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Translational Control of Immune Evasion in Cancer

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Abstract

Mechanisms that control translation play important roles in tumor progression and metastasis. Emerging evidence has revealed that dysregulated translation also impacts immune evasion in response to cellular or oncogenic stress. Here, we summarize current knowledge regarding the translational control of immune checkpoints and implications for cancer immunotherapies.

Tumor Immune Evasion

Human cancers use diverse mechanisms to evade immune surveillance. Tumor cells avoid immune recognition by co-opting immune checkpoint pathways, by silencing components of their antigen presenting machinery, and by recruiting immunosuppressive cells in the microenvironment. The discovery of immune checkpoint pathways represents one of the most exciting scientific breakthroughs of the past 20 years. The programmed cell death protein 1 (PD-1) is a critical inhibitory receptor expressed in T cells. High expression of programmed cell death ligand 1 (PD-L1) in tumor cells and other cell types in the tumor microenvironment leads to engagement of PD-1 by PD-L1, resulting in the suppression of T cell growth, survival, and other effector functions. The cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) receptor is another well-characterized immune checkpoint protein expressed on cytotoxic and regulatory T cells that competes with the T cell costimulatory molecule CD28 to inhibit T cell activation [1]. Clinically approved antibodies targeting PD-1/PD-L1 or CTLA-4 restore T cell-mediated antitumor immunity, resulting in remarkable clinical benefits for melanoma, non-small cell lung cancer, and kidney cancer patients [1]. Despite the excitement surrounding these therapies, only a subset of patients responds to immune checkpoint blockade, and many patients develop resistance.

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Declaration of Interests

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The factors dictating an effective antitumor response in patients involve a complex interplay between the tumor microenvironment and tumor intrinsic signaling. Interferon gamma (IFNγ) or tumor necrosis factor alpha (TNFα) secreted by immune cells in the microenvironment stimulate *PD-L1* transcription in tumor cells to drive immune suppression. Tumor-intrinsic alterations also play a critical role in immune evasion. For example, high tumor cell mutational burden results in enhanced presentation of tumor antigens and immune infiltration. Tumor intrinsic WNT/β-catenin signaling results in T cell exclusion in melanomas [2]. PD-L1 upregulation in multiple tumor types occurs through a variety of mechanisms to promote immune evasion. For example, oncogenic drivers, such as *EGFR* mutations or MYC overexpression, stimulate *PD-L1* transcription in human cancers [2]. Structural variations disrupting the 3′ untranslated region (UTR) of the *PD-L1* gene lead to stabilization of the *PD-L1* transcript and PD-L1 overexpression in human cancers [3]. Thus, the molecular alterations present in tumor cells play a critical role in antitumor immunity.

Translational Control of Tumor Growth and Immune Escape

There is a growing appreciation that aberrant translational control is an important mechanism controlling tumor growth and immune evasion. Initiation is one of the most highly regulated steps in translation, with eukaryotic initiation factors (eIFs) dictating both the specificity and rate of translation of a given mRNA. Assembly of the eIF4F complex, which consists of the cap-binding protein eIF4E and other critical initiation factors, serves as a critical node of translational control in human cancers. The eIF4F complex functions to recruit the small ribosomal subunit to the 5′ cap, where it initiates scanning for the initiation codon. Tumor cells use multiple mechanisms to enhance the activity of eIF4F to drive translation. For example, genetic loss of eIF4E-binding proteins, which inhibit eIF4F, enhance protein synthesis. Additionally, oncogenes, including MYC, transcriptionally upregulate ribosomal proteins and eIF4F complex components to enhance translational output and promote cellular transformation [4].

The formation of the ternary complex (TC) at the initiation step is another critical node of translational control in cancer cells, particularly in response to cellular stress. The active TC, which comprises the eIF2 complex (α, β, and γ units), initiator tRNA $\left(\text{tRNA}_i^{\text{Met}}\right)$, and GTP, couples binding of $\text{tRNA}_i^{\text{Met}}$ to the AUG start codon to GTP hydrolysis. Upon GTP hydrolysis, eIF2-GDP is recycled by the guanine nucleotide exchange factor eIF2B for subsequent rounds of initiation. Under conditions of nutrient deprivation, hypoxia, or endoplasmic reticulum (ER) stress, cancer cells activate one of four eIF2α kinases: RNA-activated protein kinase (PKR), general control nonderepressible 2 kinase (GCN2), PKR-like ER kinase (PERK), and heme-regulated inhibitor (HRI). Phosphorylation of the α subunit of eIF2 (eIF2α) on serine 51 by these kinases inhibits the guanine nucleotide exchange activity of eIF2B by forming a sequestered eIF2-eIF2B complex. This leads to impaired eIF2 recycling and attenuation of global translation in response to physiologic and pathologic stress while preferentially enhancing the translation of select mRNAs. This pathway is collectively referred to as the integrated stress response (ISR). ISR activation was

recently shown to enhance the translation of oncogenic mRNAs to drive tumor initiation and promote prostate cancer metastasis [5,6].

Emerging evidence has revealed that tumor cells exploit translation regulation to evade immune surveillance (Figure 1A). eIF4F complex formation stimulates *STAT1* mRNA translation, which in turn increases *PD-L1* transcription, thus driving immune suppression in melanoma cells (Figure 1B) [7]. A genome-wide CRISPR/Cas9 screen revealed that human lung cancers activate the ISR in response to heme deficiency or hypoxia, which promotes *PD-L1* translation and the suppression of antitumor immunity (Figure 1C) [8]. Moreover, transgenic expression of MYC in a mouse model of $Kras^{G12D}$-induced liver cancer resulted in eIF2α phosphorylation, enhancing *Pd-l1* translation and tumor progression (Figure 1D) [9]. Thus, translational control of the PD-L1 immune checkpoint under physiologic or oncogenic stress represents a novel mechanism of immune evasion in human cancers. Interestingly, oncogenic MYC may utilize multiple mechanisms to elicit translational control of immune modulators in human cancers. Singh *et al.* [10] recently showed that MYC expression may also govern site choice for translation initiation in lymphoma cells.

The utilization of upstream open reading frames (uORFs) in the 5′ UTRs of mRNAs is emerging as an important mechanism of translational control in response to cellular stress. Recent studies have demonstrated that ISR activation promotes the translation of specific mRNAs harboring uORFs in their 5′ UTRs (including *ATF4, GADD34*, and *GCN4*), allowing for their selective translation to restore cellular homeostasis [11]. Consistent with this, ISR activation in skin squamous carcinoma redirected the translational machinery to the 5′ UTRs of select mRNAs [6]. In this study, a subset of oncogenic mRNAs containing uORFs were preferentially translated at early stages of tumorigenesis.

Interestingly, both human and mouse *PD-L1* harbor inhibitory uORFs in their 5′ UTRs that suppress baseline translation of PD-L1. Transgenic MYC expression activates the ISR to overcome uORF-mediated inhibition and drive *Pd-l1* translation in liver cancer [9]. Similarly, ISR activation (through heme deficiency) allows for the bypassing of inhibitory uORFs and enhances *PD-L1* translation in lung cancer [8]. The weakened activity of the TC that results from eIF2α phosphorylation is postulated to promote leaky scanning through 5′ UTRs, bypassing inhibitory uORFs and increasing translation at canonical translation start sites.

Alternative Initiation Factors in Cancer

The recruitment of alternative translation initiation factors represents an intriguing mechanism of translational control that may be exploited in cancer cells. Recent studies have revealed that eIF2A or eIF5B may substitute for eIF2 under conditions of cellular stress. For example, eIF2A was shown to facilitate translation initiation from 5′ UTRs of oncogenic mRNAs in skin squamous cell carcinoma [6]. Interestingly, eIF5B, but not eIF2A, directed ISR-dependent *PD-L1* translation in human lung cancer, suppressing $CD8^+$ T cells to sustain tumorigenesis *in vivo* [8]. This study also revealed that eIF5B overexpression is frequent in human lung adenocarcinoma (LUAD), associates with poor survival of LUAD patients, and is sufficient to increase PD-L1 levels in human lung cancer cells. Furthermore, eIF5B was

found to facilitate $tRNA_i^{Met}$ delivery to ribosomes in hypoxic cells, suggesting additional contexts that may engage this mechanism to activate the immune checkpoint in cancer cells [12]. However, the precise mechanism(s) by which eIF2A or eIF5B substitute for eIF2 remains to be elucidated. Additional studies are needed to understand how alternative initiator recruitment occurs in response to distinct cellular or oncogenic stress. For example, does eIF2α phosphorylation promote eIF2A or eIF5B recruitment? Is the GTPase activity of eIF5B, a potentially druggable activity, necessary for driving *PD-L1* translation? Addressing these questions, and characterizing the translational programs orchestrated by eIF5B and other alternative eIFs, will reveal new mechanisms of translational control in tumor progression and immune evasion.

Translational Control: Beyond Tumor Cells

Translational control of immune evasion extends beyond tumor cells and can also occur in immune cells. For example, expression of the RNA-binding protein YTHDF1 in dendritic cells promotes the translation of proteases to degrade antigens and reduce T cell-mediated tumor killing [13]. During T cell activation, it has been suggested that microtubule complexes traffic inhibitory checkpoint mRNAs, such as *PD-1, CTLA-4, LAG3*, and *TIM3*, into stress granules for preferential translation [14]. Phosphorylation of eIF4E also promotes neutrophil accumulation in the tumor microenvironment, thereby promoting metastasis in a mouse mammary tumor model [15].

Concluding Remarks

Collectively, these findings underscore the importance of understanding how translational control regulates immune evasion in cancer and suggest that targeting translational regulation may provide new therapeutic opportunities. Treatment with a compound that inhibits phosphorylation of eIF4E reduced neutrophil survival and suppressed metastasis in a mammary tumor model and decreased *PD-L1* translation and tumor progression in a liver tumor model [9,15]. Furthermore, treatment with ISRIB, an ISR inhibitor that suppresses the effects of eIF2α phosphorylation by enhancing eIF2B activity, repressed PD-L1 protein levels in lung cancer and liver cancer cells [8,9]. These findings suggest that inhibiting the ISR pathway or directly targeting components of the translation machinery may induce antitumor immunity alone or in combination with existing immunotherapies. The integration of these exciting functional and mechanistic studies with human clinical studies will undoubtedly lead to new therapeutic strategies to overcome immune evasion.

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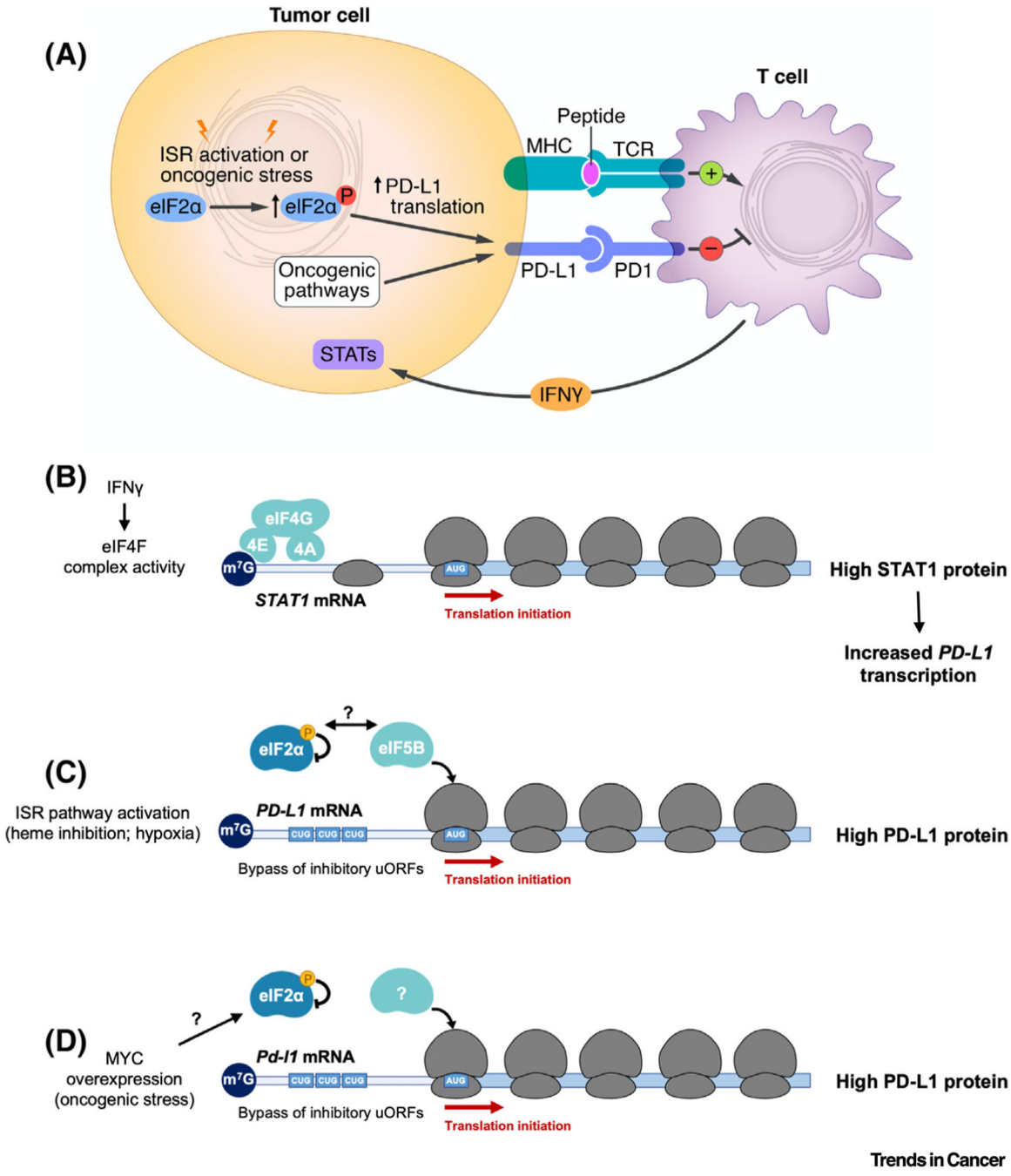

Figure 1. Translational Control is an Emerging Mechanism of Programmed Cell Death Ligand 1 (PD-L1)/Programmed Cell Death Protein 1 (PD-1) Regulation in Cancer.

(A) The image depicts PD-L1 on tumor cells engaging the T cell PD-1 receptor. PD-L1 upregulation in multiple tumor types occurs through a variety of mechanisms to promote immune evasion. These include transcriptional activation through interferon gamma (IFNγ)-induced signal transducer and activator of transcription (STAT) signaling and translational control (depicted later). (B–D) Three examples of translational control of the PD-1/PD-L1 checkpoint are illustrated. (B) Eukaryotic initiation factor 4F (eIF4F) complex activity promotes *STAT1* translation, which in turn increases *PD-L1* transcription in response to

IFNγ stimulation in melanoma cells [7]. (C) Integrated stress response (ISR) pathway activation through heme synthesis inhibition or hypoxia facilitates eIF5B-mediated translation of *PD-L1* in lung cancer [8]. An open question is whether eIF2α phosphorylation promotes eIF5B recruitment to *PD-L1* and other mRNAs with upstream open reading frames (uORFs). (D) Oncogenic MYC enhances *PD-L1* translation in liver cancer [9]. In (C) and (D), eIF2α phosphorylation and weakened ternary complex (TC) activity is hypothesized to promote leaky scanning through the 5′ untranslated region, bypassing inhibitory uORFs and increasing translation at the *PD-L1* canonical translation start site. Unanswered questions include how MYC overexpression results in eIF2α phosphorylation and whether an alternative initiation factor plays a critical role in this context. Abbreviation: TCR, T cell receptor.