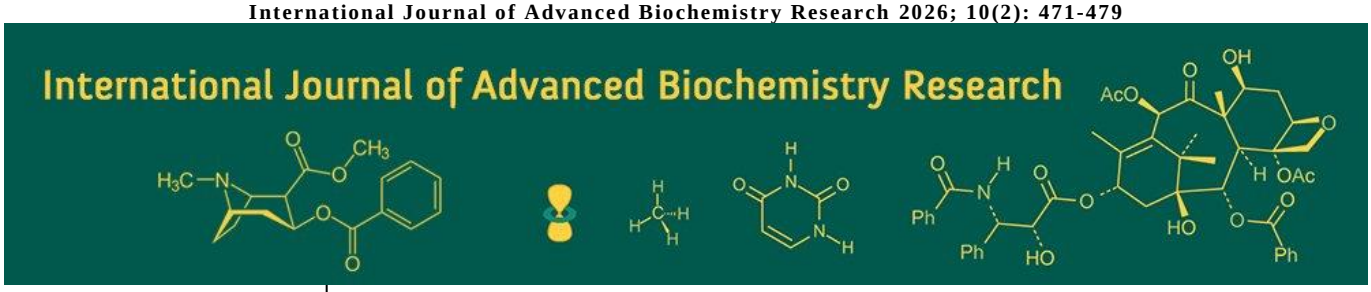

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Review on the *Helicobacter pylori*-driven NF-κB and STAT3 signaling in gastric carcinogenesis: Molecular mechanisms and therapeutic targets

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Abstract
Helicobacter pylori infection is the most important etiological factor, but gastric cancer is a major cause of cancer related death all over the world. The continuous colonization of the gastric mucosa by *H. pylori* causes chronic inflammation which leads to gastric carcinogenesis in complex host-pathogen interactions. The prolonged activation of the nuclear factor kappa B and signal transducer and activator of transcription 3 (STAT3) signaling pathways that act as critical molecular hubs between inflammation and oncogenic transformation are central to the process. *H. pylori* virulence factors, such as CagA, VacA, and urease, activate innate immune receptors and downstream adaptor molecules that cause NF-κB nuclear translocation and transcription of proinflammatory cytokines, including IL-1b, IL-6, and IL-8 and TNF-alpha. Such cytokines, in turn, amplify the action of inflammatory signaling and enhance the activation of STAT3 through the JAK/STAT axis through a self-perpetuating inflammatory circuit. NF-κB and STAT3 are activated in a coordinated and persistent manner that triggers an extensive repertoire of oncogenic programs such as epithelial-mesenchymal transition, anti-apoptotic response, immune evasion, stemness acquisition and metabolic re-programing. Interaction between these pathways also enhances tumor-promoting cues and lead to genomic instability and epigenetic disruption in the development of gastric cancer out of chronic gastritis. There is growing evidence that NF-κB/STAT3 signaling elements and their downstream targets may serve as effective diagnostic, prognostic, and predictive biomarkers. Besides, specific therapeutic approaches to interfere with such pathways individually or in combination-have shown promising preclinical and early clinical results. This review provides a summary of existing knowledge on *H. pylori*-induced NF-κB and STAT3 signaling pathways and addresses new therapeutic targets that can be used to implement precision medicine in gastric cancer.

Keywords: *Helicobacter pylori*, NF-κB signaling, STAT3 pathway, gastric carcinogenesis, therapeutic targets

1. Introduction
One of the most common causes of cancer related deaths is gastric cancer in the world. More than 1.5 million new diagnoses and almost 1 million deaths were reported in 2020, with the rates being significantly higher in the less developed countries [1]. The mechanisms of gastric carcinogenesis should be understood to come up with new early detection and treatment measures. The risk factor that is most significant in gastric cancer is the infection with *Helicobacter pylori*. *H. pylori* is believed to infect 75% of the gastric cancer patients [2]. The bacterium secretes numerous virulence factors such as cytotoxin-associated protein A (CagA), vacuolating cytotoxin A (VacA), and urease that cause the inflammatory reaction and are actively engaged in the tumor process [2].
The long-term *H. pylori* infection causes chronic inflammation, which leads to such precancerous lesions as gastric atrophy and intestinal metaplasia. Herein this contextual tumor microenvironment, the activation of the NF-κB signaling pathway by *H. pylori*-derived factors (e.g., CagA, urease) and the release of proinflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) are common. This is a proinflammatory cytokine, adhesion molecule, and chemokine-stimulating pathway, hence a procarcinogenic pathway. Activation of signal transducer and activator of transcription 3 (STAT3) in gastric epithelial cells by infection with *H. pylori* has also been reported and the extent of phosphorylated STAT3 is associated with the extent of gastric inflammation and development of gastric cancer [3].

STAT3, a transcription factor of the family of comparable factors in a variety of cellular processes, regulates the expression of several oncogenes in different cancers. All of these discoveries indicate that *H. pylori* infection is consistently linked with chronic inflammation and offer evidence that an *H. pylori*-mediated inflammatory network governed by NF-κB and STAT3 signaling is activated in the early stages of gastric-cancer progression [4]. Nevertheless, the mechanisms underlying this are not completely understood and have not been clearly spelt out. Therefore, learning the relationship between *H. pylori* and gastric carcinogenesis can be an important component in revealing the precise mechanisms that can be followed and coming up with new modes of treatment [5, 6].

2. Epidemiology and Clinical Relevance

Gastric cancer is the fifth most frequent malignancy and third leading cause of cancer-related mortality worldwide, with an estimated 1 million new cases and 769, 000 deaths in 2018. The incidence varies widely, being highest in East Asia, Eastern Europe, and Latin America and lowest in North America and most of sub-Saharan Africa. Persistent infection with *Helicobacter pylori*, classified as a group I human carcinogen by the International Agency for Research on Cancer, is the most important risk factor for gastric cancer. Roughly 50% of the global population carries *H. pylori*, and strains expressing the virulence factor CagA are associated with increased gastric cancer risk. CagA-positive strains are present in over 60% of infected individuals in high-risk areas but in fewer than 25% in low-risk regions. Concordant with these epidemiological observations, several studies have shown that *H. pylori* infection promotes precancerous lesions such as chronic gastritis, atrophy, intestinal metaplasia, and dysplasia. Gastritis related to *H. pylori* is classified as an important type B carcinogen, sufficient to induce gastric cancer in the Mongolian gerbil model and capable of promoting gastric cancer in transgenic mice expressing oncogenic K-Ras in the stomach . *H. pylori* colonization drives chronic inflammation and tumor progression throughout the precancerous stages of gastric cancer development [7, 8]. *H. pylori* infection activates key inflammatory signaling pathways, including NF-κB and STAT3, that affect many homeostasis and immune responses, and NF-κB and STAT3 activation are among the earliest events observed upon *H. pylori* infection. Thus, *H. pylori*-driven chronic inflammation and subsequent progression to dysplasia and cancer are at least partially mediated by the chronic activation of the NF-κB and STAT3 pathways [9].

3. *Helicobacter pylori*: Pathogenic Features and Virulence Factors

Helicobacter pylori is a common pathogen that can persist in the human gastric mucosa for life. Researchers consider *H. pylori* one of the most successfully adapted species that colonize the stomach following its ascent from the oral cavity. It is the only cancer-associated pathogen classified as a group I carcinogen by the International Agency for Research on Cancer. *H. pylori* colonization remains a global public health issue [10]. In 2018, 51% of the global population was estimated to be infected, with considerable geographical variation. The majority of cases are found in low-income countries, where 71% of the population is believed to be infected. Asia holds the largest burden, with an estimated 60% of the population being colonized 10. Infection is associated with gastric ulcer and non-ulcer dyspepsia. In 1994, The World Health Organization recognized *H. pylori* as a Class I carcinogen capable of causing stomach cancer 1. The carcinogenic potential of *H. pylori*-related inflammation depends on strain virulence and host susceptibility [11, 12]. Three main virulence factors correlated with increased gastric cancer risk have been identified: cytotoxin-associated gene A (CagA), vacuolating cytotoxin A (VacA), and blood-group antigen-binding adhesion A (BabA). Other factors, such as outer membrane protein A (OipA) and sialic acid-binding adhesin (SabA), also modulate host adhesion and immune response, although their direct link to carcinogenesis remains less clear. Carcinogenesis is linked to persistent inflammation through the production of pro-inflammatory cytokines. Prolonged and dysregulated cytokine signaling, which may activate oncogenic pathways, is influenced by *H. pylori* through the upregulation of interleukin-1β (IL-1β), IL-6, and IL-8 levels. These cytokines stimulate tumor-associated pathways such as Janus kinase (JAK)-signal transducers and activators of transcription (STAT) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), orchestrating the inflammatory response and driving oncogenic signaling [13, 14].

4. NF-κB Signaling Pathway: Activation by *H. pylori* and Implications for Gastric Carcinogenesis

Infection with the human gastric pathogen *Helicobacter pylori* is the most important risk factor for developing gastric cancer. The main virulence factor of *H. pylori*, the CagA protein, exerts this function by stimulating a complex and interconnected signaling network upon entry into host cells through type IV secretion. Interestingly, CagA also can induce different transcriptional programs, without the need of nuclear recruitment [15]. The infection with *H. pylori* triggers chronic inflammatory reaction, which is mediated by NF-κB, STAT3, and MAPK signaling and results in the release of various inflammatory cytokines and growth factors. The NF-κB pathway may be induced through the canonical and non-canonical pathways. In the canonical pathway, diverse pattern-recognition receptors located on gastric epithelial cells recognize *H. pylori* antigens, triggering the recruitment of the MyD88, TRIF, or TRAM adaptors. Subsequently, tumor necrosis factor receptor-associated factor 6 activates the IKK complex, leading to IκB degradation and the release of p65/p50 heterodimers. In the non-canonical pathway, the predominant receptor belonging to the TNF receptor superfamily is lymphotoxin β. The downstream MyD88-independent signaling cascade evokes the phosphorylation of NF-κB-inducing kinase and the activation of the IKKα homodimer, resulting in the processing of unprocessed p100 into p52 and the generation of a p52/RelB complex. Both pathways, therefore, converge on the NF-κB family of transcription factors and promote an inflammatory milieu that favors *H. pylori*-driven gastric carcinogenesis [16, 17].

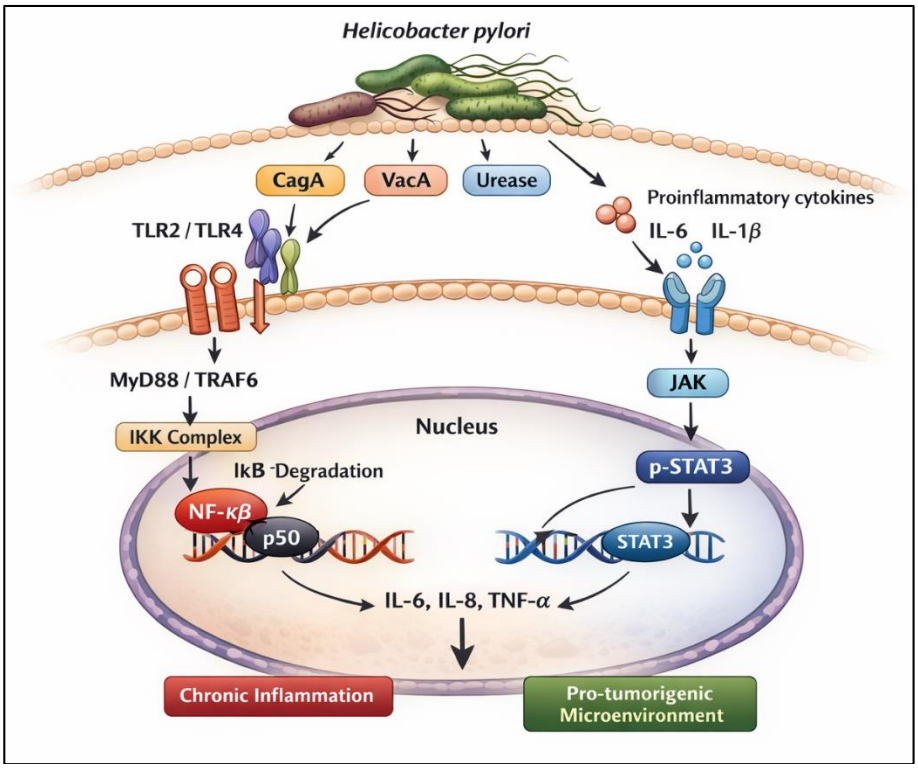

Fig 1: *Helicobacter pylori*-Induced Activation of NF-κB and STAT3 Signaling Pathways in Gastric Epithelial Cells

5. STAT3 Signaling Pathway: Activation by *H. pylori* and Implications for Gastric Carcinogenesis

Chronic inflammation of the gastric mucosa characterizes the progression of *Helicobacter pylori*-driven gastric cancer through atrophy, intestinal metaplasia, dysplasia, and carcinoma in the Correa cascade. Persistent *H. pylori* infection relies on the steady production of proinflammatory cytokines due to the continuous activation of nuclear factor kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3), respectively, which is involved in the tumorigenesis of multiple cancers. *H. pylori* induces the transcription of numerous proinflammatory cytokines and other oncogenic molecules that further exacerbate inflammatory responses and establish a conducive tumor-promoting environment via the canonical NF-κB pathway, whereas STAT3 signaling regulates inflammation-related cytokines and many oncogenic factors to trigger gastric carcinogenesis. The chronic *H. pylori* infection activates the NF-κB signaling pathway and its critical role in gastric carcinogenesis, and the mechanisms involved in the *H. pylori*-induced activation of the STAT3 signaling pathway remain poorly defined and overflowed [18, 19].

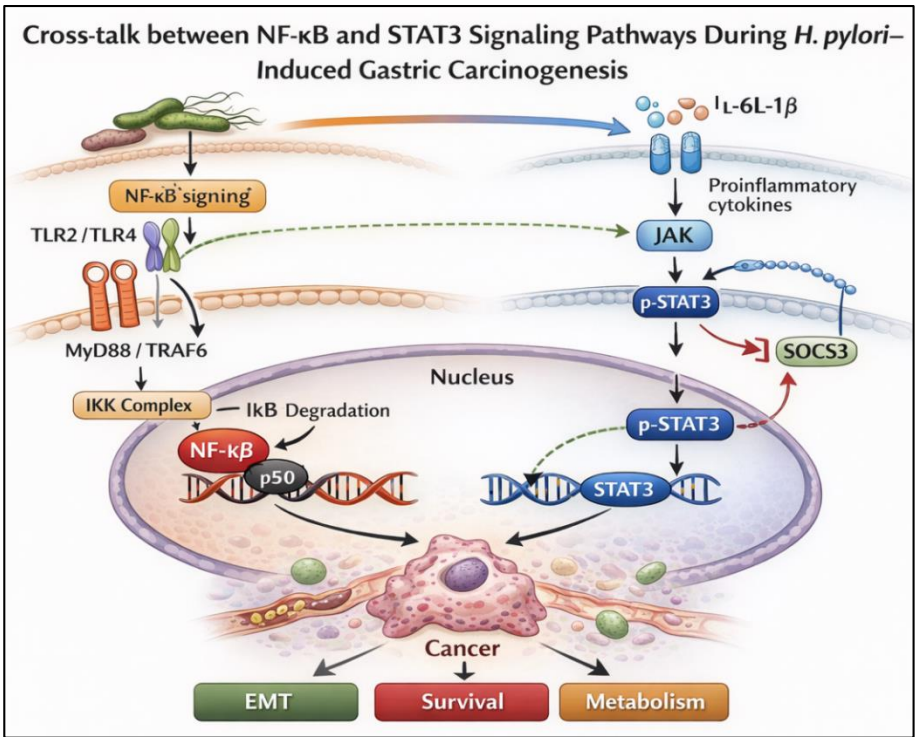

Fig 2: Molecular Cross-Talk Between NF-κB and STAT3 Signaling Pathways During *H. pylori*-Driven Gastric Carcinogenesis

6. Cross-talk Between NF-κB and STAT3 Pathways in the Gastric Mucosa

Infection with *Helicobacter pylori* and the consequent activation of NF-κB and STAT3 signaling are among the most prominent factors implicated in gastric carcinogenesis worldwide. Current literature provides evidence that these two signaling cascades establish a feedback network that enhances expression of fertilization-related protein 1, JAK3, and other downstream targets promoting gastric tumorigenesis. The potential synergy between *H. pylori*-driven NF-κB and STAT3 signaling remains to be systematically studied [20].

H. pylori infection triggers sustained, bidirectional cross-talk between the NF-κB and STAT3 signaling pathways in human gastric epithelial cells. *H. pylori*-activated NF-κB directly upregulates transcription of multiple inflammatory cytokines such as interleukin-6 (IL-6) and IL-8, which in turn activate the JAK2-STAT3 pathway [21, 22]. Conversely, the inflammatory cytokine IL-1β induces NF-κB-dependent expression of cyclooxygenase-2, which is known to promote prostate and other tumors through STAT3 activation. Both pathways are mandatory for *H. pylori*-induced inflammatory cytokine expression and cooperate to coordinate production of an IL-6-dominant cytokine network and other tumor-promoting gene products. Multiple mechanisms of cooperation between the pathways amplify their respective signaling outputs and orchestrate the tissue-specific expression of target genes within the context of chronic inflammation. *H. pylori* also delineates a distinct context in which NF-κB and STAT3 mutually enhance transcription of individual target genes via cooperative binding of NF-κB and STAT3 to shared regulatory elements [23, 24].

7. Downstream Targets and Oncogenic Programs

Sustained NF-κB and STAT3 activation induced by *H. pylori* drives the expression of a network of oncogenic effectors that acts in concert to promote gastric cancer initiation and progression. As detailed below, these effectors include proinflammatory cytokines (IL-1β and IL-6), growth factors (EGF and FGF-2), anti-apoptotic proteins (Bcl-2 and survivin), epithelial-mesenchymal transition (EMT) inducers (SNAIL, SLUG, and TWIST1), and metabolic adaptors (CPT1A and SREBF1). The individual or combined action of these downstream effectors supports a range of oncogenic programs, including inflammation, cell proliferation, survival, migratory and invasive capability, stemness, and metabolic adaptation, that facilitate *H. pylori*-driven gastric carcinogenesis and allow neoplastic cells to acquire secondary mutations [25, 26].

One of the earliest proinflammatory cytokines expressed in *H. pylori*-infected gastric epithelial cells, IL-1β is upregulated through NF-κB and induces the NF-κB and STAT3 pathways in both autocrine and paracrine manners [27]. IL-1β-driven inflammation promotes gastric precancerous lesions, and patients with *H. pylori*-induced gastritis showing elevated IL-1β or activation of its upstream regulator, NLRP3, exhibit a higher risk of developing gastric cancer. High levels of IL-6 are also associated with gastric cancer and correlate with inflammation-induced genetic instability. In *H. pylori*-infected cells, IL-6 is activated by NF-κB and induces the expression of epithelial growth factor (EGF) also activated by NF-κB which itself stimulates STAT3 and sustains the inflammatory response [28]. EGF-driven *H. pylori*-induced proliferation mirrors the proliferative response to IL-1β. Moreover, *H. pylori* induces the expression of basic fibroblast growth factor (bFGF, also termed FGF-2) in human epithelial AGS and other epithelial cell lines. IL-6, secreted upon *H. pylori* infection, is a direct regulator of bFGF, which stimulates proliferation. Thus, the induction of IL-1β, IL-6, EGF, and bFGF establishes an interconnected signaling circuit via NF-κB and STAT3 that promotes inflammation and proliferation in infected gastric epithelial cells [29].

The first anti-apoptotic protein upregulated by *H. pylori*-induced STAT3 activity, Bcl-2 has been directly linked to the early stage of *H. pylori*-induced gastric carcinogenesis. Levels of Bcl-2 and phosphorylated STAT3 are elevated in gastric cancer specimens from *H. pylori*-infected patients and correlate with cancer stage. In *H. pylori*-infected gastric epithelial cells, STAT3-dependent activation of survivin, an inhibitor of apoptosis and regulator of mitosis, enhances cell viability. SNAIL, SLUG, and TWIST1, transcription factors involved in embryonic development and fundamental biological processes in diverse cancer types, are directly regulated by *H. pylori*-induced STAT3 and upregulated in infected cells [30, 31]. These SNAIL family members are essential for *H. pylori*-induced epithelial-mesenchymal transition (EMT) and conferring gastric cancer stem cell properties. SNAIL, SLUG, and TWIST1 are also identified as early *H. pylori*-induced genes. Carnitine palmitoyltransferase I (CPT1A), a rate-limiting enzyme in fatty acid oxidation, and sterol regulatory element-binding transcription factor 1 (SREBF1), a key player in lipid metabolism, are upregulated by *H. pylori*-induced STAT3 activity. This genetic program induces fatty acid oxidation and intracellular lipid accumulation in gastric epithelial cells and serves as a metabolic adaptation mechanism that supports malignant transformation [32, 33]. Overall, sustained NF-κB and STAT3 activation caused by *H. pylori* impinges on multiple oncogenic programs through the concerted action of diverse downstream effectors and interconnected signaling circuits [34].

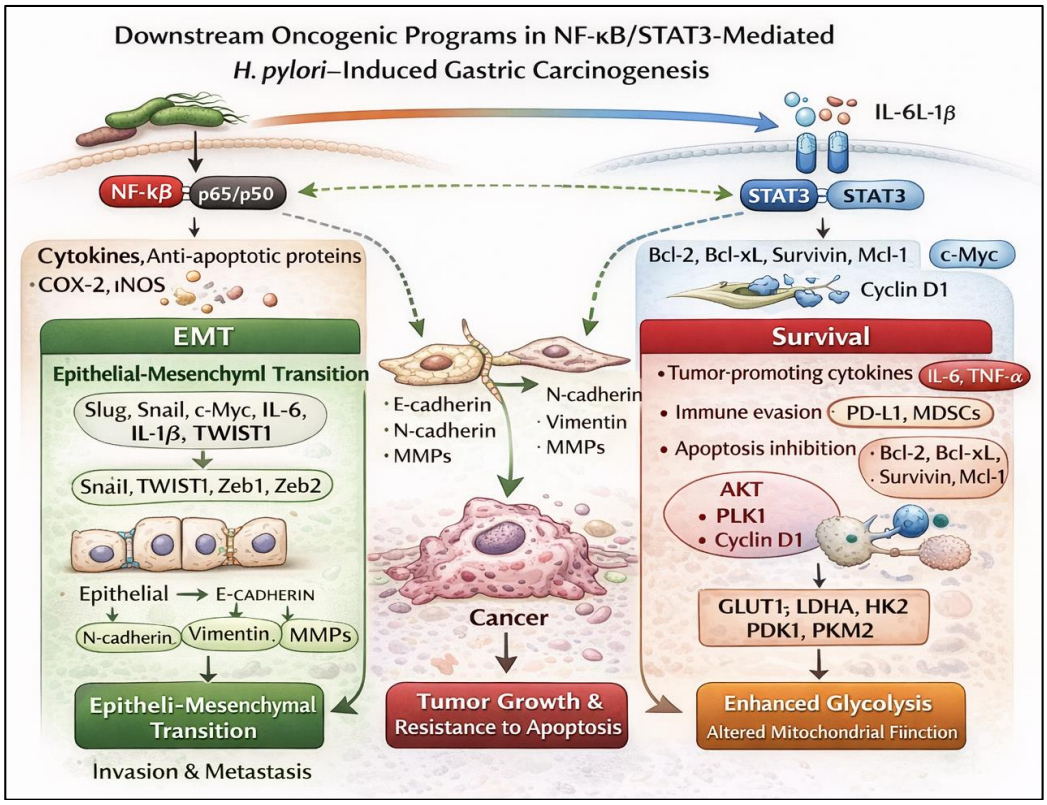

Fig 3: Downstream Oncogenic Programs Mediated by NF-κB and STAT3 Signaling in *Helicobacter pylori*-Associated Gastric Cancer

8. Epigenetic and Microenvironmental Modulators of NF-κB/STAT3 Signaling

Methylation of CpGs in the promoter of NR4A3 a TGF-β target gene and tumor suppressor—is an epigenetic event that renders NR4A3 transcriptionally inactive and predicts poor prognosis in gastric cancer [35, 36]. Aberrant promoter methylation of NR4A3 occurs through a mechanism mediated by JAK/STAT signaling. Secreted IL-6 activates the JAK/STAT pathway by interacting with the IL-6 receptor, and subsequently p-STAT3 binds to an IL-6 response element within the NR4A3 promoter, inducing NR4A3 transcription. The transcriptional induction of NR4A3 results in the upregulation of the TGF-β signal transducer SMAD4, which constitutes a negative-feedback mechanism. Conditioned medium from cancer-associated fibroblasts increases the proliferation and migration of gastric cancer cells via JAK/STAT3-mediated signalling and subsequent NR4A3 silencing [37, 38]. Enzymes involved in DNA methylation are upregulated by palmitate, leading to methylation of the NR4A3 promoter. Thus, aberrant JAK/STAT activation establishes an epigenetic modification including NR4A3 methylation and determines the malignant phenotype of gastric cancer cells [39].

Two main epigenetic modifications regulate chromatin structure: DNA methylation and covalent post-translational modification of histones. Hypermethylation in the promoter CpG region of several tumor suppressor genes is frequently observed in gastric cancer [40, 41]. Gomez *et al*. highlight that DNA methyltransferase enzymes (DNMTs) are frequently overexpressed in gastric cancer and that hypermethylation in the promoters of tumor suppressor genes occurs through the deregulation of these enzymes [42]. DNMTs and histone deacetylases cooperate in gastric cancer through the regulation of a set of target genes. Activating the prostaglandin E2 signalling pathway leads to the transcriptional upregulation of the type 4 prostanoid receptor (EP4) through β-catenin-dependent transcription, which results in increased expression of the DNMT1 gene. DNMT1 and the class I histone deacetylase HDAC1 cooperate to repress the expression of the retinoblastoma gene product, which contributes to the development and progression of gastric cancer. Histone modifications (e.g., methylation) also cooperate with *H. pylori* in gastric cancer [43, 44].

9. Therapeutic Targets Within NF-κB and STAT3 Pathways

Targeted inhibition of the NF-κB or STAT3 pathway directly at the receptor, ligand, adaptor, or kinase levels is feasible. Generally, a selective approach is preferred to minimize off-target toxicity or disruption of physiological functions, particularly in the context of inflammation. Many agents are repurposed from research on other cancers and therefore have documented resistance mechanisms, sometimes limiting single-agent use to clinical testing; combinations that target upstream kinases, such as JAK, MEK, and PI3K rather than receptors or ligands, are therefore being prioritized. Preclinical assessments in *H. pylori*-positive and-negative systems outline additional elements for consideration, including inherent resistance to specific inhibitors or counterselective benefit from co-targeting parallel signaling pathways [45, 46]. NA-1 is noteworthy for its ability to engage either mechanism: targeting JAK2/STAT3 represses clonal outgrowth, while inhibition of NF-κB, combined with JAK/STAT blockade, is sufficient to regress pre-existing *H. pylori*-dependent lesions [47, 48].

More flexible decoy strategies that merely disrupt NF-κB or STAT3 interactions with their respective transcription factors are in exploration; combinations of the two decoys are synergistically effective [49]. Aside from *H. pylori*, parallel, counteracting signals trigger either adaptive or

oncogenic broad-spectrum MAPK activation; further evolution can permit selection among these options. Outside the stomach, downstream transcriptomes differ markedly. Even undisruptive isoforms of the *H. pylori* cag system confer direct selective advantages; targeting the outer-membrane pore clashes with an alternate, neutral exposition to p65-NF-κB—widely exploited by other microbial species [50, 51].

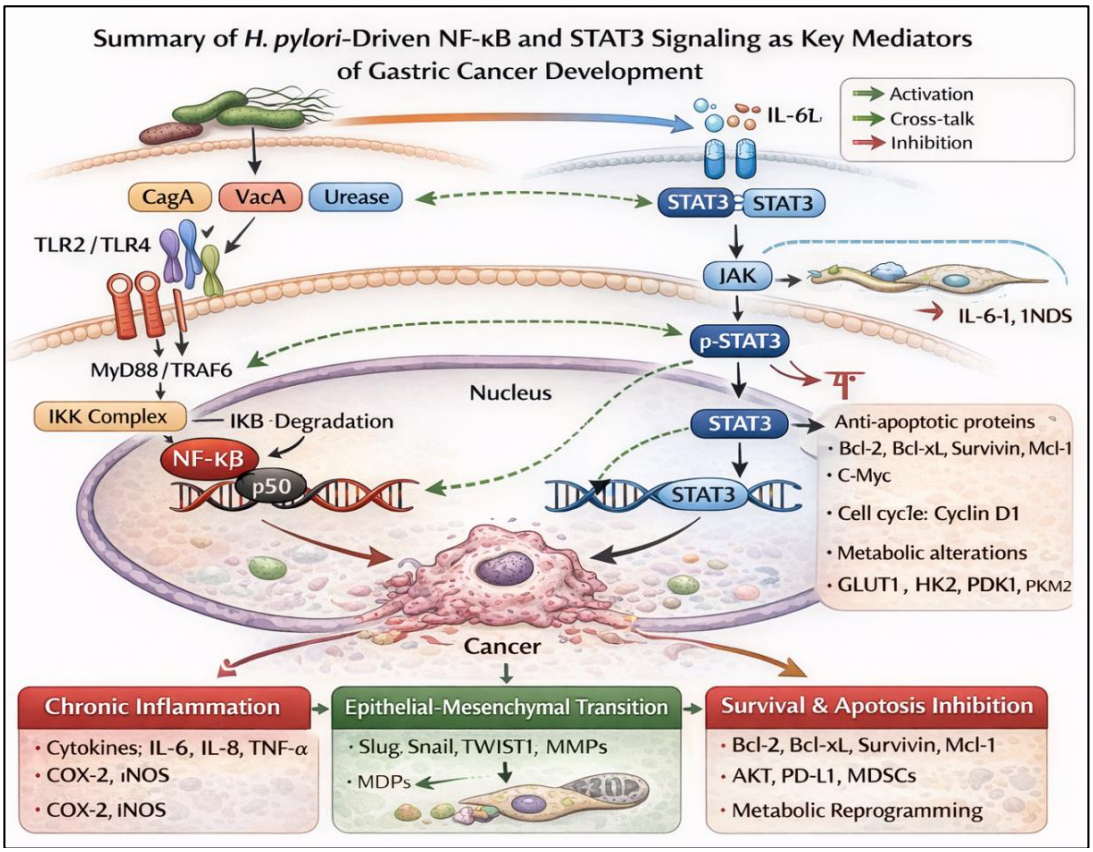

Fig 4: Integrated Model of *Helicobacter pylori*-Driven NF-κB and STAT3 Signaling Networks in Gastric Carcinogenesis

10. Preclinical and Clinical Evidence for Targeted Therapies

As NF-κB and STAT3 pathway activation has been established as a key consequence of *H. pylori* infection, extensive efforts have focused on evaluating the efficacy of targeted agents in preclinical models and clinical trials [52, 53]. A variety of human tumor cell lines, genetically engineered mouse models, and patient-derived organoids carrying the *H. pylori* metagastritis signature have been used to test drug combinations and prioritize therapeutic strategies. Such studies have demonstrated that even single agent targeting of NF-κB, STAT3, or downstream effectors is sufficient to inhibit key oncogenic programs, significantly block growth factor autonomy and invasion, and extend the survival of tumor-bearing mice, providing a compelling rationale for the clinical implementation of *H. pylori* target therapy despite the existence of several additional co-active drivers [54, 55].

Multiple inhibitors of NF-κB, STAT3, or their joint downstream effectors have entered human trials and appear to be well tolerated, with some yielding promising signals of antitumor efficacy in multiple advanced and/or refractory settings across diverse tumor types [56, 57]. Marks of pathway activity, target gene expression, and *H. pylori* status can inform patient stratification for targeted therapy across multiple drug modalities, suggesting a broader relevance beyond gastric cancer *H. pylori*-driven metagastritis. While detailed evaluations of the combined metabolic, proliferation, and stemness dependencies arising from NF-κB and STAT3 co-activation and their functional interconnections remain to be comprehensively scrutinized, several options have been established for precise therapeutic intervention [58].

11. Biomarkers and Precision Medicine Approaches

In parallel with the development of specific anti-*H. pylori* therapies, gastric cancer prevention strategies may benefit from targeted biomarker identification. Diagnostic, prognostic, and predictive biomarkers directly linked to, or enriched in, the NF-κB and STAT3 cascades represent candidates for stratifying risk and forecasting clinical outcomes in *H. pylori*-infected patients [59, 60]. Such markers may help identify individuals at high risk of stenosis requiring early endoscopy and intestinal biopsy screening 59. Other markers might guide selection of patients for existing or emerging therapies, optimizing treatment efficacy and minimizing toxic effects [61, 62].

Gastric cancer ranks third in cancer-related deaths worldwide, with *H. pylori* infection an established risk factor. Infection is most commonly initiated by CagA-positive strains. After CagA and receptor-mediated binding, intracellular pathways are activated, sometimes leading to STAT3 phosphorylation [62, 63]. In top biopsy specimens, analysis of C11orf87 methylation revealed hypomethylation in clinical stage I and II gastric cancers. In thus infected tissue, C11orf87 hypomethylation was associated with low to undetectable expression of other epigenetic modulators linked to CagA and STAT3. C11orf87 methylation reflects

progression from chronic gastritis to intestinal metaplasia and moderate-to-severe dysplasia and may therefore serve as a biomarker for gastric cancer detection, prognosis, or patient management [64, 65].

12. Challenges, Limitations, and Future Directions

H. pylori is associated with chronic inflammation and gastric cancer; yet the specific mechanisms of infection-related gastric carcinogenesis remain unclear. Three main hypotheses address these mechanisms, including the possibility that *H. pylori*-induced inflammation results in cancer-promoting alterations of stem or progenitor cell populations. These hypotheses are supported by a wealth of experimental evidence [66].

Throughout the body, environmental signals affect epithelial cell homeostasis by either promoting cell turnover or inducing differentiation. The epithelial compartment of the stomach is particularly stable, with only occasional, minor regeneration; hence a signal that initiates cellular proliferation could lead to the generation of a premalignant lesion. *H. pylori* induces a wide variety of pro-inflammatory cytokines from treated gastric epithelial cells, many of which are known to drive epithelial cell proliferation 2. In addition to direct proliferation, *H. pylori* alters the profile of secreted factors found in cultured gastric epithelial cells, which may further impact the regulation of epithelial cell homeostasis. The available evidence indicates that *H. pylori* infection produces the signals that are likely to initiate perturbation of epithelial cell compartmentalization, linking inflammation to gastric cancer [67].

In the stomach, *H. pylori* alters the NF-κB signaling pathway through multiple direct and indirect mechanisms; in particular, TLR2 and TLR4 upregulation allows more efficient activation of the NF-κB pathway. Increased and aberrant NF-κB activity takes place independently of canonical or non-canonical pathways and links *H. pylori* infection to gastric cancer. *H. pylori* induces tripartite interactions among RelA, c-Rel, and c-Jun, resulting in the concomitant upregulation of cyclin D1. *H. pylori* infection activates the c-Jun N-terminal MAPK pathway, which, together with NF-κB, cooperatively regulates the expression of several *H. pylori*-responsive genes. The combination of persistent and aberrant NF-κB activity and constitutive c-Rel/c-Jun interactions may thus represent a unique cancer-promoting mechanism [68].

13. Conclusion

NF-κB and STAT3 are crucial mediators of the *H. pylori* driven gastric carcinogenic cascade, functioning primarily as effectors of proinflammatory signaling. Further knowledge about the respective functions of these pathways, the connection of cross-talk, and downstream networks these pathways trigger, has obvious translational significance. Attacking particular aspects of the *H. pylori*-NF-κB/STAT3 axes is a potentially potent approach to block malignant progression in the case of *H. pylori* infection. Specifically, inhibitors that impair the activity of single downstream effectors can be beneficial, since these proteins complement the signal outputs of NF-κB and STAT3 and regulate the implementation of *H. pylori*-dependent oncogenic developmental programs.

14. Funding

None

15. Declaration of Competing Interest

The author declare there is no conflict of interest.

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