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Translation Control: A Multifaceted Regulator of Inflammatory Response
Barsanjit Mazumder,* Xiaoxia Li,† and Sailen Barik‡

A robust innate immune response is essential to the protection of all vertebrates from infection, but it often comes with the price tag of acute inflammation. If unchecked, a runaway inflammatory response can cause significant tissue damage, resulting in myriad disorders, such as dermatitis, toxic shock, cardiovascular disease, acute pelvic and arthritic inflammatory diseases, and various infections. To prevent such pathologies, cells have evolved mechanisms to rapidly and specifically shut off these beneficial inflammatory activities before they become detrimental. Our review of recent literature, including our own work, reveals that the most dominant and common mechanism is translational silencing, in which specific regulatory proteins or complexes are recruited to cis-acting RNA structures in the untranslated regions of single or multiple mRNAs that code for the inflammatory protein(s). Enhancement of the silencing function may constitute a novel pharmacological approach to prevent immunity-related inflammation. The Journal of Immunology, 2010, 184: 3311–3319.

Regulating gene expression at the level of protein translation offers several benefits, including rapidity of response and reversibility. Translational control can be subdivided into two major classes: global and transcript specific. Although the first mechanism regulates most transcripts, the second permits translation regulation of a limited ensemble of proteins. Transcript-specific regulation is generally mediated by the interaction of RNA-binding proteins with cognate cis-elements in the untranslated region (UTR) of the target transcripts, causing translational repression (1, 2). Although not significantly emphasized, an important role of translational control in regulating acute inflammation is evident from emerging studies. It is obligatory for the cells of the immune system to rapidly activate the inflammatory protein synthesis in response to infection or its blockade when they are no longer needed. Translational control offers a strategic advantage to these cells, because the use of the pre-existing mRNAs bypass the lengthy nuclear control mechanisms (e.g., transcription, splicing, and transport). At the same time, it provides the reversibility through modifications of the regulatory intermediates, mainly via reversible phosphorylation. Together, these two features allow rapid activation or termination of synthesis of a specific protein or group of proteins required for inflammation.

Acute inflammation is a highly orchestrated, tissue-based response to trauma incited by tissue injury or microbial invasion of the host (3, 4). Initiated by responsive leukocytes and lymphocytes, a key component of the process is the trafficking of inflammatory cells to the sites of injury or infection. The cytokine/receptor interactions on the surface of these cells culminate in the expression of new gene products that efficiently kill or injure the invading organisms. However, uncontrolled production of inflammatory products is injurious to host cells and even leads to neoplastic transformation (5). Therefore, endogenous mechanisms have evolved to limit the production of inflammatory molecules and permit the resolution of the inflammatory response (3, 6). In-depth studies of these mechanisms are important because defects in the pathway may contribute to the progression of chronic inflammatory disorders, and the pathway itself may present targets for novel anti-inflammatory therapeutic strategies.

Outstanding past reviews summarized the resolution of inflammation (3, 6), as well as stress-mediated, global translational control mechanisms (2, 7–9). A recent article reviewed how a number of cytokine mRNAs can be regulated at the level of mRNA stability (10). In addition, the role of one particular RNA-binding complex in the control of inflammation was the subject of a recent review (11). In this article, our goal is to present and defend the hypothesis that transcript-specific translational

Abbreviations used in this paper: 4E-BP, 4E-binding protein; ARE, AU-rich element; COX-2, cyclooxygenase-2; Ct, ceruloplasmin; DAPK, death-associated protein kinase; eIF, eukaryotic translation initiation factor; DICE, differentiation induced control element; EFRS, glutaryl-prolyl-tRNA synthetase; GAIT, IFN-γ-activated inhibitor of translation; HIF, hypoxia-inducible factor; hRIP, heterogeneous nuclear ribonucleoprotein; IRES, internal ribosome entry site; IRF, IFN regulatory factor; miRNA, microRNA; MMP, matrix metalloproteinase; MRE, microRNA response element; mTOR, mammalian target of rapamycin; PKR, protein kinase R; RFLAT, RANTES factor of late-activated T lymphocytes; SOCS, suppressor of cytokine signaling; TIA, T cell intracellular Ag; TIAR, T cell intracellular Ag-1–related protein; UTR, untranslated region; VEGF, vascular endothelial growth factor; ZIPK, zipper-interacting protein kinase.

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control is the prime determinant of the onset, progression, and resolution of acute inflammation.

Translational regulations offer stringent control of highly inflammatory cytokines

TNF-α, which is synthesized and secreted by lymphocytes, mast cells, and activated macrophages, has multiple proinflammatory functions geared toward protection of the host from infection. TNF-α induces fever via induction of PGE₂ synthesis by the hypothalamic vascular endothelium (12), activates synthesis of complement factors (3), and recruits leukocytes to the sites of infection via induction of adhesion molecules (13, 14). The high potency and diversity of proinflammatory functions require stringent control of TNF-α expression. Indeed, expression of TNF-α in unstimulated mouse peritoneal macrophages is extremely low, in part because of low mRNA expression and as a result of a block in translation (15). Treatment of macrophages with LPS, a cell wall component of Gram-negative bacteria, induces a 10,000-fold increase in TNF-α protein secretion resulting from simultaneous activation of transcription and derepression of the translational blockade (16).

Our knowledge of the translational control mechanisms has been advanced by the discovery of several proteins that bind AU-rich elements (AREs). Found in the 3' UTRs of various mRNAs, AREs are of enormous physiological significance because they recruit protein factors that regulate the stability of the target mRNA. Interestingly, a number of ARE-containing mRNAs, which include TNF-α and cyclooxygenase-2 (COX-2), are associated with the inflammatory response. The embedded ARE sequence clearly offers protection against the overexpression of TNF-α, because transgenic mice that express TNF-α mRNA lacking ARE exhibit elevated levels of circulating TNF-α and developed joint- and gut-associated immunopathology (17). Although TNF-α is an arm of innate immunity, its highly inflammatory property must have necessitated multiple checkpoints for stringent control.

The ARE-based mechanisms are orchestrated by a complex ensemble of RNA-binding proteins that are recruited to ARE, such as heterogeneous nuclear ribonucleoprotein (hnRNP)-A1, HuR, T cell intracellular Ag (TIA)-1, TIA-1–related protein (TIAR), and TTP. Basal translation of TNF-α mRNA can be silenced by hnRNP-A1 binding to the ARE element. Phosphorylation of hnRNP-A1 by Mnk, a kinase downstream of p38 MAPK, derepresses the translational blockade (16). Another critical target of TIAR (23) that is predominantly nuclear but rapidly translocates to the cytoplasm following stress. Interestingly, CUG-binding protein 2 binds to two sets of AREs within the COX-2 3' UTR, and unlike the previous mechanism, it stabilizes COX-2 mRNA, although it inhibits its translation nonetheless. Another critical target of TIAR is human matrix metalloprotease (MMP)-13, which is expressed in chronic inflammation and cancer and may remodel the extracellular matrix (24). MMP-13 mRNA is translationally silenced by an alternate spliced form of TIAR (25). Genome-wide analysis of TIA-1–bound transcripts identified a bipartite stem-loop as the target element and predicted that up to 3000 transcripts may contain this element (26). An important physiological role of the TIA-1/TIAR translational silencing pathway is suggested by the uncontrolled cartilage inflammation and arthritis in TIA-1–null mice (19) and in transgenic mice that overexpress ARE-less TNF-α (17). Studies with TIA-1–deficient macrophages also showed that HuR-mediated translational silencing requires TIA-1. Furthermore, myeloid-restricted overexpression of HuR inhibits the macrophase inflammatory response in vivo (27). In summary, translational control by TIA-1/TIAR and others is critical for the maintenance of the basal, noninflammatory state in several cell types. Reciprocally, its derepression is necessary for maximal induction of target transcripts during the early initiation phase of acute inflammation.

The first line of innate antiviral defense in host cells is a robust production of type I IFNs (α and β) (28) induced by the transcription factor IFN regulatory factor (IRF)7, which, in turn, is regulated by the translational repressors 4E-binding protein (4E-BP)1 and 4E-BP2 (29). Mouse embryonic fibroblasts lacking these repressors are resistant to multiple viruses, such as influenza, encephalomyocarditis, vesicular stomatitis, and Sindbis. This enhanced antiviral response is caused exclusively by the significant upregulation of IRF7 translation (29). Contrary to its positive role in innate and adaptive immunity, the activation of mammalian target of rapamycin (mTOR) in phagocytic cells can also limit the inflammatory response. mTOR downregulates the expression of proinflammatory cytokines IL-12 and -23; reciprocally, the inhibition of mTOR by rapamycin promotes the expression of IL-6, -12, and -23 and TNF-α and downregulates the expression of the anti-inflammatory cytokine IL-10 (30). Despite the multifaceted role of mTOR in immunity (31), it remains unknown whether its activation directly influences the de novo translation of the mRNAs coding for these cytokines, perhaps via a common RNA element. The lack of knowledge is probably due to the preferential attention bestowed on the upstream and downstream signaling cascade of mTOR, rather than identifying the target mRNAs. It is also possible that mTOR targets a critical transcription factor common to this array of cytokine genes. The recent report of mTOR-mediated direct translational repression of IRF7 mRNA is consistent with this notion (29).

Studies of IL-10 have provided strong evidence for the role of translational control in anti- and proinflammatory pathways (Fig. 1). mRNAs of inflammatory proteins (e.g., TNF-α, COX-2, and MMP-2) are translationally repressed by ARE-binding proteins in the 3' UTRs. Inflammatory stimuli activate p38 MAPK, which targets ARE-binding proteins and derepresses the translation. As an anti-inflammatory protein, IL-10 blocks this process by inhibiting p38 MAPK (32) (Fig. 1). Interestingly, occupancy of the adenosine receptor by its ligands activates translation of IL-10 mRNA, thus playing an important role in the anti-
inflammatory activity of these ligands (33). However, in a proinflammatory role, IL-10 stimulates ferritin translation by reducing the affinity of the translational repressor, the iron response element-binding protein, to the 5′ UTR of ferritin mRNA (34). Considering the role of ferritin in iron sequestration, this may lead to hyperferritinemia and limited iron availability for the progenitor cells in bone marrow, a condition typically seen in the anemia of chronic inflammation (Fig. 1).

**Activation of T lymphocytes**

The proliferation and migration of T lymphocytes promote inflammation and the eukaryotic translation initiation factor (eIF) 4E-BP kinase mTOR plays a pivotal role in this process. mTOR targets Kruppel-like factor 2, an essential transcription factor of CCR7 and L-selectin that is crucial for the migration of CD8+ T lymphocytes into lymph nodes (35). Indeed, G1 to S phase progression in IL-2–stimulated T lymphocytes can be blocked by rapamycin, an inhibitor of mTOR (36). In apparent contrast, a recent report revealed that inhibition of mTOR has immunostimulatory effects. This report showed that rapamycin significantly enhances the quantity and quality of virus-specific CD8+ T cells and identified eIF4E as a downstream effector molecule of mTOR (37). In addition, a recent study showed that activation of mTOR is required for regulatory and effector T cell lineage commitment (38). A subsequent study also showed that single IgG IL-1–related receptor, a negative regulator of IL-1R and TLR signaling, controls Th17 cell development and effector function by blocking the IL-1–induced activation of mTOR (39). Together, these results show that translational control by mTOR is critical for the regulation of adaptive immunity and raise new hope for the management of inflammation by its pharmacological manipulations.

**Chemoattraction of T lymphocytes**

The chemoattraction of T lymphocytes to the site of injury is an obligatory component of inflammation, and RANTES is a major player in this process (40). A rheostat function of regulating RANTES expression at the site of inflammation is crucial for the rapid response to stress, cytokines, and other proinflammatory factors in the local microenvironment of T lymphocytes (41). This precise control is achieved by regulating the translation of RANTES factor of late-activated T lymphocytes (RFLAT)-1 (Fig. 2). RFLAT-1 is a transcription factor that activates the RANTES gene; although its mRNA remains constant in resting and activated T cells, the protein is expressed only 3–5 d after T cell activation (42). This occurs through an interesting mechanism, in which two upstream open-reading frames and a highly structured 5′ UTR of RFLAT-1 mRNA promote translational silencing. Conversely, phosphorylation of 4E-BP

![FIGURE 1. Pro- and anti-inflammatory axis of IL-10 depends on translation regulation. Left, Inflammatory stimuli activate p38 MAPK that disengages ARE-binding proteins and derepresses the translation of inflammatory proteins. In a global anti-inflammatory role, IL-10 negatively regulates this process by abrogating the activation by p38 MAPK. Right, Occupancy of the adenosine receptors by its ligands relieves the imposed translational repression of IL-10 mRNA and activates the synthesis of IL-10 protein (blue circles). As a proinflammatory molecule, IL-10 stimulates ferritin translation by removing the translational repressor (the iron response element-binding protein) from 5′ UTR. Overproduction of ferritin causes sequestration of available iron (rust-colored circles) for bone marrow, leading to the characteristic anemia of inflammation.](http://www.jimmunol.org/)

![FIGURE 2. Chemoattraction of T lymphocytes by RANTES is under translation control. RFLAT, a transcription factor of RANTES, is silenced at the level of translation in unstimulated cells by 4E-BP. Phosphorylation of 4E-BP by mTOR promotes dissociation of 4E-BP, allowing assembly of the translation initiation factors (eIFs) on RFLAT mRNAs. This activates the translation of RFLAT protein and promotes the transcription of RANTES gene. Expression of RANTES (blue circles) is required for the chemoattraction of T lymphocytes to the sites of injury.](http://www.jimmunol.org/)
and eIF4E itself by mTOR and p38 MAPK/ERK rescues RFLAT-1 mRNA from silencing (Fig. 2) (41). The extracellular signals that activate these kinases are unknown. Nevertheless, the translational control of RFLAT clearly helps to precisely control RANTES, which, in turn, may be required to constantly monitor the environment as T lymphocytes move through extracellular spaces to the sites of injury (41).

Neutrophil influx

Neutrophils are major players in innate immunity and provide early links between the innate and adaptive inflammatory responses. Upon activation by cognate signals, the neutrophils rapidly translate their constitutive mRNAs. For example, translation of IL-6 soluble receptor is induced when neutrophils are activated by platelet-activating factor (43), a signaling phosphopeptide implicated in homeostatic and injurious inflammation (44). The mechanisms that limit neutrophil influx demonstrate nicely how the signal to resolve inflammation has been embedded in the signal for initiation. Neutrophil-derived arachidonate serves as substrate for neutrophil 5-lipoxygenase to generate the inflammatory leukotriene B4. However, the infiltrating neutrophils also deliver arachidonate to tissue cells that express 15-lipoxygenase; this catalyzes the conversion of arachidonate to lipoxins, which inhibit neutrophil influx (3, 45) (Fig. 3). Consistent with these findings, a defect in lipoxin-mediated anti-inflammatory activity was reported in the cystic fibrosis airway (46). 15-Lipoxygenase that produces lipoxins, a signal for inflammation resolution, can be regulated at the level of translation by the binding of hnRNP-K and E1 to the differentiation induced control element in its 3′ UTR (47), which blocks the 60S ribosomal subunit from joining (Fig. 3) (48). Unexpectedly, the activation of c-Src kinase causes phosphorylation of hnRNP-K, abrogating its RNA-binding activity and derepressing 15-lipoxygenase mRNA translation (Fig. 3) (49). These results add to the mounting evidence for the importance of translational control in the interface between proinflammatory and anti-inflammatory responses, in this case from neutrophils using arachidonate in a context-specific fashion.

NK cell-mediated cytotoxicity

Contact-dependent cytotoxicity is critical for innate immunity and depends upon the rapid synthesis of perforin and granzymes (50). There is compelling evidence that blockage of perforins and granzyme mRNA translation underlies the minimal cytotoxicity of resting NK cells and that removal of this blockage is crucial for NK cell activation (51). The finding that the activation signal(s) cause an immediate release of the translation brake of the killer proteases could offer a novel opportunity for therapeutic intervention.

Monocyte adhesion and platelet activation

Adhesion of monocytes and activation of platelets are vital steps in hemostasis and inflammation (52). A series of observations made by Zimmerman and colleagues showed that both processes pass through checkpoints executed by translational control of some key molecules. Engagement of P-selectin gp1 to the plasma membrane of monocytes delivers outside-in signals that activate mTOR and, hence, phosphorylate 4E-BP. The latter then activates translation of urokinase plasminogen activator receptor, a critical cell surface protease receptor required for cell adhesion and cell surface phenotype (53). Thrombin stimulation induces platelet adhesion and aggregation, and the activated platelets cause translational activation of Bcl-3 (54), the oncogene product of B cell lymphoma-3. The secretion of Bcl-3 mediates adhesion and outside-in signaling of these cells by engagement of αIIb/β3 integrin. The lack of transcriptional activity in the platelets, a longstanding observation, argues that Bcl-3 may be regulated at the level of translation. Metabolic labeling of thrombin-activated platelet showed that Bcl-3 is indeed activated directly at the level of translation and requires activation of mTOR and 4E-BP phosphorylation (54).

Macrophage survival in injured tissue

Low levels of oxygen and glucose, as well as high concentrations of lactate and reductive metabolites, characterize the surroundings of the injured tissues (55). To maintain viability and activity in such challenging conditions, the cells of the innate immune system must adopt a strategy to maintain the cellular ATP pool. The long-standing question of how the cells achieve this feat has been answered by studies from Johnson and colleagues (56). Using gene knockout mice, these studies showed the essential role of hypoxia-inducible factor (HIF)-1α in the process of myeloid cell survival and inflammation. The expression of the mRNAs of the glycolytic enzymes phosphoglycerate kinase (57), lactate dehydrogenase (57), pyruvate kinase M (58), and glucose transporter-1 (59) is HIF-1α-dependent and required for survival of the macrophages. In agreement with this hypothesis, genetic abrogation of HIF-1α causes profound defects in myeloid cell aggregation, motility, invasiveness, and bacterial killing (56). The 5′ UTR of HIF-1α mRNA is highly structured and contains an internal ribosome entry site (IRES) responsible for translational activation (60, 61). The IRES-mediated translation of HIF-1α under hypoxic conditions is particularly important, because hypoxia inhibits cap-dependent translation by reducing the availability of eIF4E and by

![FIGURE 3. A translationally regulated enzyme 15-lipoxygenase controls neutrophil influx. A neutrophil (magenta) is recruited to the tissue from the lumen. This process is mediated by leukotriene B4 synthesized from arachidonate and catalyzed by 5-lipoxygenase within the neutrophil. The recruitment of neutrophil in the tissue is depicted to bring in arachidonate that produces lipoxins, a signal for inflammation resolution, can be regulated at the level of translation by the binding of hnRNP-K and E1 to the differentiation induced control element in its 3′ UTR (47), which blocks the 60S ribosomal subunit from joining (Fig. 3) (48). Unexpectedly, the activation of c-Src kinase causes phosphorylation of hnRNP-K, abrogating its RNA-binding activity and derepressing 15-lipoxygenase mRNA translation (Fig. 3) (49). These results add to the mounting evidence for the importance of translational control in the interface between proand anti-inflammatory responses, in this case from neutrophils using arachidonate in a context-specific fashion.](http://www.jimmunol.org/doi/pdf/10.4049/jimmunol.1700360)
phosphorylation of translation initiation factor eIF2α (62, 63), thus creating a highly compromised condition. Under these conditions, IRES-mediated translation might be an effective means to sustain the synthesis of the survival proteins for the macrophages. It is tempting to speculate that resolution of inflammation results from inhibition of IRES activity, downregulation of HIF-1α, and the subsequent loss of monocytes/macrophages from the site of injury.

Controlling the immune and inflammatory responses by microRNAs

A major breakthrough in translational regulation is the recent recognition of the RNA interference pathway, variations of which are found in all metazoan cells. In the RNA interference pathway, small noncoding RNA molecules, broadly called microRNAs (miRNAs), bind to partially complementary sequences in the 3′ UTR of target mRNAs, called miRNA response element (MRE), and repress translation (64). In the dendritic cells, bacterial LPS or viral dsRNA binds to TLRs, triggering a signaling cascade that ultimately leads to T cell activation and elaboration of a plethora of inflammatory cytokines, including the type I IFNs. Recent studies showed how miRNAs could impose restraints on this process to protect the cells from uncontrolled immune response. Microarray analysis of macrophages after exposure to dsRNA (or IFN-B) revealed that miR-155 is the only miRNA that was substantially upregulated by LPS and dsRNA, suggesting that miR-155 is a common target of a broad range of inflammatory mediators (65). In-depth studies revealed that miR-155 silenced transcripts that code for several proinflammatory proteins, such as the Fas-associated death domain protein, I-κB kinase-α, TNFR superfamily-interacting serine-threonine kinase 1, and TAK1–associated binding protein-2. An unexpected observation was that miR-155 also targeted the TNF-α mRNA 3′ UTR and actually enhanced TNF-α translation, the mechanism of which remained unexplored (66). In fact, transgenic mice expressing recombinant miR-155 produced higher levels of TNF-α when exposed to LPS and were hypersensitive to LPS-induced septic shock, suggesting that the TNF-α–stimulating role of miR-155 may have a dominant effect in pathology (66). Altogether, these results show a balancing act of miR-155 in acute inflammation and sepsis, perhaps in a context-dependent manner.

In another study (67), miR-9 was found to be upregulated in polymorphonuclear neutrophils and monocytes by multiple proinflammatory signals, such as TLR4, TLR2, and TLR7/8 agonists, and by the proinflammatory molecules LPS, TNF-α, and IL-1β but not by IFN-γ. A number of these agonists activate the proinflammatory transcription factor NF-κB that, in turn, acts as a transcription factor to induce miR-9 expression. Interestingly, NF-κB translation was reciprocally silenced by miR-9 via an MRE in the 3′ UTR of the NF-κB mRNA. Overall, these data suggest that NF-κB rapidly increases the expression of miR-9 that operates a feedback control of the NF-κB–dependent acute inflammatory response triggered by multiple signals.

Evidence of miRNA-mediated silencing of inflammatory genes in nonimmune cells has only begun to appear, and a recent example comes from studies of pulmonary inflammation. The epithelial lining of the mammalian lungs is constantly exposed to inflammatory signals in the inhaled air. A recent study revealed that stimulation with IL-1β, a proinflammatory cytokine, results in a rapid increase in miR-146a expression in pulmonary cells (68). The increased miRNA-146a promoted translational silencing of the proinflammatory chemokines IL-8 and RANTES. In an interesting twist, IL-1β also activates NF-κB (69), and NF-κB activates the transcription of miR-146a (70) and IL-8 genes (71). Clearly, this is an intricate feedback inhibition operating at multiple levels, such that the initial trigger, IL-1β, rapidly activates the two chemokines via NF-κB and, at the same time, induces the synthesis of a silencer miRNA of the chemokines. Such controls limit the severe inflammation that would otherwise accompany the innate immune response of the pulmonary epithelia.

Translational control of the negative regulators of inflammation

Response to ILs and IFNs are negatively regulated by the members of a family of Src homology 2 domain-containing adaptor molecules, suppressor of cytokine signaling (SOCS). Expression of SOCS-1 is repressed at the level of translation initiation by two upstream open reading frames in the 5′ UTR (72). Induction of RNA helicase activity relieves the repression, permitting an increase in SOCS-1 protein expression and subsequent inhibition of the cytokine-induced response. Regulation of SOCS-1 exemplifies how translational control of a single gene can be crucial for simultaneous control of an array of inflammatory genes.

The proinflammatory cytokine IL-6 is negatively regulated by an unsuspected player, the tumor suppressor p53, a defect in which leads to the pathogenesis of rheumatoid arthritis (73, 74) and autoimmune inflammation (75). In both diseases, lack of p53 function leads to overexpression of IL-6 (74) and a heightened response to LPS and IFN (75). Interestingly, p53 mRNA itself is a target of the translational silencing mechanism that requires a region of its 3′ UTR (76). This region is also targeted by the RNA-binding protein HuR that relieves the translational repression (77, 78). Together, these findings show that translation upregulation of p53 can be important in resolving inflammation.

Translational control of IFN-γ expression

The entire IFN-γ axis, including the synthesis of IFN-γ and its downstream signaling, is under translational control, as we describe in this section and the next. Production of IFN-γ by T lymphocytes is subject to at least two distinct translational control mechanisms. IL-18 (originally designated as IFN-γ–inducing factor) is an epithelial and stromal cell product and is a potent and specific inducer of IFN-γ transcription in T lymphocytes. In a rat glomerular nephritis model, IL-18 mRNA is translationally silenced by its 5′ UTR, resulting in minimal induction of IFN-γ (Fig. 4) (79). Additionally, T cell expression of IFN-γ is autoregulated at the level of translation, again by a 5′ UTR element, but using an unusual and indirect mechanism. A pseudoknot in the IFN-γ 5′ UTR recruits and activates dsRNA-activated protein kinase R (PKR) (Fig. 4) (80), which, in turn, phosphorylates eIF2α and inhibits IFN-γ translation. Unexpectedly, global protein synthesis remains unaltered, suggesting that the cellular region of PKR activation remains highly restricted. Therefore, in this feedback mechanism, the pseudoknot essentially acts as a PKR sensor, preventing the overproduction of IFN-γ.

IFN-γ–activated inhibitor of translation pathway: the translational master regulator of IFN-γ–induced inflammation

IFN-γ is a major cytokine activator of macrophages that contributes to innate immunity toward pathogens (81). A series of studies from our group and other investigators discovered a unique translational silencing mechanism that is triggered by IFN-γ exposure of monocytic cells (Fig. 4) (82–89). We found robust transcriptional activation of ceruloplasmin (Cp) within
Translational silencing of a group of inflammatory proteins by the GAIT blocks translation by intercepting the recruitment of 40S ribosomal subunit from its parental complex. The binding of silencing-competent GAIT subunit proteins from their parental complex triggered by phosphorylation events (phosphate groups in red). Formation of GAIT complex requires the release of its signal that is eventually silenced by an ordered assembly of the GAIT complex components and stoichiometric release of L13a and EPRS from their parental complexes (84, 86). To test this, we conducted a genome-wide screen for target mRNAs of GAIT-mediated translational silencing in IFN-γ-activated monocytes (89) through an analysis of polysome-bound and -unbound mRNA pools. This led us to identify a cohort of mRNAs that follow the same pattern of regulation as Cp. Functional mapping of the GAIT-like elements in the 3’ UTRs of these putative targets validated the translational silencing mechanism. Importantly, many of these mRNAs coded for inflammatory proteins, such as chemokines and their receptors and proteins important in cytokine response and signaling. The chemokines and their receptors, for example, are responsible for activation-directed migration of leukocytes to the sites of inflammation during immune surveillance (97), which is now also recognized as a major contributor to the pathogenesis of inflammatory disease, such as atherosclerosis (98, 99), and necrotic, infectious, allergic, and autoimmune diseases (100). A potential therapeutic approach would be to enhance the formation of the GAIT complex, perhaps by triggering the phosphorylation and release of L13a from its 60S ribosomal depot. This approach could be used to identify a powerful anti-inflammatory drug because of its ability to silence all inflammatory mRNAs of this posttranscriptional operon using a natural mechanism.

**Conclusion and Future Directions**

Translational regulation, primarily through the recruitment of specific proteins to cognate sequences in the UTRs of the target mRNAs, is gaining new recognition. By virtue of its mechanism,
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