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Review Article

The Relationship Between Janus Kinase Pathways and MicroRNAs

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HIGHLIGHTS

- Janus kinase family consists of four signaling enzymes involved in cytokine signaling pathways.
- Modifications of JAK enzymes resulted in various pathological conditions.
- JAK2 modification is reported in several types of cancers.
- JAK modulators have been approved by FDA for treatment of several immunological and neoplastic disorders.

ABSTRACT

Janus Kinase (JAK) family is a group of four signaling enzymes composing of four distinct domains and involved in the intracellular pathways of cytokine downstream signaling. There are two kinase domains at C-terminal of protein, one of which is regulatory and the other has the main functionality in phosphorylation of target proteins. JAKs involve in the critical physiological processes, including immune response, growth, and differentiation. Mutations or malfunction of JAKs gene can result in pathological conditions like immuno-inflammatory diseases and malignancies. Targeting of JAK enzymes has been considered as effective therapeutic approaches in immuno-inflammatory disorders and different types of hematopoietic cancers or solid tumors. Rather than cytokines that are the natural modulators and the small chemical inhibitors developed as the therapeutic modulators of JAK enzymes, miRNAs can exert regulatory activity on JAKs. miRNAs are valuable biomarkers and regulatory elements of different pathophysiological conditions, particularly cancers. The relationships between JAK enzymes and miRNA are bi-directional, as the JAKs activity through JAK-STAT pathway as well as some other non-STAT pathways, control the expressions of various genes. These connections help scientists to design and develop novel therapeutic agents and predict the prognosis of disease following therapeutic regimens, based on these two critical components of cell biology.

Introduction

Intracellular signaling pathways emerge in various communications under different physiological or pathological conditions. The Janus kinase (JAK) family including JAK1, JAK2, JAK3 and TYK2 (tyrosine kinase 2), involve in the intracellular signaling network through the cytokine receptors. Albeit, the exact mechanisms of the activation, regulation, and multi-functionality of these signaling enzymes have not been described completely,

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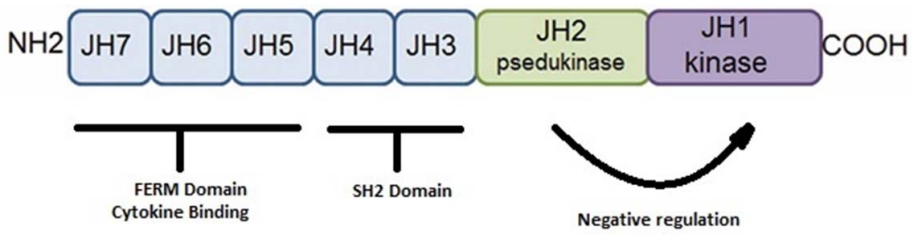

Figure 1. The sequential presentation of domains in JAK enzymes. JH7-5 are in the FERM domain involved in cytokine receptor interaction. JH4-3 in SH2 domain. With some modification from (Abroun et al., 2015).

until now. JAK mutations could result in several human diseases, including inflammatory diseases, haemopoietic malignancies, and immunodeficiency conditions (Babon et al., 2014).

Different members of JAK family play various roles in diverse physio-pathological conditions. JAK3 as the critical modulator of interleukins (ILs) including IL-2, 4, 7, 9, 15, and 21, is specifically expressed on hematopoietic cells. Malfunction of JAK3 as the key component of lymphocyte development and survival, result in severe combined immunodeficiency. JAK1 and 2 as well as TYK2 are universally expressed. Dysfunction of TYK2 can also lead to primary immunodeficiency with increased IgE. The studies on mice exhibited the lethal effect of malfunction of JAK1 or JAK2. In contrast, JAK activity enhancement could result in leukemia, lymphoma, polycythemia vera, and myelofibrosis (Yamaoka, 2016). Structural and functional aspects of JAK enzymes and the role of these enzymes in signaling pathways of cancer cells are illustrated in the distinct following sections.

MicroRNAs (miRNAs) are short non-coding double stranded RNAs produced by the RNA interference systems from a long single stranded premiRNA. Mature miRNAs can modulate the gene expression through the binding to the 3′ untranslated region (3′ UTR) of mRNAs, and subsequently result in target degradation or prevention of target translation. The miRNAs' activity is not completely selective and one miRNA can regulate the expression of various genes. In normal physiological state, some miRNAs regulate the gene expression according to the cell requirement and some others contribute to the cellular response such as cell growth and differentiation according to the external stimuli. In the pathological state, miRNA profiles of the cell and biological fluids are changed. Different miRNAs can exhibit complete contrary function in tumor pathology. First report about the miRNA deregulation in cancer was in 2002 that expressed the function of miRNA-15 and miRNA-16 in chronic lymphocytic leukemia (CLL). Some miRNAs inhibit tumor suppressor genes and therefore, they are oncogenic, but the others have tumor suppressive function and inhibit the oncogenic genes (Hayes et al., 2014; Lin and Gregory, 2015).

One of the important pathways in cancer control is JAK-STAT (signal transducer of activators of transcription) that may interact with various miRNAs. The effect of different miRNAs on JAK pathways are discussed completely in a separate section.

Janus kinase (JAK): structure/activity

Structural analysis of JAK enzymes revealed that they consist of four domains with different functionalities, including: (i) an N-terminal FERM domain with direct interaction with cytokine receptors, (ii) a Src homology-2 (SH2)-like domain whose exact function is not clear, (iii) a pseudokinase domain (JAK homology-2, JH2) whose kinase activity regulates the function of other kinase domain (JH1) and (iv) a C-terminal tyrosine kinase domain (JH1) which exert the main kinase activity in phosphorylation of target tyrosines. Generally, JAK enzymes contain two highly similar phosphate-transferring domains with different and distinct activities, JH1 and JH2. The JH2 negatively regulates the kinase activity of the other domain named kinase domain (JH1) (Bandaranayake et al., 2012; Babon et al., 2014) (Fig. 1).

Interaction of JAK enzymes with various receptors results in the JAK activation following the ligand binding to the receptors (cytokine-receptor interaction). The mechanism of JAK activation was studied and showed that the cytokine-induced receptor dimerization result in the phosphorylation of Tyr1007/Tyr1008 and activation of JAK catalytic domain. In addition, there are JAK activation mechanisms independent of receptor dimerization named as atypical or noncanonical activation. These mechanisms can activate through Gprotein-coupled receptors (GPCRs), oxidative stress and hypertonicity (Kurdi and Booz, 2009).

JAK activity in healthy cells

JAK kinases have the physiological role in the cytokine

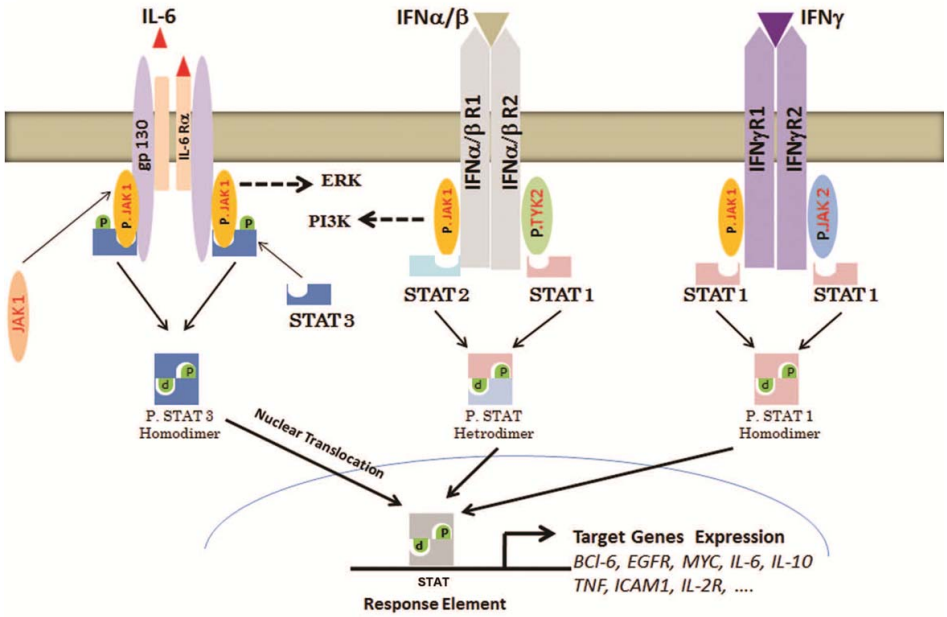

Figure 2. Different signaling pathways that JAK enzymes involved in (Abroun et al., 2015).

signaling pathways and also involve in the signal transduction of colony-stimulating factors, and several stimulating hormones (Fig. 2). Among these kinases, JAK1 and JAK2 have a wide functionality in the host defense mechanisms, hematopoiesis, growth, and neural development and it was stated that the deletion of JAK1 or JAK2 could be lethal in mice. In addition, mutations of JAK3 and TYK2 could result in primary immunodeficiency diseases, such as severe combined immune deficiency (SCID) (O'shea et al., 2013).

It was previously stated that JAK3 selectively associates with gamma chain (γc) and no other cytokine receptors. As a result, its malfunction has a dominant role in severe combined immunodeficiency. In addition, wide distribution of JAK1 in different cells and its activity in signaling transduction of different cytokine receptors, particularly IFN related and also the receptors that use gp130 and γc had also been stated (O'Shea et al., 2002). But now, it is confirmed that JAK1 collaborates with JAK3 in cytokine signaling through γc of receptors in the hematopoietic cells and its inactivation, regardless of the JAK3 status, could result in complete abolishment of STAT5 phosphorylation. Therefore, malfunction of JAK1 can dominantly induce the immune-suppressive condition (Haan et al., 2011).

JAK2 is widely expressed and associating with single chain hormone receptors, the common β chain family, and certain members of the class II receptor cytokine family (O'Shea et al., 2002). The function of JAK pathway in the proliferation and differentiation of neuronal precursor cells (NPCs) following the effect of growth factors was studied and the results confirmed the different regulatory effect of JAK members. In this regard, JAK2 play an important role in the proliferation, maintenance, and proliferation start of NPCs, though JAK3 involves in the NPCs differentiation. JAK3 knock-down lead to the NPCs differentiation into neurons and oligodendrocytes, but not to astrocyte (Kim et al., 2010).

The relationship between cytokine signaling and JAK enzymes through JAK-STAT pathways have been highly investigated (Fig. 3).

JAK activity in cancerous cells

All of the JAK family members are the upstream kinases of STAT proteins that phosphorylate them and result in down-stream regulatory functions. Importance of JAK/STAT pathway in various types of cancers had been comprehensively illustrated (Thomas et al., 2015). It was reported that the signaling pathway of JAK2/STAT3 was involved in different types of cancer, including lung (Chuang et al., 2017), pancreatic cancer (Wang et al., 2014), breast (Watson and Hughes, 2014), and hepatocellular carcinoma (Mohan et al., 2014). Mutations of JAK2 (most frequently V617F mutation) are discovered in the myeloproliferative neoplasms, polycythemia vera, essential thrombocythemia, and primary myelofibrosis (O'shea et al., 2013).

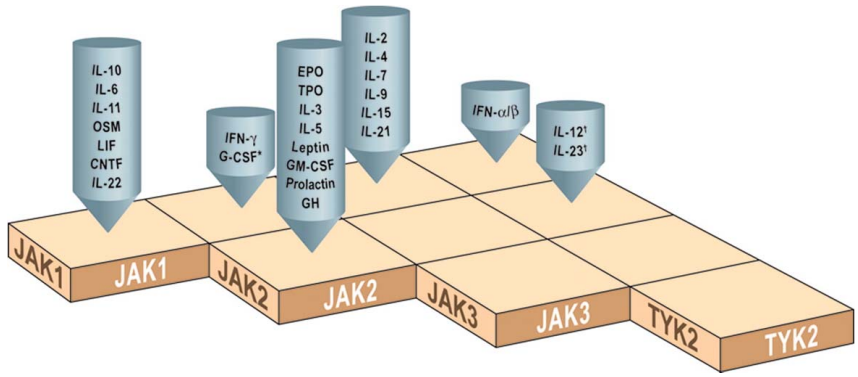

Figure 3. The association of JAK enzymes with different types of cytokines. Most of cytokines use two or more JAK members that shown in this schematic presentation (Murray, 2007).

Other members of JAK family can also involve in gene regulation and cancer development, such as JAK1in B cell lymphoma that could be the direct effect of JAK activity on the chromatin phosphorylation and subsequently, perturbs the gene expression (Rui et al., 2016).

It was also confirmed that targeting of JAK1/STAT3 and blockage of this pathway effectively suppressed ovarian tumor progression (Wen et al., 2014). The therapeutic effect of JAK1 inhibitors in other cancer types such as lung (Wu et al., 2016), prostate (Handle et al., 2016), gastric (Song et al., 2016), colorectal (Celtikci et al., 2014), and breast (Kaushik et al., 2017) have been demonstrated.

Several types of JAK3 mutations were reported in lymphoma and leukemia. In a case of lung cancer, two types of JAK3 mutation were identified that activate the JAK3. It promoted the programmed cell death-1 (PD-1) protein induction and according to the T-cell immunity inactivation resulted to the therapeutic resistancy and progression of cancer cells. It can be concluded that alteration of JAK3 may have influence on the therapeutic activity of PD-L1 inhibitors (Van Allen et al., 2015). Moreover, JAK3 interaction with zeste homologue 2 (EZH2) involving in the epigenetic control of gene expression through histone methylation, was confirmed and it was shown that JAK3 could phosphorylate EZH2 on tyrosine residue 244 and suppress EZH2 methyltransferase activity and as a result, the survival and proliferation of lymphoma cells promote. In contrast, JAK3 inhibition may suppress the survival and proliferation of lymphoma cells (Karantanos and Boussiotis, 2016). In cervical cancer cell lines, activation of JAK3 independent of JAK1 activity through IL-2 receptor, could lead to the proliferation of cancer cells. That was different from the normal lymphocytes that IL-2 activation results in JAK1 phosphorylation and then JAK3 activation. Consequently, JAK3 inhibitor could be a promising treatment for cervical cancer (Valle-Mendiola et al., 2014).

JAK modulators

The JAK-STAT pathway provides an important mechanism for controlling gene expression by extracellular factors. Along with four members of JAK family, seven types of STAT proteins have been identified in mammalians that each one is related to particular signaling pathway. JAK and STAT kinases may be independently activated and insert the down-stream functions on gene expression, instead of JAK/STAT pathway. Malfunction or modification of JAK or STAT proteins can result in several disorders including immunodeficiency disorders and malignancies. Therefore, modulation of these pathways through JAK or STAT members can exhibit promising therapeutic activity in cancers (O'Shea et al., 2015). For example, MLS-2384 (6-bromoindirubin) is a dual JAK/Src kinase inhibitor. Related study confirmed that it could suppress growth of various human cancer cells, such as prostate, breast, skin, ovarian, lung, and liver. Inhibition of JAK and Src kinases also led to a dose-dependent inhibition of the phosphorylation of STAT3 (Liu et al., 2014). There are various types of small chemicals with JAK inhibitory function studied as potential therapeutic agent of cancers, autoimmune, and inflammatory disorders (Kettle et al., 2017; Kettle et al., 2017).

Natural compounds have been evaluated as the JAK modulator, as well. In this regard, Brevilin A as an active compound extracted from medicinal herb, exhibited strong STAT3 signal inhibition and subsequent cell growth inhibition. Moreover, Brevilin A could also inhibit STAT1 signaling for cytokines induced phosphorylation of STAT3 and STAT1. Therefore, it could affect the expression of the target genes. In addition, Brevilin A could block the JAKs JH1domain and decrease the JAKs kinase activity (Chen et al., 2013).

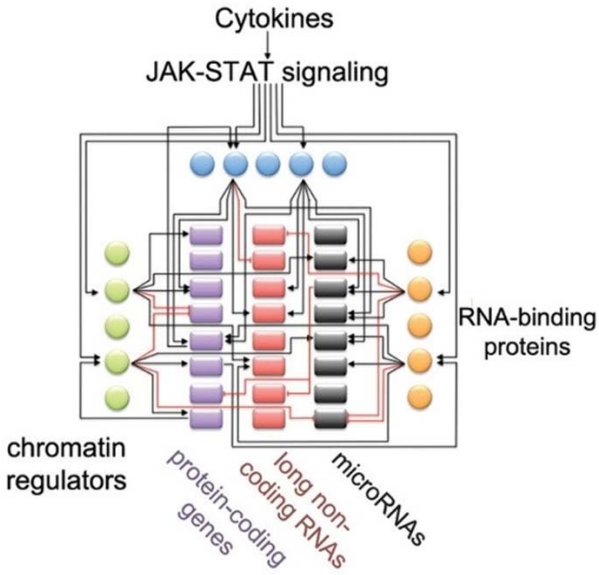

Figure 4. Schematic presentation of JAK-STAT pathway control on miRNAs (Witte and Muljo, 2014).

It was stated that the highly conserved structure of the JAK ATP binding pockets can be an attractive target for the design and development of highly selective JAK inhibitors as pharmacological agents. In this regard, different types of chemical molecules have been introduced (Tan et al., 2015; Leroy and Constantinescu, 2017).

In the design of anti-cancer therapeutic agents, it should be noted that the cooperation between JAK1 and JAK3 in T-cell transformation and incidence of different mutations in immune response promotion may lead to the resistance in cancer treatment with JAK inhibitors (Springuel et al., 2014).

Clinical applications of JAK modulators

JAK agonists and antagonists, that respectively, activate or inhibit JAK phosphorylation activity, can result in different functionalities. Since the Janus kinases are the key enzymes in the signal transduction of multiple immunomodulatory cytokines, inhibition of their functions can result in immunosuppression; especially inhibitors of JAK3 can be good candidates for immune diseases. In addition, effective role of JAK enzymes in a wide range of malignancies led to the development of small chemical JAK inhibitors as the anticancer agents. Currently, several JAK inhibitors have been approved by FDA for clinical application (Aittomäki and Pesu, 2014).

Ruxolitinib is the first FDA-approved inhibitor of JAK1/JAK2 in Nov. 2011 marked for the clinical application in the treatment of myelofibrosis and also in 2014, it was approved for Polycythemia Vera. The effectiveness study of Ruxolitinib in acute leukaemia, lymphoma, multiple myeloma, essential thrombocythaemia, prostate cancer, breast cancer, pancreatic cancer and rheumatoid arthritis are in progress in various phases of clinical trials (Aittomäki and Pesu, 2014).

FDA also approved Tofacitinib in Nov. 2012, for the treatment of Rheumatoid Arthritis. It exhibited the inhibitory effect on JAK1 and JAK3 with low selectivity for JAK2. Several clinical trials are in progress for Tofacitinib evaluation in ulcerative colitis, psoriasis, renal transplantation, juvenile idiopathic arthritis, and dry eyes (Aittomäki and Pesu, 2014; Wu et al., 2015).

The other JAK inhibitor approved in 2013 as a veterinary medication is Oclacitinib, for the treatment of pruritus associated with allergic dermatitis and also atopic dermatitis in dogs. Human clinical applications of JAK inhibitors in dermal disorders have been studied and JAK inhibitors were suggested as efficacious therapeutics for alopecia areata, atopic dermatitis, psoriasis, and vitiligo (Damsky and King, 2017)

MicroRNAs as the JAK modulators

MicroRNAs (miRNAs) are a class of small, noncoding regulatory RNAs that negatively regulate target gene expression. They involve in a wide range of biological processes. The pattern of miRNAs in different cells and healthy or disease states are changed. Accordingly, miRNAs can be considered as valuable biomarker in diagnosis and treatment of various diseases (Lin and Gregory, 2015; Hao et al., 2017). The role of miRNAs

Table 1. The relationships between miRNA and JAK enzymes in different diseases (several examples).

miRNA	JAK #	Type of relationship	Disease	Ref.
miR-9	JAK1	miR-9 down-regulate JAK1/STAT1 signaling pathway	Atherosclerosis	(Wang et al., 2017)
miR-23a	JAK1	miR-23a mediated inactivation of the JAK1-STAT3 pathway	Acute erythroid leukemia (AEL)	(Su et al., 2016)
miR-30c	JAK1	mRNA levels of JAK1 were decreased when miR-30c was overexpressed	Porcine reproductive and respiratory syndrome virus infection	(Zhang et al., 2016)
miR-448	JAK1	Upregulation of the JAK1 mRNA was inversely correlated with the miR-448 level	pancreatic ductal adenocarcinoma	(Yu et al., 2017)
miR-340	JAK1	miR-340 suppressed the JAK1/STAT3 pathway	Hepatocellular carcinoma	(Yuan et al., 2017)
miR-133a	JAK2	Overexpression of miR-133a down regulated JAK2 mRNA	Heart failure	(Chen et al., 2015)
miR-204	JAK2	miR-204 suppressed JAK2 and p-JAK2 expression	Breast Cancer	(Wang et al., 2015)
miR-375	JAK2	miR-375 over-expressing down-regulate JAK2/ STAT3	Colorectal cancer	(Wei et al., 2017)
miR-135b	JAK2	miR-135b-5p negatively targeted JAK2	Myocardial ischemia/ reperfusion	(Xie et al., 2017)
miR-133b and miR-135a	JAK2	miR-133b and miR-135a inhibit JAK2 expression and JAK2-STAT3 pathway	Renal carcinoma	(Zhou et al., 2016)
miR-29b and miR-198	JAK3	miR-29b/miR-198 down-regulate JAK3	Renal carcinoma	(Gigante et al., 2016)

in severe disorders such as cancers is highly important and they regulate metastasis, cell proliferation and cell death. JAK-STAT pathways can influences on the miRNA patterns. It was reported that miR-21, MiR-29a and miR-29b-1 were induced through the JAK-STAT pathways and resulted in different incidents, as miR-21 is oncogene but MiR-29a and miR-29b-1 are tumor suppressors (Witte and Muljo, 2014).

MicroRNAs can also affect the JAK-STAT pathways through controlling the expression of JAK or STAT genes (Zhang et al., 2011; Wu et al., 2012; Yuan et al., 2017). The mechanisms involved in miRNA activity on cell fate are highly varied; however, the key regulatory pathways of the cells such as JAK pathways, may be the main mechanism. miRNAs released from the cancerous cells could activate the JAK-STAT pathway especially STAT3 and result in the tumor progression (Lam et al., 2013). The relationships between different miRNAs and JAK pathways, especially JAK-STAT pathways, have been studied in a wide range of physio-pathological states (several examples were presented in Table 1).

Tumor suppressor miRNAs can have influence on the IFN-γ signaling pathway; including anti-proliferative activity of miR-375 and miR-135a on gastric cancer and miR-216a on pancreatic cancer that affected JAK2 expression (Eichmüller et al., 2017). Some of miRNAs

controlled the JAK-STAT pathway indirectly, such as the impact of miR-142a on cytokine signaling and T cell differentiation. The miR-142a directly suppress SOCS1 (suppressor of cytokine signaling 1) and as a result, upregulate the JAK2-STAT1 signaling in autoimmune diseases (Talebi et al., 2017).

Regard to the miRNAs regulation of JAK pathways, it was stated that two miRNAs (the exact type of miRNA was not published) inhibited JAK2-mediated −1 PRF (programmed −1 ribosomal). The -1 PRF is a regulatory pathway in human gene expression including the mRNAs encoding JAK2 and STAT1. JAK2-mediated −1 PRF can likely emerge a regulatory feedback loop in cytokine signaling (Dinman et al., 2016).

Conclusion and Outlook

One of the important signaling enzymes in cancer progression and prognosis, is Janus kinase family. Most of the down-stream effect of cytokines and growth hormones emerged through the JAK-STAT signaling pathways. Targeted inhibition of this central pathway could result in different genes regulation to treat patients with immunological disorders, hematologic cancers, and solid tumors. This pathway has impact on the gene expression through epigenetic regulation of transcription and translation, as the phosphorylation of key proteins can alter their activity. miRNAs are important biomarkers for different physio-pathological states and nowadays, considered as potential therapeutic agents in the treatment of various diseases, especially cancers. Bi-directional relationship between miRNAs and JAK signaling pathways has been confirmed as an interesting field of study in medicine and drug discovery. miRNAs control JAK expression and function as well as JAKs activity can have influence on miRNA profile. The miRNA-JAK interactions and their impact on cell proliferation or apoptosis are extensively investigated in various types of cancers. Discovery of these interactions help scientists to introduce novel efficient therapeutic and diagnostic approaches.

Competing interests

The authors declare that they have no competing interests.

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