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The Role of FTO in the Regulation of T Cell Function and Immune Infiltration, and Its Potential Applications in Immunotherapy

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Abstract: The Fat Mass and Obesity-Associated Protein (FTO), a primary N6-methyladenosine (m6A) demethylase, has emerged as a critical regulator of T cell function, immune infiltration, and immunotherapy efficacy. This review synthesizes current evidence on FTO's enzymatic mechanisms, its impact on T cell differentiation and exhaustion, and its role in shaping the tumor immune microenvironment (TIME). We explore how FTO-mediated m6A demethylation modulates key transcripts involved in T cell survival , effector function, and metabolic pathways. Additionally, we examine FTO's influence on immune cell infiltration patterns across cancers, including hepatocellular carcinoma (HCC) and glioblastoma, and its contribution to immunosuppressive niches. The review highlights therapeutic strategies targeting FTO—such as small-molecule inhibitors and PROTAC degraders—and their synergistic potential with immune checkpoint inhibitors (ICIs), radiotherapy, and targeted agents. Finally, we address unresolved questions regarding FTO substrate specificity, context-dependent functions, and challenges in clinical translation, emphasizing opportunities for advancing cancer immunotherapy through epigenetic reprogramming.

Keywords: FTO; m6A Modification; T Cell Exhaustion; Immune Infiltration; Immunotherapy; Tumor Microenvironment.

1. Introduction

The epitranscriptomic modification N6-methyladenosine (m6A) dynamically regulates RNA metabolism through coordinated actions of "writers" (methyltransferases), "erasers" (demethylases), and "readers" (binding proteins) [1][2]. As the first identified m6A demethylase, FTO plays a pivotal role in reversing m6A marks, thereby influencing mRNA stability, translation, and decay [3]. Emerging evidence positions FTO as a master regulator of immune responses, particularly in T cell biology and tumor immunity. Dysregulated FTO expression correlates with T cell exhaustion, altered immune infiltration, and resistance to immunotherapy in cancers like HCC, acute myeloid leukemia (AML), and glioblastoma [4][5][6].

This review comprehensively analyzes FTO's biological functions, its regulatory mechanisms in T cell activation and exhaustion, and its impact on the TIME. We further evaluate therapeutic strategies targeting FTO to potentiate immunotherapy and discuss challenges in clinical translation. By synthesizing mechanistic insights and preclinical/clinical evidence, we aim to delineate FTO's potential as a therapeutic target for overcoming immune evasion and improving cancer treatment outcomes.

2. Biological Functions of FTO

2.1. Structure and Enzymatic Properties of FTO

FTO belongs to the Fe(II)/2-oxoglutarate-dependent dioxygenase family, featuring a double-stranded β-helix (DSBH) core that coordinates Fe(II) and 2-oxoglutarate (2OG) for catalytic activity [3]. Crystallographic studies reveal FTO's substrate-binding pocket accommodates diverse RNA substrates, including internal m6A, cap-proximal m6Am, and tRNA m1A [3]. Notably, FTO exhibits higher catalytic efficiency for N6-methyladenine over other modifications, with substrate specificity influenced by RNA sequence context and tertiary structure [7]. For instance, FTO preferentially demethylates GGACU and RRACU motifs, aligning with its enrichment in AC-rich sequences observed in K562 and HeLa cells [7]. Structural analyses also highlight FTO's ability to recognize both nucleobase and ribose moieties, enabling broad substrate spectrum [3]. This flexibility underpins FTO's multifaceted roles in RNA processing and cellular signaling.

2.2. m6A Modification: Molecular Mechanisms and Its Role in RNA Metabolism

m6A is the most abundant mRNA modification in eukaryotes, installed by writer complexes (e.g., METTL3/METTL14/WTAP) and reversed by erasers (FTO, ALKBH5) [1][2]. This modification recruits YTH-domain readers (e.g., YTHDF1-3, YTHDC2), which mediate downstream effects on splicing, nuclear export, stability, and translation [2][3]. For example, m6A-marked transcripts bound by YTHDF2 undergo accelerated degradation, while YTHDF1 enhances translation [3]. In T cells, METTL3-mediated m6A modification stabilizes mRNA, promoting effector differentiation [8], whereas FTO-dependent demethylation of mRNA increases its stability, triggering apoptosis in CD8+ T cells [9]. These dynamic modifications fine-tune gene expression programs critical for immune responses, and dysregulation contributes to pathological states like autoimmunity and cancer [10][11].

2.3. Impact of FTO on T Cell Exhaustion and Effector Functions

FTO is indispensable for T cell effector functions and survival. In CD8+ T cells, FTO deficiency elevates m6A

levels on mRNA, enhancing its stability via IGF2BP3 binding and promoting apoptosis [9]. Conversely, FTO overexpression sustains CD8+ T cell viability and cytotoxicity. In CD4+ T cells, FTO supports Th1 differentiation by maintaining T-bet and IFN-γ expression, thereby facilitating pathogen clearance [12]. However, chronic antigen stimulation in tumors drives exhaustion, characterized by upregulated inhibitory receptors (e.g., PD-1, TIM-3) and metabolic dysfunction [6][13]. FTO modulates this process by demethylating transcripts involved in metabolic reprogramming [4] and immune checkpoint expression [14]. Thus, FTO acts as a double-edged sword: while essential for acute T cell responses, its overactivity may sustain dysfunctional states in chronic settings.

3. The Regulatory Mechanisms of FTO in T Cell Function

3.1. FTO Regulation of T Cell Function

FTO orchestrates T cell fate through context-dependent demethylation of key targets. In CD8+ T cells, FTO directly demethylates mRNA, stabilizing it and promoting activation-induced cell death [9]. This mechanism is critical for maintaining homeostasis, as excessive FTO activity diminishes T cell persistence. In CD4+ T cells, FTO deficiency impairs Th1 polarization by reducing T-bet expression, compromising antitumor immunity [12]. Additionally, FTO regulates metabolic pathways: in T-ALL, it stabilizes mRNA, enhancing glycolytic flux and leukemogenesis [4]. FTO also modulates cytokine signaling; in macrophages, it demethylates mRNA, enabling SOCS1-mediated negative feedback on JAK-STAT/NF-κB pathways under high-stiffness conditions [15]. These findings highlight FTO's pleiotropic roles in balancing T cell activation, survival, and metabolic fitness.

3.2. The Role of m6A Modification in T Cell Differentiation and Activation

m6A modification is fundamental to T cell lineage commitment and activation. METTL3-mediated m6A methylation of mRNA stabilizes it, driving CD8+ T cell effector differentiation [8]. Similarly, WTAP-dependent m6A modification of mRNA promotes regulatory T (Treg) cell differentiation post-kidney transplantation [16]. Conversely, FTO-mediated demethylation can counteract these processes. In systemic lupus erythematosus (SLE), METTL3 inhibition destabilizes mRNA, skewing CD4+ T cells toward pro-inflammatory states [17]. m6A also influences dendritic cell (DC) activation: METTL3 enhances translation of CD40 and CD80, boosting T cell priming [18]. These data underscore m6A's role as a rheostat, with writers and erasers collectively shaping T cell phenotypes through precise transcriptomic control.

3.3. The Potential Role of the FTO-m6A Axis in T Cell Exhaustion

The FTO-m6A axis is a critical determinant of T cell exhaustion. Chronic antigen exposure increases FTO expression in exhausted CD8+ T cells, demethylating transcripts that enforce dysfunction [14]. FTO also sustains metabolic pathways linked to exhaustion; in T-ALL, it promotes ELK3-driven glycolysis, supporting a proliferative yet exhausted phenotype [4]. Furthermore, FTO inhibition reduces m6A demethylation of PD-L1 mRNA, destabilizing it and enhancing ICI efficacy [19]. Epigenetically, FTO interacts with exhaustion-associated transcription factors like TOX, which reprograms chromatin accessibility in exhausted T cells [20][21]. Targeting FTO-m6A with inhibitors (e.g., FB23-2) reverses these changes, reinvigorating T cell functions [22]. Thus, the FTO-m6A axis represents a promising lever to modulate T cell exhaustion.

4. The Role of FTO in Immune Cell Infiltration

4.1. m6A Modification in Immune Cell Migration and Infiltration

m6A modification governs immune cell trafficking by regulating chemokine/receptor expression. For instance, METTL3-mediated m6A methylation of Kdm6b mRNA stabilizes it, promoting macrophage activation via JAK-STAT signaling [23]. In glioblastoma, m6A patterns correlate with immune infiltration subtypes, with high m6A clusters exhibiting enhanced cytotoxic T cell recruitment [24][25]. FTO indirectly influences infiltration by demethylating transcripts like VEGFA; in glioma stem cells, FTO inhibition elevates m6A on VEGFA, suppressing its expression and normalizing vasculature to facilitate T cell entry [26]. Additionally, m6A readers (e.g., ELAVL1) modulate PD-L1 therapy responses by affecting immune cell trafficking [24]. These mechanisms highlight m6A's role in shaping immune landscape topography.

4.2. FTO's Regulatory Role in Immune Infiltration Within the Tumor Microenvironment

FTO critically sculpts the TIME by modulating immunosuppressive and inflammatory pathways. In HCC, FTO demethylates GPNMB mRNA, enhancing its expression and promoting immune evasion [5]. FTO also drives expression of FLAD1 via m6A-YTHDF2, fostering an immunosuppressive niche [27]. In breast cancer, FTO reduces m6A on NFKBIE, augmenting NF-κB signaling and recruiting myeloid-derived suppressor cells (MDSCs) [28]. Conversely, FTO inhibition reprograms the TIME: in gastric cancer, FTO knockdown increases m6A, altering cytokine profiles to favor CD8+ T cell infiltration [29]. Single-cell analyses in glioblastoma reveal that FTO-high tumors exhibit fewer exhausted CD8+ T cells, whereas FTO loss correlates with "hot" microenvironments [24]. Thus, FTO activity dictates immune cell composition and functional states within tumors.

4.3. FTO-m6A Axis and the Formation of an Immune-Suppressive Microenvironment

The FTO-m6A axis fosters immunosuppression through metabolic and epigenetic reprogramming. In HCC, FTO upregulates FLAD1, boosting NAD+ synthesis and inhibiting T cell cytotoxicity [27]. FTO also stabilizes VEGFA in glioma, promoting abnormal angiogenesis and excluding immune cells [26]. Moreover, FTO-mediated demethylation of BACH1 sequesters iron, reducing ferroptosis in tumor cells and dampening immunogenic cell death [30]. In prostate cancer, FTO suppresses EGR2 via m6A, enabling immune escape [31]. These changes are reinforced by crosstalk with stromal cells; cancer-associated fibroblasts (CAFs) exploit FTO to secrete TGF-β, inhibiting T cell infiltration [32].

Collectively, the FTO-m6A axis establishes a feedback loop that sustains immune deserts and therapy resistance.

5. FTO-m6A Axis and Its Relationship with Immunotherapy

5.1. FTO-m6A Axis and Immunotherapy

FTO inhibition synergizes with immunotherapies by reversing immune evasion. Small-molecule FTO inhibitors (e.g. FB23-2, CS1) enhance antitumor immunity by increasing m6A levels and promoting T cell infiltration [14][22][33]. In AML, FB23-2 reduces leukemic stem cell self-renewal and sensitizes cells to T cell cytotoxicity [14]. PROTAC degraders (e.g., QP73) achieve superior antileukemic effects by inducing FTO proteolysis, upregulating differentiation genes [34]. Clinically, CS1 shows promise in AML trials, validating FTO as a druggable target [33]. These strategies underscore the therapeutic potential of modulating the FTO-m6A axis.

5.2. Role of m6A Modification in Immune Checkpoint Inhibitor Efficacy

m6A regulators dictate ICI responsiveness by influencing immune checkpoints and T cell function. METTL14 enhances CD8+ T cell activation and PD-1 blockade efficacy in lung cancer [19]. In HCC, high FTO expression correlates with poor ICI response due to GPNMB-mediated immunosuppression [5]. Conversely, m6A reader ELAVL1 improves PD-L1 therapy outcomes in glioblastoma by regulating immune cell trafficking [24]. FTO inhibition also downregulates PD-L1 via m6A-dependent mRNA decay, augmenting ICI efficacy [19]. These findings suggest m6A patterns could serve as biomarkers for ICI stratification and that targeting FTO may overcome resistance.

5.3. Combined Therapeutic Strategies Involving FTO Inhibitors

Combination regimens amplify the benefits of FTO inhibition. FTO inhibitors synergize with radiotherapy in glioma and head-and-neck cancer by impairing DNA damage repair (VEGFA suppression) and enhancing immunogenic cell death [26][35]. In AML, FTO inhibition potentiates hypomethylating agents by reducing immune evasion [14]. Notably, FTO inhibitors combined with BTK inhibitors suppress breast cancer malignancy by targeting parallel survival pathways [36]. Triple therapies (e.g FTO inhibitors + ICIs + anti-VEGF agents) are being explored for unresectable HCC, leveraging multi-modal TIME reprogramming [37][38]. These approaches highlight the versatility of FTO targeting in combinatorial oncology.

6. Discussion

The FTO-m6A axis is a master regulator of immunity, with profound implications for cancer therapy. Evidence shows FTO demethylates transcripts governing T cell survival, metabolism , and immune checkpoints, thereby influencing exhaustion and infiltration [4][9][27]. However, key gaps persist. First, FTO's substrate specificity is context-dependent; for example, it suppresses ovarian cancer stem cells by targeting PDE1C, PDE4B but promotes AML via LILRB4 [14][39]. This duality necessitates precision targeting to avoid unintended consequences. Second, off-target effects of FTO inhibitors (e.g DHODH inhibition by FB23-2) challenge specificity [40]. Third, clinical translation hurdles include drug delivery to immune cells and managing metabolic side effects, given FTO's role in obesity [41][42].

Strengths of existing studies include mechanistic depth and translational relevance [33]. Limitations involve overreliance on murine models and heterogeneity in m6A detection methods. Controversies exist regarding FTO's role in prostate cancer, where it acts as a tumor suppressor via EGR2 [31], contrasting its oncogenic role elsewhere.

7. Conclusion

FTO-mediated m6A demethylation is a pivotal axis regulating T cell function, immune infiltration, and immunotherapy responsiveness. By modulating transcripts critical for T cell survival, metabolism, and exhaustion, FTO shapes antitumor immunity in a context-dependent manner. Therapeutic targeting of FTO—through inhibitors, degraders, or combinatorial regimens—holds promise for overcoming immunosuppression and enhancing ICI efficacy. However, challenges in substrate specificity, drug selectivity, and clinical translation must be addressed. Advancing this field requires integrating mechanistic insights with biomarker-driven clinical trials to harness the FTO-m6A axis for precision immunotherapy.

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