tyrosine kinases expressed almost exclusively in myeloid lineage cells. HCK activity skews macrophages toward an M2-like, immunosuppressive phenotype and amplifies production of STAT3-stimulating cytokines such as IL-6/IL-11. Those cytokines engage gp130/JAK/STAT3 signalling in tumor and stromal cells, creating a paracrine loop that promotes proliferation, survival, angiogenesis and immune evasion. The HCK-mediated STAT3 pipeline has been demonstrated in solid-tumour models and myeloid-driven malignancies, as well as Multiple Myeloma (MM), an IL-6-dependent blood cancer. This review synthesizes preclinical evidence that myeloid HCK amplifies gp130/STAT3 signalling, surveys available HCK-directed tool compounds and early dual-inhibitors, and proposes experimental strategies to test HCK inhibition as a therapeutic strategy for MM. Given MM's reliance on IL-6/gp130-driven survival signals and the pharmacological tractability of SFK inhibitors, targeting HCK represents a promising complementary approach to disrupt tumor-supportive TAM circuits. This paper synthesizes current research on HCK inhibition as an emerging Multiple Myeloma (MM) treatment strategy, focusing on HCK-triggered gp130/JAK/Stat3 cascade, function in TAMs, and impact of the TME while addressing barriers in pharmacologically targeting HCK and possible new strategies.

Keywords: Hematopoietic Cell Kinase (HCK), Tumor-Associated Macrophages (TAMs), Multiple Myeloma (MM), Interleukin-6 (IL-6), STAT3, SFK Inhibitors

Introduction

The hematopoietic cell kinase (HCK) is a member of the SRC family of nine cytoplasmic tyrosine kinases (SFKs) which also includes SRC, YES, FYN, LCK, FGR, BLK, LYN, and YRK. However, only eight of these kinases are expressed in humans, excluding YRK which is exclusively expressed in chickens. SFKs consist of similar structure containing and functions; specifically, they all consist of an N-terminal domain, three Src homologous domains (SH3, SH2, and SH1) and the C-terminal

(Figure 1B), and are critical in managing cell adhesion, invasion, proliferation, survival, and angiogenesis during tumor development (Kim et al., 2009; Luo et al., 2023; Poh et al., 2015).

HCK is expressed predominantly in cells of the myeloid and B-lymphoid lineages. HCK hyperactivation and overexpression is associated with several types of blood cancers and plays the role of enhancing cell proliferation and survival by association with oncogenic fusion proteins interactions with receptor tyrosine kinases. Furthermore, HCK interacts directly with interleukin-6, a major driver of multiple myeloma (MM), in the gp130 receptor complex that promotes tumor-supportive microenvironments by skewing macrophages towards immunosuppressive (M2-like) phenotypes and enhancing pro-survival cytokine signaling. Elevated HCK activity is also observed in many solid malignancies including breast and colorectal cancer, and correlates to worse prognosis (Luo et al., 2023; Poh et al., 2017).

Multiple Myeloma (MM) is considered the second most common hematologic cancer, yet still incurable. Despite technological and medical developments for MM, this disease tends to consistently relapse and leads to 106 000 deaths per year worldwide (Opperman et al., 2021). MM is characterized as an abnormal growth of plasma cells in the bone marrow and most significantly impacts the immune system. Myeloma cells uncontrollably proliferate inside the bone marrow, overcrowding and disrupting the creation of other blood cells leading to anemia and leukopenia. With the lack of functioning immunity system, the body is also considered immunocompromised. Myeloma cells produce an abnormal antibody called monoclonal protein (M protein). Alongside the characteristics of high levels of M protein, myeloma can create many complications such as bone fractures, tumors, kidney damage, impaired immune function and other blood disorders. Treatment of MM includes traditional chemotherapy drugs, anti-inflammatory drugs, proteasome inhibitors, and immunomodulatory drugs (Opperman et al., 2021).

HCK promotes M2-like TAM polarization and enhances production of STAT3-stimulating cytokines (Luo et al., 2023). These cytokines engage the gp130 receptor complex in the TME, which activate the JAK/STAT3 signalling cascade that promotes cancer hallmarks such as uncontrolled cell proliferation, cell death resistance, and immune evasion. STAT3 driven genes can also induce chemokines (e.g. CCL2/CSF1) that recruit more TAMs, creating a positive feedback loop, and exacerbating cancer progression (Chang et al., 2013; Johnson et al., 2018). This paracrine circuit is why HCK in cancers are hyperactive and directly related to poor prognosis (Luo et al., 2023)

Tumor-associated macrophages (TAMs) are among the most abundant immune cells within the tumour microenvironment (TME) (Luo et al., 2023). Depending on cues from the microenvironment, macrophages range from classically activated, pro-inflammatory M1 phenotypes to alternatively activated, tissue-repairing M2 phenotypes; in most cancers TAMs adopt an M2-like profile that supports tumour growth, angiogenesis, matrix remodeling and immune suppression (Cencini et al., 2023; Luo et al., 2023).

A central node coordinating many pro-tumour functions is the gp130/JAK/STAT3 signalling pathway, frequently activated by IL-6 cytokines secreted both by tumour cells and by myeloid populations (Chang et al., 2013). Specifically, in Multiple Myeloma (MM), interleukin-6 (IL-6)–driven STAT3 signalling is a major driver of plasma-cell survival, proliferation, and resistance to apoptosis (Chang et al., 2013; Podar et al., 2004).

Although MM remains incurable, the disease progression is highly dependent on IL-6/gp130-STAT3 signalling, so targeting HCK as a druggable node could reveal new therapies that synergize with

existing anti-myeloma treatments. This paper synthesizes current research on HCK inhibition as an emerging Multiple Myeloma (MM) treatment strategy, focusing on HCK-triggered gp130/JAK/Stat3 cascade, function in TAMs, and impact of the TME while addressing barriers in pharmacologically targeting HCK and possible new strategies.

This review discusses the significance and viability of HCK as an inhibiting target for MM treatment. Particular attention is given to the gp130/JAK/Stat3 signalling axis, which is driven by HCK and IL-6 signalling, and its downstream effects on malignant plasma cell survival. Aberrant HCK activity promotes an immunosuppressive tumor microenvironment (TME) by skewing tumor-associated macrophages (TAMs) through STAT3-dependent polarization, thereby supporting disease progression. In addition to outlining these mechanisms, this review addresses current challenges in pharmacologically targeting HCK and considers emerging strategies that may overcome these barriers and establish HCK inhibition as a viable treatment approach for MM.

HCK structure and mechanistic link

As shown in Figure 1B, HCK retains the canonical modular structure of Src-family kinases (SFKs): an N-terminal region undergoing lipidation, SH3 and SH2 regulatory domains, a catalytic SH1 kinase domain, and a C-terminal tail with a regulatory tyrosine (Luo et al., 2023). More specifically shown in Figure 1B, the two isoforms of human-expressed HCK, p59 and p61 are differentiated based on the N-terminal lipidation: specifically, p59 undergoes both myristoylation and palmitoylation and is directed to the plasma membrane, whereas p61, lacking palmitoylation, localizes more broadly, including to lysosomal compartments (Figure 1B) , (Robbins et al., 1995; Poh et al., 2015; Carréno et al., 2000). This isoform diversity causes HCK to be distributed differently within the cell, which may be especially important in bone marrow macrophages, where being near cytokine receptors such as gp130 determines the efficiency of IL-6 triggered JAK/STAT3 signal amplification. In this context, p59 HCK at the plasma membrane is optimally positioned to amplify signals from IL-6 receptors, while p61 may participate in intracellular or endosomal signaling, potentially modulating the strength or duration of the cellular response (Carréno et al., 2000).

HCK's SH2 and SH3 domains act as regulatory 'safety locks' that keep the kinase inactive: the SH2 domain binds the phosphorylated C-terminal tail (YT; human Y521), while the SH3 domain binds a proline-rich region in the linker between SH2 and SH1, blocking access to the kinase active site (Figure 1A) (Luo et al., 2023; 9; Alvarado et al., 2010). Upon phosphorylation of YT by upstream kinases such as CSK/CHK (C-terminal Src kinase and CSK-homolog), the SH2 linker binds the SH3 domain and phosphorylated YT engages the SH2 domain, rearranging HCK into an inactive structural conformation. Many stimulatory factors such as LPSTLR4, IL-2, IL-6, and GM-CSF, can activate HCK. As shown in Figure 1A., YT is dephosphorylated by phosphatases such as CD45 or SHP1, which leads to the phosphorylation of the activation loop tyrosine (YA; human Y410) that stabilizes the activation state. Once activated, HCK phosphorylates substrates including Bcr/Abl, Tel/Abl, PAG, STAT5, and STAT3, thereby contributing to cell proliferation, evasion, and apoptosis. Phosphorylation of YT thus acts as a brake to prevent excessive activation, while mutants lacking this C-terminal inhibitory tyrosine display higher kinase activity and enhanced myeloid initiation.

These inhibitory interactions can be released by upstream signals or membrane recruitment, allowing rapid activation in response to stimuli such as IL-6. HCK's SH1 domain contains an ATP-binding lobe and a substrate-binding lobe, and phosphorylation of its activation loop tyrosine (YA; human Y410) stabilizes the active kinase, enabling efficient phosphorylation of downstream targets such as Gab1 and Gab2 (Figure 1A) (Johnson et al., 2018).

In the MM microenvironment, IL-6 signaling can override these inhibitory controls, allowing TAM-expressed HCK to amplify gp130/JAK/STAT3 signaling and promote MM cell survival and proliferation. This mechanistic understanding informs therapy: inhibitors targeting the SH1 domain or SH2/SH3 regulatory interactions can suppress HCK activity, disrupting TAM-mediated support of MM cells and highlighting HCK as a pharmacological target in IL-6–dependent cancers (Poh et al., 2015; Johnson et al., 2018).

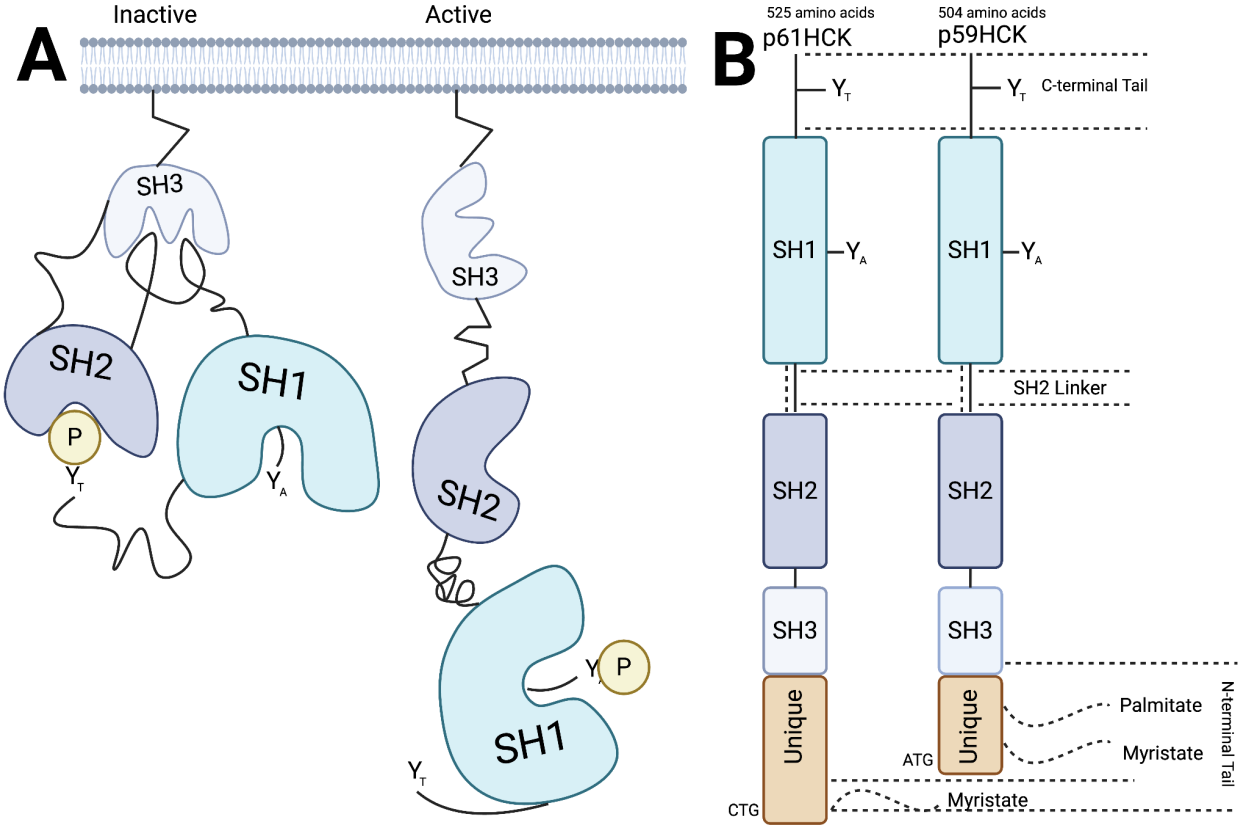

Figure 1. (**A)** Simplified schematic representation of HCK in its inactive (left) and active (right) conformations. In the inactive state, the SH2 domain binds to a phosphorylated tyrosine residue in the C-terminal tail (Y_T), and the SH3 domain interacts with the SH2-kinase linker, maintaining a closed and auto-inhibited conformation. Upon dephosphorylation of Y_T, and/or phosphorylation of the activation loop tyrosine (Y_A) within the SH1 kinase domain, the protein adopts an open, active conformation, allowing substrate access and kinase activity. (**B)** Domain architecture of the two human HCK isoforms, p61HCK and p59HCK. Both isoforms share similar structures except the N-terminal tail due to alternative start codons (CTG for p61HCK and ATG for p59HCK), resulting in different lipid modifications. p61HCK undergoes dual acylation (myristoylation and palmitoylation), targeting it to the plasma membrane, while p59HCK only myristoylated, affecting the nuanced subcellular localization and function. Created in https://BioRender.com

Mechanisms of HCK in gp130/JAK/STAT3 Signaling HCK and Cancer signaling

As illustrated in Figure 2., once interleukin-6 (IL-6) binds to the IL-6 receptor gp130 complex, HCK is activated through direct interaction with an acidic domain of gp130. This activation facilitates the recruitment of adapter proteins such as Grb2 and Shp2 to the receptor complex. Grb2, in turn, associates with the guanine nucleotide exchange factor Sos, leading to the activation of Ras and subsequent activation of the extracellular signal-regulated kinase (ERK) pathway. Simultaneously,

Shp2 dephosphorylates Pyk2, inhibiting apoptotic signaling pathways. Additionally, HCK enhances the activation of phosphoinositide 3-kinase (PI3K) through the recruitment of its p85 regulatory subunit, further promoting cell survival and proliferation (Figure 2). The cumulative effect of these signaling events is the sustained activation of STAT3, a transcription factor that translocates to the nucleus to promote the expression of genes involved in cell survival, proliferation, and immune evasion. In MM, this persistent STAT3 activation contributes to the malignant phenotype by enhancing tumor cell proliferation and resistance to apoptosis (Luo et al., 2023; Schaeffer et al., 2001; Johnson et al., 2018). In summary, HCK acts as a critical amplifier of the gp130/JAK/STAT3 signaling pathway in MM, promoting tumor progression and survival. Targeting HCK may offer a therapeutic strategy to disrupt this oncogenic signaling axis.

The kinase also engages other oncogenic pathways. HCK can interact with receptor tyrosine kinases such as Epidermal Growth Factor Receptor (EGFR) and Platelet-derived Growth Factor receptor (PDGFR) to drive Extracellular Signalling Regulated Kinase (ERK), Protein Kinase B (AKT), and STAT3 signaling, thereby promoting proliferation in solid tumors and hematological malignancies (Poh et al., 2015). According to Poh et al. (2015), there is also association of HCK with the gene abnormality break point cluster region/abelson oncogene (BCR/ABL), leading to persistent STAT5 activation and cytoplasmic retention, where STAT5 enhances cell survival through AKT signaling (Poh et al., 2015; Klejman et al., 2002). HCK also cooperates with TEL/ABL fusion proteins to reinforce AKT and ERK pathway activation, further promoting proliferation, survival, and invasion (Poh et al., 2015). These findings underscore the broader oncogenic potential of HCK, though its role in IL-6–driven STAT3 activation remains particularly relevant in MM.

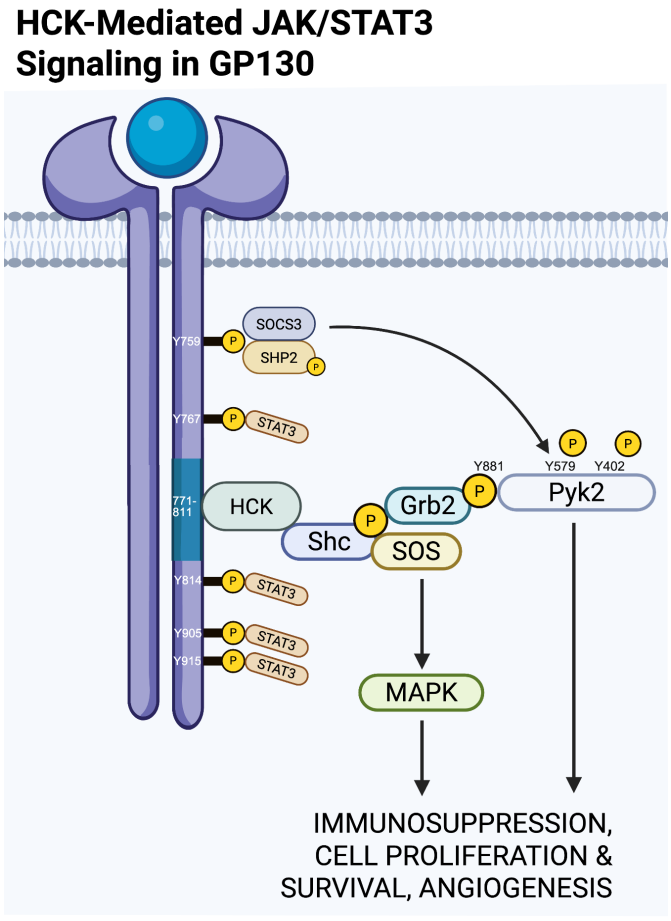

Figure 2. HCK binds the acidic domain of gp130 (amino acids 711–811) upon IL-6 stimulation, leading to phosphorylation of tyrosine residues that recruit adaptor proteins Grb2 and Shp2. This activates the ERK and PI3K/AKT pathways to promote cell survival and proliferation, while sustained STAT3 activation drives oncogenic transcriptional programs. Phosphorylated tyrosines (P) indicate residues targeted by HCK. Created in https://BioRender.com

HCK Function and TAM Polarization

HCK is highly expressed in myeloid cells, including macrophages, and plays a pivotal role in shaping their functional polarization within the tumor microenvironment. In particular, elevated HCK activity has been shown to bias macrophages toward an alternatively activated, pro-tumoral M2-like phenotype, characterized by enhanced expression of immunosuppressive and pro-angiogenic factors (Abram, 2008). Mechanistically, constitutive activation of HCK promotes the secretion of vascular endothelial growth factor (VEGF), interleukin-10 (IL-10), and matrix metalloproteinases (MMPs), which collectively foster tumor vascularization, immune evasion, and extracellular matrix remodeling (Poh et al., 2015). In Poh et al.'s (2022) mouse models of gastric tumors, using HCK small molecule inhibitor RK20449, the results showed that excessive HCK activity enhances the capacity of M2-like macrophages in invading and degrading extracellular matrix (Poh et al., 2020).

In the context of MM, this polarization dynamic is particularly significant because TAMs provide critical survival signals to malignant plasma cells. By sustaining IL-6 production and activating downstream gp130/JAK/STAT3 signaling, TAMs create a microenvironment that protects MM cells from apoptosis and promotes proliferation. HCK, through its role in macrophage polarization, reinforces this feedback loop (Chang et al., 2013; Johnson et al., 2018): M2-like TAMs not only provide trophic cytokines but also suppress cytotoxic T-cell activity, further supporting tumor progression (Poh et al., 2015; Li et al., 2022). Thus, HCK acts at the intersection of macrophage biology and oncogenic signaling, both directly amplifying IL-6/STAT3 signaling and indirectly sustaining MM through immunosuppressive TAM programming.

Targeting HCK therefore represents a dual therapeutic strategy: disrupting its kinase activity could simultaneously weaken TAM-driven IL-6/STAT3 signaling and reprogram the tumor microenvironment toward an anti-tumoral state. This potential is supported by preclinical studies where HCK inhibition decreased tumor burden and restored immune surveillance in models of hematologic malignancy (Poh et al., 2017; Poh, Love, et al., 2022; Poh, O'Brien, et al., 2022).

Drug Development and Therapeutic Targeting Implications of HCK

Efforts to pharmacologically target HCK have largely relied on ATP-competitive SFK inhibitors; this class of drugs blocks activity by binding to the ATP-binding pocket of the kinase. A-419259 (also known as RK-20449) is a prototypical SFK inhibitor with nanomolar activity against HCK, LYN, and FGR. Crystallographic and biochemical studies revealed its hinge-binding mode and interactions in the ATP pocket, allowing rational optimization of related scaffolds (Selzer et al., 2024). In vivo, A-419259 has demonstrated efficacy in preclinical models of cancers such as gastric cancer, validating HCK as a tractable kinase target (Poh et al., 2020). However, its selectivity is not limited to HCK but also affects other SFKs, such as LYN and FGR, complicating attribution of specific phenotypes to HCK inhibition.

Dual-targeting approaches have also emerged: KIN-8194 is a potent, non-covalent dual BTK/HCK inhibitor that showed superior in vitro/rodent efficacy in MYD88-mutant lymphoma models and

acceptable PK/tolerability in preclinical studies (Yang et al., 2021). This strategy suggests that partial polypharmacology, if rationally chosen, could be advantageous. Conversely, clinical-grade SFK inhibitors such as dasatinib and bosutinib inhibit HCK along with BCR-ABL and many other kinases. While these molecules provide insight into the druggability of HCK, their lack of target specificity introduces significant off-target effects such as peripheral toxicity (Cortes et al., 2018), confounding their translational utility for mechanistic studies.

The major challenge for HCK-directed therapy lies in achieving myeloid-specific inhibition. Since HCK is expressed predominantly in macrophages and neutrophils, systemic inhibition risks unintended immune modulation or toxicity. Preclinical genetic ablation of HCK in mice is generally well tolerated and reduces tumor-promoting TAM phenotypes, suggesting a reasonable therapeutic window (Poh et al., 2015; Poh, Love, et al., 2022; Poh, O'Brien, et al., 2022). Strategies to improve HCK-targeted therapy include selective ATP-site or allosteric inhibitors to minimize off-target effects, and targeted delivery, via antibody-drug conjugates or nanoparticles, to restrict HCK inhibition to tumor-associated myeloid cells, enhancing tumor microenvironment specificity while reducing systemic toxicity.

An alternative to ATP-site inhibition is to target the protein–protein interface between receptor and kinase. Notably, Hausherr et al. (2007) reported that a myristoylated 18-residue acidic peptide (derived from the acidic domain of gp130) could selectively inhibit IL-6–dependent growth of multiple myeloma cells by blocking the physical association between gp130 and Src family kinases (specifically Hck, Lyn, and Fyn) (Hausherr et al., 2007). In those experiments, ~100 μM peptide reduced growth by ~75 %, and the peptide also induced apoptosis to a similar degree as IL-6 withdrawal. This result provides proof-of-concept for targeting the gp130–SFK interaction (rather than kinase active sites) as a means to disrupt IL-6 signaling (Hausherr et al., 2007).

These strategies would address the barrier of selectivity seen in current HCK inhibitors which are often general SFK inhibitors. Profiling of small molecule protein kinase inhibitors show that many SFKi also affect kinases such as FLT3, SYK, or JAK family members (Roskoski, 2024). Depending on the disease context, such non-selectivity may be detrimental or synergistic. For example, in multiple myeloma, co-inhibition of SYK or JAK2 could complement HCK blockade by further dampening IL-6/STAT3 signaling. Rational drug design must therefore balance molecular selectivity with the potential benefits of poly-targeting (Zeng et al., 2024).

Finally, combination strategies are attractive. Preclinical rationale supports pairing HCK inhibition with JAK/STAT inhibitors or immunomodulatory drugs (IMiDs) to simultaneously suppress TAM-driven signaling and sensitize malignant cells. In MM, combining HCK inhibition with proteasome inhibitors or IMiDs could exploit both tumor-intrinsic and microenvironmental vulnerabilities, particularly by reducing IL-6-mediated STAT3 activation and reprogramming TAMs toward anti-tumoral phenotypes. Overall, HCK has high potential for a therapeutic target, the development of selective, clinically viable HCK inhibitors, rationally designed polypharmacologic agents, and targeted delivery systems remains a central unmet challenge (Zeng et al., 2024).

Conclusion

Hematopoietic Cell Kinase (HCK) emerges as a pivotal regulator of tumor-associated macrophage function and IL-6/gp130-driven STAT3 signaling, both of which are central to Multiple Myeloma (MM) pathogenesis. By promoting M2-like TAM polarization and creating a cytokine-mediated positive feedback loop, HCK sustains tumor proliferation, immune evasion, and resistance to apoptosis.

Preclinical studies with SFK inhibitors and dual-targeting compounds demonstrate the tractability of HCK as a pharmacologic target, yet challenges remain, including limited inhibitor selectivity and the need for myeloid-targeted delivery strategies. Moving forward, the rational design of selective inhibitors, protein-protein interaction (PPI)-disrupting strategy, and combination therapies that exploit microenvironmental vulnerabilities could unlock the therapeutic potential of HCK inhibition. Collectively, these efforts position HCK-targeted interventions as a promising avenue to complement existing treatments and disrupt tumor-supportive circuits in MM.

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