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Research Progress of T-Cell Immunoglobulin and Mucin Domain-Containing Protein-3 (Tim-3) in Respiratory Diseases

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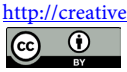

Abstract

T-cell immunoglobulin and mucin domain-containing protein-3 (Tim-3), an emerging immune checkpoint molecule, was found to critically regulate the pathogenesis of respiratory disorders, including chronic obstructive pulmonary disease (COPD), bronchial asthma, and bronchogenic carcinoma, through its dynamic expression patterns and genetic polymorphisms. This review synthesized current knowledge on the structural and functional characteristics of Tim-3, delineated its roles in COPD, asthma, and lung cancer, and evaluated its therapeutic potential, thereby offering novel perspectives for targeting Tim-3 in respiratory disease management.

Keywords

COPD, Tim-3, Asthma, Lung Cancer

1. Introduction

Tim-3, encoded by the HAVCR2 gene on human chromosome 5q33.2, functioned as a negative immunoregulatory glycoprotein expressed on Th1/Th17 cells, activated CD8+ T cells, and innate immune cells (e.g., macrophages, dendritic cells). Tim-3, a pivotal immune checkpoint molecule initially characterized in 2002 [1], displayed interspecies structural divergence. Murine Tim family members encoded on chromosome 11B1.1 contained 281 amino acid residues, contrasting with the human ortholog (chromosome 5q33.2) comprising 302 residues. This 63% amino acid sequence conservation between species provided critical phylogenetic evidence supporting translational research from murine models to therapeutic development. Tim-3 is a transmembrane glycoprotein comprised of 5 structural domains: a signal peptide, a characteristic IgV domain, a mucin region, a

transmembrane region and an intracellular tail containing phosphorylation sites (**Figure 1**) [2]. Tim-3 has been found to be a negative regulator of IFN-γ secreting CD4+ Th1, CD8+ T cells and an important player in T cell exhaustion in multiple settings. Tim-3 is associated with IFN-γ-producing T cells, cytokines that are involved in effector T cell subset differentiation were believed to have important roles in the induction of Tim-3 expression [3].

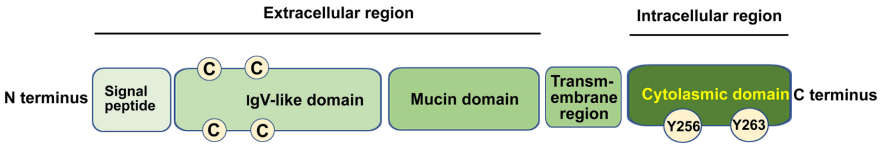

Figure 1. Structure of Tim-3. Tim-3 is a transmembrane glycoprotein comprised of 5 structural domains: a signal peptide, a characteristic IgV domain, a mucin region, a transmembrane region and an intracellular tail containing phosphorylation sites.

The human Tim family demonstrated selective expression profiles, with detectable transcripts limited to Tim-1, Tim-3, and Tim-4. Immunohistochemical analyses revealed predominant localization on activated Th1, Th17, and Tc1 lymphocyte subsets. Of particular significance, Tim-3 was the inaugural family member confirmed to be expressed on Th cells across both murine and human models. Co-expression patterns were further identified in innate immune lineages, encompassing macrophages, dendritic cells, mast cells, and natural killer cells.

Mechanistically, Tim-3 exerted immunosuppressive effects through high-affinity binding with its canonical ligand galectin-9 (Gal-9). This molecular interaction induced caspase-dependent apoptosis in effector T lymphocytes, thereby enforcing peripheral immune tolerance. Such functional attributes positioned Tim-3 as a strategic target for next-generation immunomodulatory therapies. Emerging evidence substantiated its pathophysiological relevance in pulmonary disorders, including chronic obstructive pulmonary disease, bronchial asthma, and non-small cell lung carcinoma.

2. Tim-3 in Chronic Obstructive Pulmonary Disease Pathogenesis

Chronic obstructive pulmonary disease (COPD), a clinically modifiable heterogeneous condition targeting small airways, presented as chronic inflammatory crosstalk involving neutrophils, macrophages, T-lymphocytes, and structural components (airway/alveolar epithelial cells, fibroblasts). This immunopathological network engaged both innate (neutrophils, macrophages, eosinophils, mast cells) and adaptive immunity (T/B lymphocytes). Contemporary research emphasized macrophage-derived protease activation and neutrophil-dominated cytokine storms as pivotal contributors to COPD pathobiology, with histopathological evidence demonstrating lymphocyte accumulation in pulmonary interstitium and bronchial walls.

T-lymphocyte subtyping followed MHC-mediated antigen recognition pat-

terns: CD4+ subsets (Th1, Th2, Th17, Tregs) and CD8+ cytotoxic cells. COPD pathophysiology exhibited Th1 hyperactivation driving persistent inflammation and emphysematous destruction via IFN-γ overproduction [4]. Paradoxically, Th2-derived IL-4/IL-5 displayed dual anti-inflammatory/pro-fibrotic activities. Th17-mediated IL-17A secretion potentiated neutrophilic infiltration during acute exacerbations, while dysfunctional Tregs failed to resolve inflammation, collectively exacerbating tissue remodeling.

Critical mechanistic insights identified Th17 lymphocytes as principal cellular targets of Tim-3 immunomodulation. Ubiquitous Tim-3 surface expression on Th17 populations enabled Gal-9 ligand binding to suppress IL-17 transcription via JAK2/STAT5 inhibition, effectively attenuating pro-inflammatory cascades [5]. Longitudinal investigations identified Tim-3 as a stage-responsive biomarker for COPD trajectory monitoring [6]. The expression of Tim-3 in peripheral blood mononuclear cells of COPD patients increases with the severity of the disease and increases with the decline of pulmonary function. Tim-3 expression was maintained at a low level in the mild patient group compared to the healthy physical examination subjects, while expression was significantly increased in the moderate and severe patient groups. After treatment, Tim-3 expression decreased with remission of the disease. ROC curve analysis established 0.324 ng/mL as optimal threshold for therapeutic monitoring, achieving 80% diagnostic sensitivity and 75% specificity [7].

3. Tim-3 and Bronchial Asthma Pathogenesis

Bronchial asthma (hereafter termed asthma) was defined as a chronic inflammatory airway disorder characterized by variable airflow limitation. The principal clinical manifestations comprised airway inflammation, hyperresponsiveness, remodeling, and obstruction. The pathogenic mechanisms were found to involve complex interactions among multiple cell types and cytokines, regulated through immunological, genetic, and neural pathways. Critical to disease progression was the observed imbalance between helper T lymphocyte subsets (Th1/Th2). Experimental data indicated that Th2 cell overactivation suppressed autoimmune responses, whereas Th1 cell predominance exhibited immunomodulatory effects.

Accumulating evidence revealed regulatory functions of T-cell immunoglobulin and mucin domain-containing (Tim) molecules in Th1/Th2-mediated immune processes. Tim-3 was identified as a key modulator of Th1 cells, while Tim-1 and Tim-2 were demonstrated to primarily regulate Th2 cells [8]. Concurrently, Th17/Treg imbalance was confirmed to contribute to asthma pathogenesis. Recent studies established that Tim-3 and its genetic polymorphisms were mechanistically associated with asthma development. Specifically, elevated Tim-3 expression in asthmatic patients was shown to enhance Th2 cytokine production while suppressing Th1-mediated immunity.

In both murine models and clinical studies, researchers documented significantly lower proportions of Tim-3+/CD4+ Th cells in peripheral blood and bron-

choalveolar lavage fluid from non-asthmatic controls compared to asthmatic subjects [9]. Parallel RT-PCR analyses detected reduced Tim-3 mRNA expression levels. Li Jisheng's team reported statistically distinct genotype ($P = 0.045$) and allele ($P = 0.047$) frequencies at the -882T>C locus within the Tim-3 promoter region between asthmatic and non-asthmatic individuals in Shandong's Han Chinese population [10].

A comprehensive meta-analysis of 1241 cases and 1005 controls demonstrated that carriers of the GT genotype at Tim-3-574G>T (rs10515746) had 3.06-fold higher asthma risk than GG homozygotes in the Han Chinese cohort. Furthermore, T allele carriers exhibited 3.31-fold increased susceptibility relative to G allele carriers [11]. Subgroup analyses confirmed that both adults and children with GT genotype had higher risk of disease than those with GG homozygote. Mechanistic investigations revealed that the T allele mutation augmented Tim-3 activity, increased IFN-γ secretion, and upregulated Gal-9 ligand expression. Subsequent binding of Gal-9 to Th1 cell-surface Tim-3 induced excessive calcium influx, leading to Th1 apoptosis and Th2-biased immune polarization. This phenomenon was particularly pronounced in pediatric populations due to immature immune systems and heightened environmental sensitivity, potentially exacerbating Tim-3-574 mutation rates. Consistent patterns were subsequently replicated in Korean and Iranian demographic studies.

4. Tim-3 and Lung Cancer

Primary bronchogenic carcinoma, clinically designated as lung cancer, ranked among malignancies with the highest global disease burden due to its elevated incidence and mortality. Epidemiological data from China positioned this neoplasm as the foremost contributor to cancer-related morbidity and mortality across both sexes [12]. National cancer statistics from 2022 recorded 1,060,600 incident cases (22% of total malignancies) and 733,300 fatalities (28.5% of cancer deaths). The asymptomatic progression of early-stage disease frequently delayed clinical detection, with 80% of patients diagnosed at advanced stages demonstrating an aggregate 5-year survival rate of approximately 20%.

Immune checkpoint molecules, functioning as critical regulators of immune tolerance, were recognized for their capacity to attenuate anti-tumor responses via negative feedback mechanisms. Pharmacological inhibition of these molecules was shown to restore durable anti-tumor immunity, establishing immune checkpoint inhibitors as transformative therapeutic agents in oncology [13]. Tim-3 expression was ubiquitously detected across multiple tumor types, prompting clinical investigations into Tim-3-targeted monoclonal antibodies, adoptive cell therapies, and combinatorial treatment strategies. These efforts highlighted its potential as a mechanistically distinct immunomodulatory target [14].

Experimental evidence established that Tim-3 binding to its cognate ligand Galectin-9 (Gal-9) modulated the activity of Th1, Th2, and Th17 immune effector subsets. Pathological overexpression profiles were consistently documented

in renal cell carcinoma, oral squamous cell carcinoma, pulmonary malignancies, and colorectal adenocarcinoma. Aberrant expression patterns were further observed in myeloid-derived suppressor cells, natural killer cells, and dendritic cell populations. Mechanistic studies revealed Tim-3-mediated immune evasion through dual pathways: amplification of regulatory T cell clonal expansion and suppression of dendritic cell maturation. In non-small cell lung cancer (NSCLC) cohorts, elevated Tim-3 expression in peripheral blood monocytes paralleled increased Gal-9 levels. This molecular interaction was demonstrated to compromise cytotoxic T lymphocyte function by inhibiting IFN-γ secretion in CD8+ T cells [15].

Multicenter clinical investigations identified significant Tim-3 upregulation in lung adenocarcinoma and squamous cell carcinoma patients, exhibiting positive correlations with advancing age and higher TNM stages [16]. Quantitative stratification revealed incremental Tim-3 elevation corresponding to adverse histopathological features: poor differentiation status, larger tumor dimensions, advanced-stage disease, and metastatic progression. Post-therapeutic surveillance demonstrated significant reductions in circulating Tim-3 levels, which exhibited positive covariance with serum carcinoembryonic antigen (CEA) concentrations. A systematic meta-analysis confirmed Tim-3 overexpression as an independent prognostic factor for diminished overall survival, accelerated disease recurrence, and shorter progression-free survival in NSCLC populations [17]. Multivariable regression models further revealed significant associations with lymphatic metastasis, TNM stage escalation, and PD-L1 positivity.

Advances in multi-platform genomic profiling during the 21st century progressively delineated Tim-3's pleiotropic immunoregulatory functions. Germline polymorphism analyses uncovered significant associations with cancer susceptibility loci and metastatic potential. Chronic overexpression in tumor microenvironments was mechanistically linked to immune dysfunction through synergistic pathways: caspase-dependent apoptosis of Th1 lymphocytes; transcriptional suppression of perforin/granzyme B in CD8+ T cells; co-inhibitory signaling with PD-1 to reinforce T cell exhaustion [18]-[20]. Notwithstanding ongoing debates regarding its context-dependent roles, cumulative translational evidence validated Tim-3 as a robust predictor of adverse clinical outcomes, supporting its incorporation into prognostic biomarker panels for solid tumors [21].

In conclusion, Tim-3 was characterized as a novel immune checkpoint molecule with pathophysiological significance in respiratory oncology. Its stage-dependent expression dynamics and multimodal mechanisms of immune suppression underscored its potential as a therapeutic target for precision immunotherapy regimens.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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