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REVIEW

IRF2BP2: A new player in the regulation of cell homeostasis

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Abstract

The IRF2BP2 (IFN regulatory factor 2 binding protein 2) protein was identified as a nuclear protein that interacts with IFN regulatory factor 2 (IRF-2) and is an IRF-2-dependent transcriptional repressor. IRF2BP2 belongs to the IRF2BP family, which includes IRF2BP1, IRF2BP2, and IRF2BPL (EAP1). Recently, IRF2BP2 has emerged as an important new transcriptional cofactor in different biological systems, acting as a positive and negative regulator of gene expression. IRF2BP2 plays a role in different cellular functions, including apoptosis, survival, and cell differentiation. Additionally, IRF2BP2 may be involved in cancer development. Finally, it has been recently reported that IRF2BP2 may play a role in macrophage regulation and lymphocyte activation, highlighting its function in innate and adaptive immune responses. However, it has become increasingly clear that IRF2BP2 and its isoforms can have specific functions. In this review, we address the possible reasons for these distinct roles of IRF2BP2 and the partner proteins that interact with it. We also discuss the genes regulated by IRF2BP2 during the immune response and in other biological systems.

KEYWORDS
cell activation, cell signaling, IRF2BP2, transcriptional regulation

1 | INTRODUCTION

The IFN regulatory factor 2 binding protein (IRF2BP) family includes IRF2BP1 and IRF2BP2, the latter of which is composed of 2 splicing isoforms, A and B, and a third member IRF2BPL (also known as EAP1). The 2 last were identified as IFN regulatory factor-2 (IRF-2)-associated transcriptional corepressors.[1] This review focuses on IRF2BP2 and summarizes the recent advances in the field, as IRF2BP2 has emerged as an important new transcriptional cofactor in different biological systems. IRF2BP2 acts as a positive and negative regulator of gene expression by playing a role in different cellular functions, such as apoptosis,[2,3] survival,[2] and cell differentiation.[4] Some studies have suggested that IRF2BP2 is involved in angiogenesis during cancer development,[5] DNA repair,[2] gene fusion,[6–8] and immune system evasion.[9] Furthermore, it has been recently reported that IRF2BP2 has a role in macrophage regulation[10–12] and lymphocyte activation,[13,14] highlighting its function in the innate and adaptive immune responses.

Abbreviations: APL, acute promyelocytic leukemia; CDK5, cyclin-dependent kinase 5; CVID, common variable immunodeficiency disorder; ETO2, eight-twenty-one 2; IRF-2, IFN Regulatory Factor 2; IRF2BP2, Interferon Regulatory Factor 2 Binding Protein 2; KLF2, Kruppel-like factor 2; MGUS, monoclonal gammopathy of undetermined significance; NCOR1/SMTR, nuclear receptor corepressor/silencing mediator for retinoid and thyroid receptors; NLS, nuclear localization signal; PD-1, programmed cell death 1; PD-L1, programmed death-ligand 1; RING, real interesting new gene; UTR, untranslated region; VGLL4, vestigial like family member 4.

2 | IRF2BP2: GENE AND PROTEIN STRUCTURE

The protein-coding gene is localized on chromosome 1q42.3 in humans and has 2 exons (Fig. 1). This gene codifies 2 splicing isoforms, A and B (Fig. 1). Completing the IRF2BP family, there is also an IRF2BP1 gene, which is localized on chromosome 19q13.32. The A and B isoforms of the IRF2BP2 protein share high identity because they differ in just 16 amino acid residues, encoded by the 3′ end of the first exon, through alternative use of a splicing donor site. The zinc and real interesting new gene (RING) domain homology shared by the IRF2BP proteins characterizes this family, and it can be observed in IRF2BP1 as well.

It is important to note the long 3′UTR (untranslated region) present in the IRF2BP2 mRNA. In fact, microRNAs are important regulators of translation that also act by binding to the 3′ UTR.[15] Even though translational regulation has not been demonstrated, it has been suggested that miR-155 regulates IRF2BP2 synthesis.[16]

The IRF2BP2 protein contains 2 zinc finger domains. At the N-terminus, there is a 64 amino acid domain, which contains a C4 motif, and at the C-terminus, the final 82 amino acids include a RING domain (CH3C4 type; Fig. 2).[1] Between these domains, there is a region predicted to be unfolded with a nuclear localization signal (NLS) conserved in the members of the family (Fig. 2).[13,17] Both domains are highly conserved in the family and in different organisms (Figs. 3A and B).

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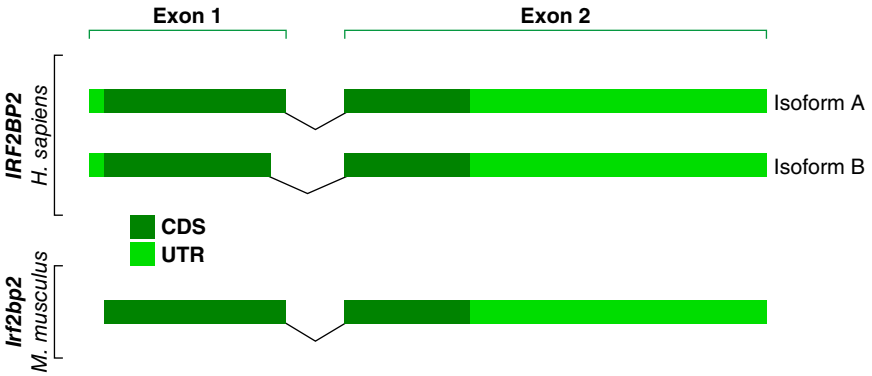

FIGURE 1 Two exons encode the IRF2BP2 protein. Schematic view of the IRF2BP2 gene, which is constituted by 2 exons, exon 1 and 2 (dark green). The intron region, which is spliced, is also represented, and the splicing results in isoform A and B. The 3′ and 5′ UTRs are also represented and demonstrate the long 3′UTR (light green). Similarly, 2 exons codify the highly conserved IRF2BP2 protein in mice

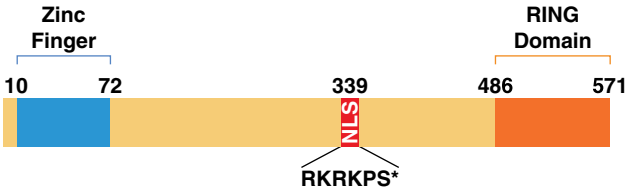

FIGURE 2 IRF2BP2 protein. IRF2BP2 is constituted by 2 zinc finger domains: the zinc finger (blue box) at the N-terminus and the RING domain (orange box) localized in the C-terminus. Here, the B isoform is represented. There is a NLS with an RKRK sequence. Near the NLS, there is a serine residue (S*), which is a target of phosphorylation and important for nuclear localization. The numbers indicate the amino acid positions

Evolutionarily, IRF2BP2 protein is observed in different organisms, from simple to complex animals, such as in an egg-larval parasitoid *Fopius* and human. Moreover, there are related gene products in *Caenorhabditis elegans* MO4G12 and *Drosophila melanogaster* CG11138 whose roles are unclear yet. It is interesting to note that IRF2BP2 is present in these organisms but IRF-2 transcription factor do not occur in them that suggests IRF2BP2 performs IRF-2-independent functions. The conservation observed in different phylos implies that IRF2BP2 may be partner of others transcription factors and participate in other pathways.

IRF2BP2 has been described as a ubiquitously expressed protein. It is present in different tissues, as related by Fagerberg and colleagues[18] in their analysis of the tissue-specific expression of IRF2BP2 using transcriptomics and proteomics. Moreover, during mouse embryonic development, high and ubiquitous expression is observed, whereas after development, expression decreases overall but remains high in the lung, heart, and skeletal muscle.[5]

3 | IRF2BP2 PROTEIN AS A GENE EXPRESSION REGULATOR

The IRF2BP2 protein was identified as a nuclear protein able to interact with IRF-2, acting as an IRF-2-dependent transcriptional repressor. Interestingly, the authors highlight the presence of IRF2PB2 in IRF-2-lacking organisms.[1] This finding suggested that IRF2BP2 also has IRF-2-independent functions. In fact, studies have demonstrated other roles for IRF2BP2 that are IRF-2-independent. The known partners will be discussed below and shown in Table 1.

Koeppel and colleagues[2] showed that IRF2BP2 favors survival and protects from apoptosis in the p53-mediated stress response, acting as repressor of p53-mediated transactivation of the p21 and bax genes. The IRF2BP2 protein also exhibits an antiapoptotic role, acting as a protector during the NRIF3-mediated death switch in breast cancer cells.[19] The same group demonstrated that IRF2BP2 participates in a protein complex with IRF2BP1 and IRF2BPL (EAP1) proteins, which together mediate the transcriptional repression of the FASTKD2 pro-apoptotic factor.[3]

In addition, our group has identified IRF2BP2 as a NFAT1 partner that is able to represses NFAT1-mediated transcriptional activity. The mechanisms of this repressor phenotype are not clear yet, but the group showed that the repression does not involve NFAT1 degradation or the reduction of NFAT1 gene expression.[13] Because NFAT1 has a key role in the immune response, it is important to clarify the repressor mechanism mediated by IRF2BP2. Increasing understanding of the importance of IRF2BP2 in the immune response, the same group demonstrated that IRF2BP2 overexpression in CD4 T lymphocytes repressed the expression of IL-2 high affinity receptor α-chain and STAT5 phosphorylation.[14] Both results demonstrated that IRF2BP2 plays an important role in lymphocyte activation. Additionally, IRF2BP2 down-regulated CD69 expression, suggesting that IRF2BP2 participates in CD4 T-cell activation.[14] These studies have demonstrated that IRF2BP2 is an important regulator, which will be discussed next.

Among these above mentioned repressor functions, some work from Stewart's group has demonstrated that IRF2BP2 also plays a role as a transcriptional activator. According to Teng and colleagues,[5] yeast 2-hybrid screen of a human heart cDNA library using vestigial like family member 4 (VGLL4) as a bait identified IRF2BP2 as VGLL4 partner. Together with a TEAD transcription factor, IRF2BP2 activates vascular endothelial growth factor A expression in cardiac and skeletal muscles, which favors revascularization after ischemia. Recent studies have reported that IRF2BP2 is a novel regulator of macrophage inflammation and lipid homeostasis. Researchers have generated mice with IRF2BP2-knockout macrophages,[10] and the IRF2BP2-deficient macrophages had an inflammatory phenotype, particularly due to the reduced expression of anti-inflammatory transcription factor Krüppel-like factor 2 (KLF2). The studies reveled that IRF2BP2 is

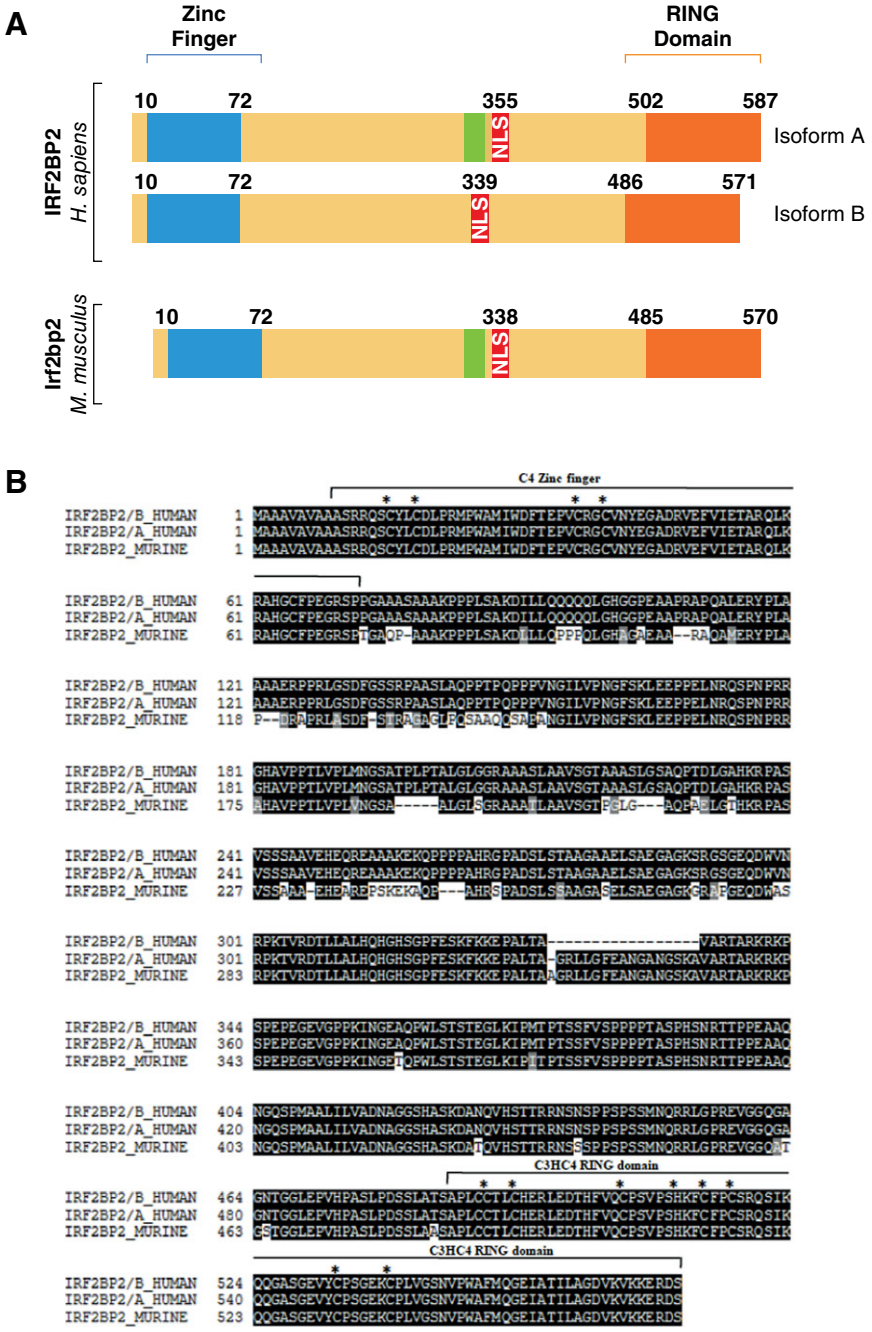

FIGURE 3 **The IRF2BP2 protein is highly conserved**. (**A**) Isoforms A and B of human IRF2BP2 differ in only 16 amino acid residues (green box). The zinc finger domain (blue box), RING domain (orange box), and NLS (red box) are conserved. In mice, there is 1 IRF2BP2 protein, and it is more similar to human isoform A. The numbers indicate the amino acid positions. (**B**) The primary amino acid sequences of human IRF2BP2, isoforms A (NP_892017.2) and B (NP_001070865.1), and murine IRF2BP2 (NP_001158070.1) were aligned using MultAlin. Isoforms A and B show high identity, differing in only 16 amino acid residues, as demonstrated in the alignment. Murine IRF2BP2 share more similarity with human isoform A. The conserved C4 zinc finger and C3HC4 RING domains at the N- and C-terminus, respectively, are highlighted, and the cysteines and histidines are indicated by asterisks

TABLE 1 IRF2BP2 partners

Partner	Method	IRF2BP2 domain	Partner domain	Reference
IRF-2	Yeast 2 hybrid, IP	Ring	Repressor domain C-terminal	1
NFAT1	Yeast 2 hybrid, Pull down, FRET	Ring	TAD-C	12
NRIF3	Yeast 2 hybrid, IP	Ring	DD1	18
IRF2BPL (EAP1)	Yeast 2 hybrid, IP	C4 zinc finger	–	3
ETO2	IP	Ring	US2	4
NCOR1	IP-MS	–	–	4
VGLL4	Yeast 2 hybrid, IP	Ring	–	5,9

FRET, fluorescence resonance energy transfer; IP, immunoprecipitation; IP-MS, immunoprecipitation followed by mass spectrometry.

required for myocyte enhancer factor 2-dependent transcriptional activation of KLF2, showing that IRF2BP2 is a positive regulator of transcription. Using the same IRF2BP2-deficient mice, it was demonstrated that IRF2BP2 is necessary for recovery from ischemic injury in microglia. Interestingly, stroke recovery occurs via IFN-β, and the other repressors of the IRF2BP family (IRF2BP1 and IRF2BPL) are not able to compensate for IRF2BP2 deficiency. These data suggest a specific function for IRF2BP2 in IFN-β signaling.[11] In addition, the same group demonstrated that IRF2BP2 in microglia is necessary for the anxiety-reducing effect of enhanced maternal care by suppressing IL-1β expression in mice.[12]

It is important to highlight the study performed by Arruda and colleagues[16] that reported that multiple sclerosis is characterized by high levels of microRNA associated with low levels of IRF2BP2. After IRF2BP2 was restored to normal levels, the immunoregulatory network was improved, especially regulatory T cells, suggesting an important role of IRF2BP2 in modulation of immune homeostasis.[16] However, future studies are necessary to clarify the mechanism involved and possible therapeutic effects.

A recent study identified IRF2BP2 as a component of a protein complex responsible for maintaining an erythroid-specific gene expression program for activation and differentiation. IRF2BP2 interacts with eight-twenty-one 2 (ETO2), constituting an IRF2BP2-ETO2 axis that recruits the nuclear receptor corepressor/silencing mediator for retinoid and thyroid receptors (NCOR1/SMTR) corepressor complex.[4] Then, this complex directly regulates the expression of the vast majority of erythroid genes and pathways for terminal differentiation, for example, key heme biosynthesis and erythrocyte membrane proteins.[4] Finally, IRF2BP2-deficient mice were generated, but animals homozygous for Irf2bp2 were rarely obtained and did not survive past 4 weeks of age due to severe growth retardation.[4] In fact, the deficient mice developed normally to E18.5, but mice died either late during gestation or immediately after birth. When analyzing the E13.5 fetal livers tissue, the authors observed reduced total cellularity and several defects in erythropoiesis, confirming that IRF2BP2 is important for effective erythropoiesis in vivo.[4]

4 | REGULATION OF IRF2BP2 EXPRESSION

Though IRF2BP2 is an important regulator of gene expression, how it is regulates gene expression and posttranslational modifications are not well-understood. Although IRF2BP2 proteins are constitutively expresses in wide type of cells, their transcriptional regulation is poorly known until now. Then, in this review, we will mostly discuss the post-translational regulation of these proteins.

It was reported that IRF2BP2 gene expression is activated by p53 in response to DNA damage through p53 binding to the enhancer sequence 9 kb upstream of the IRF2BP2-gene.[2] Moreover, studies have suggested that IRF2BP2 may be translationally regulated. First, high mRNA levels were observed, followed by quickly increasing protein levels after ischemia.[5] Interestingly, miR-155 was able to down-regulate IRF2BP2,[16] probably targeting the IRF2BP2 long 3′UTR. In addition, a 9-nucleotide deletion at the 3′UTR of IRF2BP2 was associated with lower IRF2BP2 expression.[10] Together, these data suggest possible IRF2BP2 translational regulation, which should be better studied in the future.

After translation, the IRF2BP2 protein is able to perform different biological roles in the cell. IRF2BP2 stability can be regulated by ubiquitin and proteasome-dependent degradation. This study confirmed the finding of Teng and colleagues[5] showing that VGLL4 interacts with and further showed that VGLL4 protects IRF2BP2 from ubiquitination, decreasing K48-linked polyubiquitination. Consequently, VGLL4 protects IRF2BP2 from the proteasome-dependent degradation pathway and stabilizes the protein.[9] As another posttranslational regulation, IRF2BP2 can be strongly phosphorylated. Dorand and colleagues[32] performed a phosphoproteomic analysis and identified IRF2BP2 among proteins with the largest changes in phosphorylation status. The hyperphosphorylation is linked to disruption of cyclin-dependent kinase 5 (CDK5) activity.[32] It was suggested that CDK5 inhibits the kinase that phosphorylates IRF2BP2.[31] These data are consistent with in silico analyses that predict many high probability sites for phosphorylation. However, the data do not demonstrate the effect of phosphorylation on function, except for phosphorylation of Ser360. The phosphorylation of Ser360, near the NLS, was identified in IRF2BP2 isoform A, and it was conserved in isoform B and in the family of proteins.[17] This modification favors IRF2BP2 nuclear localization.[17] Finally, among the known partners of IRF2BP2, the NRIF3 protein, which participates in the apoptosis pathway in breast cancer cells, is able to interact with and inhibit IRF2BP2 activity.[3]

On the other hand, some studies have reported gene fusions and mutations in IRF2BP2 encoding sequences found in cancer. Gene fusions and chromosomal rearrangements are frequently found in different kinds of cancer, such as hematological malignancies, sarcomas, and prostate cancers. They can constitute important markers and contribute to diagnosis, prognosis, and rational therapeutics.[20,21] Recently, the fusion between the *IRF2BP2* gene and the transcription factor *CDX1* gene was reported in mesenchymal chondrosarcomas. The fusion occurred by translocation and resulted in a fusion protein characterized by IRF2BP2 exon 1 and CDX1 exon 2, codifying the zinc finger and homeodomain of the respective proteins.[7] The biological function of the resultant protein has not been determined.

In multiple myeloma, the chromosomal aberration of the most common translocation[11,14] (q13;q32) found in the early stage of pathogenesis contains the *IRF2BP2* gene. Having high penetrance (75%), IRF2BP2 might be a potential prognostic marker and therapeutic target in the treatment and management of multiple myeloma patients with this translocation.[6] IRF2BP2 is also a potential immune target gene in monoclonal gammopathy of undetermined significance (MGUS) as shown by serological analysis of a recombinant cDNA expression library. Evolution from the preneoplastic condition MGUS to multiple myeloma occurs frequently. Thus, the identification of genes important to this process may lead to the development of successful therapies.[22]

Moreover, another fusion gene important in cancer development occurs in acute promyelocytic leukemia (APL). It is characterized by fusion of retinoic acid receptor alpha (*RARA*) and promyelocytic leukemia. However, *IRF2BP2-RARA* gene fusion was identified

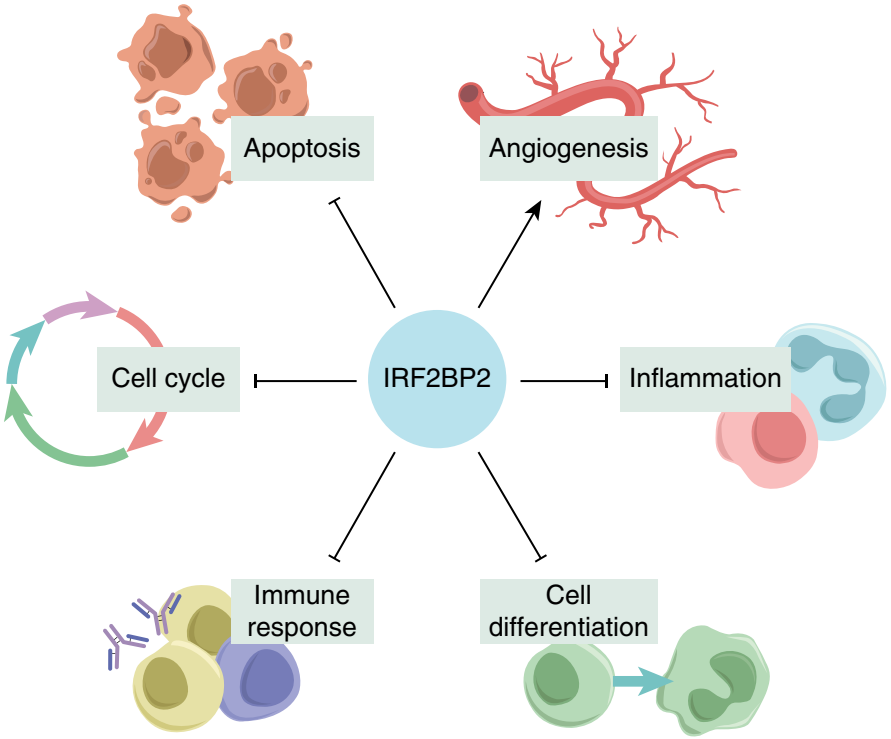

FIGURE 4 **Biological systems regulated by IRF2BP2 proteins.** IRF2BP2 proteins were shown to directly regulate the expression of genes related to cell differentiation, cell cycle, apoptosis, angiogenesis, inflammation, and the immune system, among others

and reported as a novel *RARA* partner in APL.[23] This fusion was reported in others 2 cases. This fusion has resulted in some peculiar clinical characteristics and influenced all-trans-retinoic acid-based conventional treatment.[24–26]

Furthermore, gene fusions and mutations in the IRF2BP2 gene also have been identified in some kinds of cancer, such as primary central nervous system lymphoma.[27] Another mutation was reported in a family with common variable immunodeficiency disorder (CVID).[28] Different studies have reported that IRF2BP2 has different biological functions and is linked to an increased probability of cancer development.

5 | BIOLOGICAL FUNCTION OF IRF2BP2 IN THE IMMUNE RESPONSE

Initially, IRF2BP2 was described as a corepressor of the transcriptional activity of IRF-2. The IRF2BP2 sequence is highly conserved in different organisms, including those without IRF-2 protein. This suggests IRF-2-independent functions.[1] Many studies have shown roles for IRF2BP2 as an IRF-2-independent gene expression regulator. Among its many functions, we will highlight those involved in the immune response, because IRF2BP2 is involved in the innate and adaptive immune response.

Several studies have demonstrated the important function of IRF2BP2 in macrophage-mediated inflammation. Chen and colleagues generated animals with IRF2BP2-deficient macrophages. They observed a worsening of atherosclerosis, and IRF2BP2 promoted an anti-inflammatory M2 profile in macrophages.[10] In a recent work from the same group, the loss of IRF2BP2 in the microglia caused an increased production of inflammatory cytokines.[11] On the other hand, restoring IRF2BP2 expression reduced inflammation and, consequently, decreased the risk of coronary artery disease[10] and stroke.[11] This phenotype is mediated by the effect of IFN-β.[11]

Our group has contributed to understanding the role of IRF2BP2 in the immune response. The data indicate that IRF2BP2 participates in the adaptive immune response, influencing the maintenance, production, and secretion of cytokines[13,14] and, consequently, resulting in T cell proliferation and activation.[14] Initially, they demonstrated that IRF2BP2 is a partner of NFAT1, an important regulator of T cells activation and differentiation.[13] It has been shown that the interaction of IRF2BP2 with NFAT1 is specific.[13] This interaction results in the repression of NFAT1-mediated transcription, as is seen in the IL-2 and IL-4 gene promoters in the Jurkat cell line of CD4 T cells.[13] In addition, IL-2 and IL-4 cytokine production was decreased in primary CD4 T cells by IRF2BP2 overexpression.[13] The authors demonstrated that IRF2BP2 overexpression in primary CD4 T cells reduced cell proliferation upon activation.[14] It also reduced the expression of the activation markers CD25 and CD69.[14] These data suggest that IRF2BP2 may act on lymphocyte homeostasis.

Increasing the knowledge about IRF2BP2 function in the adaptive immune response, an IRF2BP2 gene mutation was demonstrated to be associated with the development of CVID. The mutation was identified in the RING domain of IRF2BP2 in patients, and it resulted in increased levels of IRF2BP2 RNA and protein.[28] The authors suggested that IRF2BP2 participates in the maturation of plasma cells, and their maturation is associated with decreased plasmoblast production in vitro.[28]

In another study, in order to control the transformation cells, a screening was performed to identify new antigens capable of inducing an efficient immune response in patients with MGUS. Among the new antigens, IRF2BP2 was identified. However, the mechanisms involved in the expression of IRF2BP2 and the malignization of plasma cells in the evolution from MGUS to MM were not investigated.[22]

Immune checkpoints are important modulators of the immune response, such as the programmed death-ligand 1/programmed cell death 1 (PD-L1/PD-1) axis. In this case, PD-L1/PD-1 binding leads to the inhibition of T lymphocytes, cytokine production, cytolytic activity, and the suppression of the immune response.[29] The study of immune checkpoints is especially important in cancer, because escaping the immune response is a hallmark of cancer. Frequently, cancer cells express constitutive or inducible PD-L1, mainly in T cell-rich areas.[30] Among other cytokines, IFN-γ is the most potent inducer of PD-L1 expression, via IRF-1.[29] IRF-1 and IRF-2 are members of the IRF family. Both recognize the *cis*-regulatory element in IFN-inducible promoters. The IRF-2 transcription factor suppresses the effects of IRF-1.[31] Recently, the association of IRF2BP2 and VGLL4 was demonstrated to modulate PD-L1 expression. As discussed previously in this review, VGLL4 promotes IRF2BP2 protein stability. Moreover, the loss of VGLL4 led to decreased PD-L1 expression. The deletion of IRF2BP2 hampered IFN-γ-inducible PD-L1 expression at the mRNA and protein levels and enhanced DNA binding of IRF-2. Thus, the authors suggested that IFN-γ stimulation triggers the release of IRF-2 from the PD-L1 promoter and regulates the dynamic association between IRF-2 and IRF2BP2, favoring PD-L1 expression. Whether this interaction is regulated by posttranslational modification needs to be clarified.[9]

IRF2BP2 hyperphosphorylation is associated with reduced IFN-γ signaling activity and PD-L1 expression in breast cancer cells. CDK5 phosphorylation may directly or indirectly inhibit other kinase(s) that are responsible for phosphorylating IRF2BP2.[32] The high expression of PD-L1 was previously associated with the low expression of IRF2BP2 in breast cancer cells.[33] More recent studies suggest that IRF2BP2 participates in the regulation of PD-L1 by IFN-γ stimulation. The mechanism is unclear, however, and should be investigated due to its potential applicability in cancer immunotherapy.

6 | CONCLUSIONS AND PERSPECTIVES

Recently, IRF2BP2 has emerged as an important player in different biological systems, including development and cell differentiation, cell cycle, apoptosis, angiogenesis and regulation of inflammation, and the immune system (Fig. 4). Taken together, data from different groups suggest a broader role for IRF2BP2 in physiological cell homeostasis. Although IRF2BP2 protein is an important regulator of gene expression, little is known about how it is regulated. IRF2BP2 is a transcriptional cofactor that is involved in gene expression regulation in very diverse molecular contexts. The details of IRF2BP2 regulation and the mechanism by which this protein regulates gene expression will be essential to understand its role in different biological processes.

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DISCLOSURE

The authors declare no competing financial interests.

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