Review

Type I interferon system and IRF family of transcription factors in host defense regulation

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Abstract: Type I interferons (IFN-α/β) were originally identified as humoral factors, which are secreted in virally infected cells and confer an antiviral state in uninfected cells. Subsequently, their multifunctional roles have also been demonstrated, which include antitumor actions. More recently, the IFN system has been the focus of much attention in the context of the regulation of the innate and adaptive immune systems. Indeed, the IFN genes are induced in antigen-presenting cells (APCs) via the activation of distinct Toll-like receptors (TLRs), and accumulating evidence indicates the importance of TLR-induced IFN-α/β for the induction of both innate and adaptive immune responses. Two members of the interferon regulatory factor (IRF) family of transcription factors, IRF-3 and IRF-7, play mutually nonredundant functions in IFN-α/β gene induction in response to viral infection or TLR stimulation. Another unique facet of the IFN-α/β system is that IFN-α/β are produced at low levels in normally growing cells. Although seemingly futile, a weak signal by these IFNs is critical to eliciting from cells strong responses to other stimuli, thereby providing a foundation for an efficient operation of the immune system. In the context of the antitumor action of IFNs, p53 gene transcription is induced by IFN-α/β, accompanied by an increase in p53 protein level for boosting p53 responses in tumor suppression. Furthermore, a new link was discovered between p53 and IFN-α/β in antiviral immunity. In this review, we focus on recent studies on the type I IFN (IFN-α/β) system and IRF-family transcription factors with respect to immunity and oncogenesis.

Key words: Interferons; IRF; host defense; antiviral immunity; oncogenesis; p53.

Introduction. Biological systems have acquired adaptability and robustness against rapid environmental changes; one typical example is the immune system, which eradicates invading pathogens such as viruses. Type I interferons, i.e., IFN-α and IFN-β, the production of which is induced upon viral infection, are essential components of this system.1,2) IFN-α/β production is induced en masse in many cell types upon infection by a variety of viruses, and this induction is primarily controlled at the transcriptional level. As well as eliciting strong antiviral activities in target cells, IFN-α/β also activate effector cells of the innate immune system, such as natural killer (NK) cells and macrophages.1-4) More recently, the IFN-α/β system has been the focus of much attention in the context of TLR9 signalling. Indeed, it is becoming clearer that the virus-induced induction of IFN-α/β genes is mediated, although not entirely, via the activation of TLR9 subfamily members, which recognize virus-derived nucleic acids.5-8)

Given their essential function as mediators of innate immune responses against viruses, it is interesting that there are many reports on IFN-α/β production occurring in the absence of viral infection, albeit at very low levels both in vitro and in vivo.1,9-11) A weak IFN-α/β signal, transmitted independently of viral infection, is critical for priming cells to enhance their responses to other stimuli. Indeed, the weak signal renders cells “ready-to-go”, for stimulating amplified IFN-α/β production in response to viral infection, and enhances...
responses to other cytokines.\textsuperscript{12,13} Spontaneous IFN-α/β signalling is also critical for enhancing the activation of CD8\textsuperscript{+} T cells, but it needs to be properly attenuated to maintain homeostatic CD8\textsuperscript{+} T-cell responses.\textsuperscript{14} These observations offer interesting examples of how weak signals elicited by a given stimulus contribute to eliciting strong cellular responses to other stimuli. The role of a continuous, weak IFN-α/β signalling, described here in the context of the "revving-up model", may point to a broad operation of similar mechanisms in other biological systems. On the other hand, even a weak dysregulation of such a signalling system can also be the basis for disease development. More recently, a new link has been discovered between IFN-α/β signalling and the tumor suppressor p53 in the context of the contribution of the IFN-α/β system to antitumor activities.\textsuperscript{15}

**The IFN-α/β gene induction and IFN signalling: An overview.** IFN-α/β are produced by a variety of cells in response to viral infections. All IFN-α/β species interact with the same receptor complex, termed the IFN-α/β receptor (IFNAR), which consists of at least two subunits, IFNAR-1 and IFNAR-2 (Refs. 16-18; Fig. 1). The intracellular domains of IFNAR-1 and IFNAR-2 are associated with the Janus protein tyrosine kinases (Jak PTKs), Tyk2 and Jak1, respectively. The binding of IFN-α/β to IFNAR results in the cross-activation of these Jak PTKs, which then phosphorylate their downstream substrates, that is, two members of the fam-
Fig. 2. Positive feedback regulation of IFN-α/β gene induction by viral infection. There are two major pathways for IFN-α/β gene induction by virus: One is dependent on the transcriptional factor IRF-3, which is activated by virus-activated IRF-kinases, such as TBK1 or IKKe. The activated IRF-3 acts mainly on IFN-β gene induction. The other is the IRF-7-dependent pathway, wherein the IFN-induced IRF-7 is activated by the IRF-kinases and the activated IRF-7 acts on both IFN-α and IFN-β genes to amplify the IFN production. The latter step is therefore considered as a positive feedback regulation. See text for further explanation.
to constitute this family, which now consists of nine members (IRF-1 to -9; reviewed in Refs. 30, 37, 38). In a series of studies about IFN-α/β gene regulation, IRF-1, IRF-3, IRF-7 and IRF-9 were shown to be implicated in IFN-α/β gene induction by viral infection.\(^{34),(35),(39)-(41)}\)

Recent studies using the gene targeting strategy have revealed that two structurally related members, IRF-3 and IRF-7, are not only essential factors for IFN-α/β gene induction in response to viruses, but are nonredundant in their roles in IFN-α/β induction as described below.\(^{12}\)

**Constitutive expression of IFN-α/β and its biological significance.** For the sake of better understanding of the subsequent chapters, we first begin with the roles of weak IFN-α/β signalling, which occurs in the absence of any stimuli. Although IFN-α/β is massively produced upon viral infection, evidence has been provided for the constitutive expression of IFN-α/β, albeit at very low levels, without any stimuli.\(^{11),(9)-(11)}\)

Indeed, it was previously reported that IFN-α/β mRNAs can be detected in normally growing mouse embryonic fibroblasts (MEFs) and splenocytes by reverse transcriptase-polymerase chain reaction (RT-PCR) analysis.\(^{13),(42)}\)

Although there is evidence that these IFNs contribute to antiviral, anti-tumor activities and cell growth control \(^{11),(9),(11),(43)}\) in a manner similar to virus-induced IFNs, recent studies have revealed a unique molecular machinery of this system.\(^{13),(42),(46),(47)}\) The weak signal renders cells ready-to-go for the amplification or enhancement of cellular responses to rapid environmental changes, such as viral infection. This machinery is similar to a car engine revving up for thrust start and acceleration. The revving up of cells by a weak signal is implicated in eliciting robust cellular responses against infections (Fig. 3; Ref. 45). In this regard, this revving-up system is one of the unique signal-dependent regulatory mechanisms for the responsiveness, particularly in the
host defense.

Evidence has been provided that a weak IFN-α/β signal by the constitutively produced IFN-α/β is critical for eliciting strong responses of cells to IFN-γ and interleukin (IL)-6, which are major cytokines involved in adaptive immune responses (Refs. 13, 44; Fig. 3). IFN-γ-induced DNA-binding activity of activated Stat1, i.e., GAF, was found to be markedly diminished in cells from mice deficient in IFNAR-1 (Ref. 13). Further genetic analyses have revealed that it is not IFNAR-1 per se, but the IFN-α/β signalling complex that is required to evoke a complete IFN-γ response. This signalling complex mediated by spontaneously produced IFN-α/β also participates in enhancing the signals of another cytokine, interleukin-6 (IL-6), which also activates Stat-family transcription factors. Accordingly, the level of cytokine, interleukin-6 (IL-6), which also activates IFNAR-1 was detected in IFNAR-1-null MEFs, suggesting the constitutive nor IFN-γ on IFNAR-1 phosphorylation. Indeed, spontaneous IFN-α/β expression was observed, the level of which was only marginally augmented upon stimulation of CD8+ T cells by a mixed lymphocyte reaction. In the context of the revving-up system based on the constitutively produced IFN-α/β, one can postulate that IFN-α/β expressions at low levels, which are only slightly induced upon T cell activation, play a similar role in a more efficient TCR signalling in CD8+ T cells. In addition, the augmentation of local IFN-α/β concentration at the site of T cell activation may contribute to a more efficient operation of this mechanism for the activation of TCR signalling in CD8+ T cells. During viral infections, CD8+ T cells can be activated in a CD4+ T cell-independent manner, concomitant with the massive production of IFN-α/β (Refs. 54-56). As such, exogenous treatment with recombinant IFN-β enhances the proliferation of CD8+ T cells, and CD8+ T cells lacking IFN-α/β signalling are hyporesponsive to antigen stimulation. These observations additionally indicate the role of a weak IFN-α/β signalling in the efficient activation of CD8+ T cell upon the engagement of TCR with major histocompatibility complex (MHC)/peptide complexes on APCs.

As described below, evidence has also been provided for a role of a weak IFN-α/β signalling in the absence of viral infection in the regulation of innate immune responses against viruses. This signalling sustains the IFN-dependent expression of IRF-7 that leads to an efficient production of IFN-α/β upon viral infection.

Roles of IRF-3 and IRF-7 in the biphasic induction of IFN-α/β genes. One of the salient features of innate immune response is the rapid and robust induction of genes encoding effector molecules such as IFNs and other cytokines. In this regard, a
model has been proposed for the IFN gene induction mechanism, consisting of two phases, in which IRF-3 and IRF-7 are involved in the initial and late phases of gene induction, respectively. In this model, IRF-3, which is constitutively expressed in normally growing cells, plays a dominant part in the initial IFN-β gene induction. Indeed, virus infection results in the serine/threonine phosphorylation of IRF-3 at its carboxyl terminal region to become an active form; this activation is mediated by TANK-binding kinase 1 (TBK1) and IκB kinase ε (IKKε), thereby serving as “virus-activated IRF-kinases” (Refs. 62, 63). The activated IRF-3 undergoes nuclear translocation, and binds to the IFN-β promoter. Unlike constitutively expressed IRF-3, IRF-7 is short-lived and its gene expression is dependent on IFN-α/β signalling, therefore, the initial induction of IFN-β may be critical to eliciting the IRF-7-mediated IFN response from a cell for the induction of IRF-7 (Refs. 40, 64), i.e., IRF-7 induced by IFN-β, which is secreted in the initial phase, participates in the late phase of IFN-α/β gene induction (Fig. 2). Thus, the IFN-β dependency of IRF-7 may provide an underlying mechanism for the autoamplification of IFN production, whereby IRF-7 gene induction by de novo produced IFN-α/β during viral infection results in a positive feedback enhancement of IFN-α/β gene induction (Fig. 2). This positive feedback mechanism may be critical to evoke a robust IFN response against viral infections.

Although this model was initially verified in mouse embryonic fibroblasts expressing IRF-7 at very low levels in the absence of infection, this prototype model turned out to be more complex. In fact, IRF-7 in the absence of IRF-3 can initiate and sustain the positive feedback loop, depending on the cell type or the induction stimulus. Actually, the magnitude of the spontaneous IFN-α/β signalling described above is variable in distinct cell types and, in some cells, this contributes to setting the IRF-7 expression level beyond an appropriate threshold for the activation of the positive-feedback loop upon infection. In splenocytes, which express a TIR domain-containing adaptor inducing IFN-β (TRIF); also known as TICAM-1), resulting in the activation of divergent signalling cascades. Typically, TLR4 utilizes two adaptor pathways, the MyD88-TIRAP (MAL) and TRAM (TICAM-2)-TRIF (TICAM-1) pathways; the latter pathway is known to be critical to the induction of the maturation of DCs. On the other hand, TLR9 subfamily members, namely TLR9 and TLR7, transmit signals by utilizing solely MyD88 (Ref. 76). This raises an interesting issue of how signalling “input” initiated by the activation of this family can be “processed” via MyD88 alone to activate diverse downstream signal pathways so as to ensure the proper “output”, such as the induction of IFNs and other cytokines (e.g., IL-6 and IL-12), leading to the induction of the maturation of DCs.

Amongst many cytokines induced by TLR activation, IFN-α/β have been the new focus of attention in the context of linking the innate and adaptive immune responses, and the versatility of the response may be mediated at least in part by adaptor proteins that interact with TLRs to link the receptor activation to distinct downstream signalling pathways. All TLRs utilize the adaptor MyD88 for signalling, but some TLRs also utilize additional adaptors, such as TIR domain-containing adaptor inducing IFN-β (TRIF; also known as TICAM-1), resulting in the activation of divergent signalling cascades. Typically, TLR4 utilizes two adaptor pathways, the MyD88-TIRAP (MAL) and TRAM (TICAM-2)-TRIF (TICAM-1) pathways; the latter pathway is known to be critical to the induction of the maturation of DCs. On the other hand, TLR9 subfamily members, namely TLR9 and TLR7, transmit signals by utilizing solely MyD88 (Ref. 76). This raises an interesting issue of how signalling “input” initiated by the activation of this family can be “processed” via MyD88 alone to activate diverse downstream signal pathways so as to ensure the proper “output”, such as the induction of IFNs and other cytokines (e.g., IL-6 and IL-12), leading to the induction of the maturation of DCs.
that TLR4 induces the MyD88-independent, low-level IFN-β gene transcription by IRF-3 via the TRAM (TICAM-2)-TRIF (TICAM-1) pathway (reviewed in Ref. 68). In contrast, the underlying mechanism remained elusive about how these TLR9 subfamily members activate the MyD88-dependent IFN induction pathway particularly in pDCs. Neither was it known how the IFN induction pathway operates in conjunction with the MyD88-dependent IRAK/NF-κB activation pathway that is critical for the induction of other cytokines. (83-87)

Recently, we and others have provided evidence that MyD88 interacts with IRF-7 but not with IRF-3 in the cytoplasm. (88,89) It was also found that IRF-7 interacts with TRAF6, another adaptor molecule functioning downstream of MyD88. When HeLa cells expressing TLR9 mRNA were stimulated by an IFN inducing unmethylated CpG ODN (i.e., CpG-A), the nuclear translocation of IRF-7 was observed after CpG-A stimulation. Furthermore, the cotransfection of expression plasmids for MyD88 and IRF-7 together with the IFN-β promoter-driven reporter gene, the reporter gene was strongly induced. A similar observation was made by coexpressing TRAF6 and IRF-7. Although it is currently unknown how IRF-7 is activated by MyD88 or TRAF6, these results suggest that IRF-7 is activated downstream of the MyD88-TRAF6 pathway, probably by a kinase(s).

The death domain of MyD88 is responsible for its interaction with not only IRF-7 (Refs. 88, 89) but also IRAK4 kinase that is known to transduce signals between MyD88 and TRAF6 (Ref. 86). It is particularly interesting that a mutant MyD88 lacking the death domain fails to activate the IFN reporter gene, suggesting the potential involvement of IRAK4 in the IRF-7 path-
way. IFN-α production induced by CpG-A ODN or single-stranded RNA (ss-RNA) was totally abolished in splenic pDCs from IRAK4-deficient mice, supporting the view that IRAK4 is an integral member not only for the MyD88-dependent induction pathway of other cytokines (such as IL-6 and TNF-α) but also for the complex of the MyD88-TRAF6-IRF-7 pathway activated by TLR9 and TLR7. These results therefore suggest the bifurcation of the IRF-7 and NF-κB pathways downstream of the TLR9/7-dependent MyD88-IRAK4-TRAF6 signalling (Fig. 4).

These studies may have revealed an aspect of the TLR9-MyD88 signalling that activates IRF-7 via TRAF6 and possibly IRAK4, through the formation of a complex structure; the complex is critical to regulating the proper processing of the TLR signal to evoke the downstream transcriptional events; we therefore propose to name this complex the cytoplasmic transductional-transcriptional processor (CTTP; Ref. 88) (Fig. 4). In analogy to the computing terminology, in which the processor is central to converting the input to generate the output, CTTP may serve as a general cytoplasmic point of an organized array of signalling molecules and transcription factors that dynamically determines the specificity, strength and longevity of the input signal to the output of transcriptional events. However, these studies also left an unanswered question of whether these experimental findings faithfully reflect the physiological pathways of MyD88 signalling, because complex formation was examined in transient expression assays in nonimmune cells. More recently, we have definitive evidence for the absolute requirement of IRF-7 in IFN-α/β gene induction in pDCs by TLR9 signalling (K. Honda, unpublished data), and work is in progress to study further the roles of the MyD88-IRF-7 pathway in innate and adaptive immunities.

Dysregulation of IFN-α/β signalling. As described above, it was found that a weak IFN-α/β signalling is critical for efficiently eliciting robust cellular responses in the immune system, and may point to a broad operation of similar mechanisms in other biological systems. One can infer that a dysregulation of this weak signalling may give rise to a detrimental breakdown in these biological systems. Recent studies about IRF-2–/– mice provided an interesting model for clarifying this issue. IRF-2, a stable nuclear protein expressed in a variety of cells, was found to be a transcriptional attenuator of IFN-α/β signalling, which is known to negatively function at the ISRE sites of IFN-inducible genes caused by its competition with ISGF3 for these sites. Accordingly, in the absence of IRF-2, the action of ISGF3 becomes dominant, leading to the continual, elevated expression of ISGF3-dependent IFN-inducible genes, such as IFN-γ. Our recent report has shown that IRF-2–/– mice spontaneously develop inflammatory lesions, which is similarly observed in patients with psoriasis. It was also found that the development of this skin disease results from selective CD8+ T cell hyperactivation, with a marked upregulation of ISGF3-dependent IFN-stimulated genes. Other pathological conditions observed in IRF-2–/– mice, such as impaired hematopoiesis and autoimmune-like pancreatitis, may be caused by a dysregulated weak IFN signalling. These findings in IRF-2–/– mice suggest that the constitutive, weak IFN signalling should be controlled by a proper regulatory mechanism for maintaining homeostasis in the host. In this context, IRF-2 is one of the essential regulators that properly set the level of constitutive, weak IFN signalling for balancing the beneficial and harmful effects of this signalling. More recently, it has been found that IRF-2–/– mice exhibit dramatic skewing of APC subsets; a selective decrease in CD8α+ CD11b+ CD11c+ myeloid DCs and increase in CD11c+CD11b+ monocytopid cells in the spleen. Thus, the IFN-α/β system acts as a negative regulator for the development of myeloid DCs. Although it is not clear at this stage whether or not an impaired DC development contributes to the CD8+ T cell hyperactivation described above, one may speculate that the scarcity of DCs in lymphoid tissues may cause the breakage of the peripheral tolerance of T cells, possibly by the diminution of tolerogenic DC populations.

The IFN-α/β system in oncogenesis. Much evidence regarding the antitumor activities of IFNs has been so far reported (reviewed in Refs. 92, 93). Most of their functions are explained with regards to their modulatory actions on the immune system against tumors. Numerous cellular genes are transcriptionally activated after IFN stimulation. Several of these ISGs were shown to encode proteins that mediate tumor suppressor activities directly or indirectly: for example, IRF-1, dsRNA-dependent protein kinase (PKR), 2′-5′oligoadenylate synthetase (OAS), tumor necrosis factor-related apoptosis inducing ligand (TRAIL) and caspase-4/8 (Refs. 95-105). In addition, IFN-α/β can enhance the expression of class I MHC or some tumor-associated antigens on tumor cells, which facilitates recognition by immune cells. Furthermore, IFN-α/β modulate the functional activities of the immune system against tumors in various ways; IFNs act on T-lymphocytes or...
DCs to modulate their functions, which may explain IFN-induced tumor immunity (reviewed in Ref. 93).

The tumor suppressor p53, activated in response to DNA damage, induces cell cycle arrest or apoptosis through the transcriptional activation of its target genes, hence playing a central role in tumor suppression. On the other hand, IFN-α/β are critically involved in apoptotic responses in antiviral immunity, but little was known about the interrelationship between IFN-α/β and p53. Recently, a novel interrelationship has been found between IFN-α/β signalling and the p53 pathway in host defense systems (Fig. 5). IFN-α/β induce p53 gene transcription and eventually enhance the expression level of the p53 protein. The p53 gene induction by IFN-α/β is mediated in an ISGF3-dependent manner through the activation of two ISREs, which were found to be within the promoter and first-intron regions of the p53 gene. It was found that the IFN signal does not activate p53, rather, the p53 induction by IFNs contributes to boosting p53-mediated cellular responsiveness to stress signals. Evidence has been provided that the p53 gene induction by IFNs indeed contributes to tumor suppression. These findings therefore revealed a new mechanism, by which IFNs exert antitumor activity. Interestingly, p53 was found to be activated by viruses, such as VSV, Newcastle disease virus (NDV) or HSV. The activation of p53 leads to the apoptosis of virus-infected cells, thereby limiting the multiplication of the virus. Thus, p53 appears to play a critical role in the antiviral defense of the host.

Conclusions and future prospects. In this article, we reviewed new aspects of the IFN-α/β system, highlighting the functional implications of weak signalling by constitutively produced IFN-α/β in the regulation of cellular responses to other extracellular stimuli. As described in this article, it was found that a weak IFN-α/β signal confers unique signal regulatory mechanisms for its own IFN-α/β signalling system and other signalling systems of cytokines such as IFN-γ and IL-6, as well as the TCR signalling system. In this regulatory system, the weak IFN-α/β signalling in the absence of infection contributes to the control of IRF-7 expression level beyond a certain threshold that is cru-
cial for triggering the autoamplification mechanism for IFN-α/β production upon viral infection. This IFN-α/β signal-mediated revving-up mechanism through IRF-7 expression enables cells to efficiently produce IFN-α/β to achieve a robust immune response to viral infections.

In the IFN-α/β signal described here, signalling molecules remain constantly activated, albeit weakly, and the expression of target genes is maintained, thereby providing a foundation for more efficient signalling, either in that pathway or in different pathways. Thus, the consumption of cellular resources is a regulated “trade-off” to provide cells with a greater dynamic range in its response to stimuli. The IFN-α/β system may also provide an interesting illustration of the feedback loops required when such a function is operational. The advantages of highly efficient IFN-γ/IL-6 responses and the disadvantages of the failure of the IRF-2-mediated attenuation (autoimmune, psoriasis-like syndrome) indicate that the selective advantages of revving up the response can also be the basis of disease states when it is dysregulated. The possibility that this may be a key theme in the setpoint of host defense and autoimmunity is an exciting avenue for future research.

Our recent studies have revealed an intriguing crosstalk between immune responses and antitumor responses, wherein the p53 gene is induced by IFN-α/β (Refs. 15, 111) (Fig. 5). This contributes to the suppression of cell transformation. There are numerous reports on the usefulness of IFN-α/β for the treatment of some types of human cancer, including HPV-associated cervical cancer and hepatic cancer. However, the molecular basis of IFN action in cancer treatment still remains largely elusive. In this regard, this finding may offer an explanation for the antitumor activities of IFN-α/β. In addition, our study suggests the possible usefulness of treating human cancers with IFN-α/β in combination with chemotherapeutic drugs that activate p53. Recent reports show that a combination therapy with IFN-α and 5-fluorouracil(5-FU) is a promising treatment modality for intractable, advanced hepatocellular carcinoma. Combined therapy with IFN-α/β and chemotherapeutic drugs such as 5-FU may permit the use of lower doses of chemotherapeutic agents, which would otherwise exert toxic side effects via p53-independent mechanisms. This will be a clinically interesting issue that need to be addressed further.

Evidence was also provided for an important role of p53 in the innate antiviral host defense (Fig. 5). A prompt induction of apoptosis of virus-infected cells via p53 activation could be beneficial to the host in terms of limiting virus replication. On the basis of these findings, one can envisage that at the early phase of virus infection, virus-infected cells produce IFN-α/β, and eventually undergo p53-dependent apoptosis. On the other hand, virus-induced IFN-α/β may act on the surrounding, uninfected cells to help the antiviral defense by inducing cellular genes that inhibit virus replication and, in addition, by inducing p53 to prime cells for enhanced apoptosis. However, the details of how IFN-α/β and p53 cooperate in the antiviral defense need to be further clarified.

It has recently been the focus of much attention about intimate link between two major host defense systems: innate and adaptive immunities. Innate immunity initiates the protection of the host organism against invasion and the subsequent multiplication of microbes by the recognition of PAMPs (Refs. 65, 118). In the context of anti-tumor immunity, particularly interesting are the oligodeoxyribonucleotides containing unmethylated CpG-DNA that activate the induction of IFN-α/β genes through TLR9. Indeed, it has long been known that bacterial DNA is one of the most potent adjuvants that induce antitumor immunity. Recent studies have revealed the sequence of IFN-α/β-mediated events that operate during the maturation of DCs and induction of cytotoxic CD8 T cell responses initiated by TLR9 signalling. Furthermore, we now begin to understand more about the functions of other IRF members. Very recently, we found that IRF-5 is a principal transcription factor functioning downstream of the TLR-MyD88 pathway for the induction of proinflammatory cytokines, such as IL-6, IL-12 and TNF-α(A. T., T. T. and H. Yanai, unpublished data; see “Added in proof”). These studies may provide practical approaches, such as the use of an adjuvant for vaccines that enhance antitumor and antiviral immunities.

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