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Role of Galectin-9 in Chronic Lymphocytic Leukemia

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Abstract:

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries, characterized by the progressive accumulation of mature, functionally incompetent B lymphocytes. The immune microenvironment plays a pivotal role in CLL pathogenesis, influencing tumor cell survival and disease progression. Among immune-regulatory molecules, Galectin-9 (Gal-9) has emerged as a key immunomodulatory protein belonging to the β-galactoside–binding lectin family. It is known to interact with TIM-3 and other receptors, leading to T-cell exhaustion and apoptosis, thereby contributing to tumor immune evasion. Recent evidence suggests that Gal-9 may have dual roles in cancer biology, functioning either as an immune checkpoint ligand promoting tumor escape or as an apoptosis-inducing molecule depending on the cellular context. However, its exact role in the immunopathogenesis and clinical behavior of CLL remains incompletely defined.

Keywords: Chronic lymphocytic leukemia; Galectin-9; TIM-3; immune regulation; apoptosis; biomarkers.

Introduction:

Chronic lymphocytic leukemia (CLL) is a common hematological malignancy characterized by the clonal proliferation and accumulation of mature but functionally incompetent B lymphocytes in the peripheral blood, bone marrow, and lymphoid tissues. It represents the most prevalent leukemia in adults and displays a highly variable clinical course ranging from indolent to aggressive forms. (1)

The pathogenesis of CLL is closely linked to immune dysregulation, where leukemic cells create a supportive microenvironment that promotes their survival and protects them from apoptosis. The interaction between CLL cells and surrounding immune cells, particularly T lymphocytes and macrophages, contributes significantly to disease progression and resistance to therapy. (2)

Galectin-9 (Gal-9) is a β-galactoside–binding lectin that modulates immune responses by interacting with various receptors, most notably T-cell immunoglobulin and mucin domain-containing protein-3 (TIM-3). This interaction induces apoptosis and functional exhaustion of T cells, thereby suppressing antitumor immunity. (3)

Recent studies have demonstrated that Gal-9 expression is altered in several hematologic and solid malignancies, suggesting its role as an immune checkpoint regulator within the tumor microenvironment. Increased Gal-9 expression has been associated with tumor progression, immune escape, and poor prognosis in cancers such as hepatocellular carcinoma and acute myeloid leukemia. (4)

Despite these findings, the biological and clinical implications of Gal-9 in chronic lymphocytic leukemia remain largely unclear. Understanding its role may provide insights into novel immunomodulatory mechanisms and potential biomarkers for disease prognosis and therapeutic targeting in CLL. (5)

Gal-9, a lectin that binds β-galactosides, has become a crucial modulator of immune responses in hematologic cancers, especially CLL. Its interaction to T-cell immunoglobulin and mucin domain–containing protein 3 (TIM-3), a checkpoint receptor that is widely expressed on worn-out T cells, plays a major role in determining the immunological landscape of CLL. Gal-9's engagement of TIM-3 promotes the growth of

immunosuppressive regulatory T cells (Tregs) while inducing death and functional impairment of CD8+ cytotoxic T cells. The Gal-9/TIM-3 interaction is a key component of immune escape in CLL because of this dual mechanism, which efficiently reduces the anti-leukemic immune response and creates an environment that allows leukemic cells to survive and proliferate (6).

Galectin-9 as a Marker of Prognosis:

Patients with advanced CLL frequently have increased levels of galectin-9. According to studies, patients who have high levels of Gal-9 expression in their blood or leukemic B cells typically experience inferior treatment outcomes, a shorter time until treatment is required, and a faster rate of disease development.

Bojarska-Junak et al. (7), for instance, discovered that individuals with elevated B cell levels of Gal-9 mRNA required treatment sooner than those with lower levels. In other investigations, plasma Gal-9 was likewise associated with a lower survival rate and more severe disease (8, 9). Larger studies are required to determine how Gal-9 compares with well-established markers like TP53 or IGHV, but this makes Gal-9 a potential biomarker to predict outcomes.

Galectin-9 in the Microenvironment and Tumor Invasion:

"Tumor invasion" refers to the way leukemic cells enter and persist in bone marrow niches and lymph nodes in blood malignancies such as CLL. Gal-9 can aid stromal cell communication and cancer cell adhesion to their environment. Gal-9 is known to promote cell adherence and dissemination in other malignancies, however there is little direct evidence of this in CLL.

Higher Gal-9 levels in CLL are linked to increased involvement of the lymph nodes and bone marrow, indicating that it might aid the leukemic cells in settling into niches that provide protection and sustain them (10). To properly demonstrate this involvement, more laboratory research is required.

T-cell dysfunction (immune evasion) with galectin-9:

This is Gal-9's most thoroughly researched function in CLL. Gal-9 functions as a "off switch" by attaching itself to the TIM-3 receptor on T and NK cells. T cells are worn out and unable to combat malignancy when Gal-9 attaches to TIM-3. Increased regulatory T cells (Tregs) and malfunctioning CD4+ and CD8+ T cells are associated with elevated Gal-9 in CLL. In lab tests, blocking the Gal-9/TIM-3 pathway decreases leukemia cell survival and restores T-cell activity (6, 8). This demonstrates that Gal-9 is a key player in immunological escape, which makes it a viable target for novel immunotherapies in CLL.

Galectin-9's Potential as a Treatment for CLL:

Because it aids leukemia cells in evading the immune system, galectin-9 has gained significant attention in CLL research. Galectin-9 primarily functions by attaching itself to the T cell receptor TIM-3. This relationship promotes the development of regulatory T cells while decreasing the activity of cytotoxic T cells and natural killer (NK) cells. As a result, the immune system is weakened, which promotes the growth of CLL cells. As a result, a novel treatment approach that blocks the Gal-9/TIM-3 pathway has been proposed (6).

T-cell function can be restored by blocking the Gal-9/TIM-3 pathway, according to studies. In lab models, blocking antibodies against Galectin-9 or TIM-3 enhances leukemia cell death, increases interferon-γ production, and improves T-cell function. Similar strategies may be effective in CLL, as evidenced by the positive safety outcomes of early clinical trials using TIM-3 blocking medications, such as sabatolimab in myeloid malignancies (8).

Combining Galectin-9 suppression with other immune checkpoint treatments is another interesting strategy. Since several inhibitory signals contribute to T-cell depletion in CLL, addressing both Gal-9/TIM-3 and PD-1/PD-L1 jointly may be more beneficial than focusing on just one pathway. Given that CLL patients already have weakened immune systems, this combined strategy may be particularly helpful to them (11).

Additionally, galectin-9 might be a useful target for sophisticated immunotherapies. For instance, T-cell depletion has hampered the effectiveness of CAR-T cell therapy in CLL. CAR-T cells may function better

and survive longer in the body if Gal-9 is blocked. New bispecific antibodies that engage immune cells and block Gal-9 are also being investigated as novel therapy alternatives (10).

Furthermore, Galectin-9 might be a factor in resistance to standard CLL medications such BTK inhibitors (ibrutinib) and BCL-2 inhibitors (venetoclax). The effectiveness of these medications can be diminished by Gal-9, which promotes survival signals in leukemia cells. Therefore, combining Gal-9 inhibition with targeted medicines may improve their efficacy and postpone resistance (11).

All things considered, Galectin-9 has great therapeutic potential in CLL because it promotes immune evasion and leukemia cell survival. Immune function can be restored, current treatments can be more effective, and new avenues for combination immunotherapy can be opened by blocking Gal-9. For individuals with aggressive or treatment-resistant diseases, this makes Galectin-9 an attractive target (6, 8, 10, 11).

Important Galectin-9 Mechanisms in CLL:

1. Regulation of the Gal-9/TIM-3 Axis and Immune Checkpoint:

The interaction of Galectin-9 with the immunological checkpoint receptor TIM-3, which is expressed on $CD8^+$ cytotoxic T cells, $CD4^+$ helper T cells, and natural killer (NK) cells, is a key mechanism of Galectin-9 in CLL. When Gal-9 binds to TIM-3, effector T cells undergo apoptosis and their ability to produce cytokines, such as IL-2 and interferon-γ, is suppressed. As a result, T cells continue to exist but lose their ability to cytotoxically destroy leukemic cells, a condition known as T-cell exhaustion. At the same time, Gal-9 encourages the growth of regulatory T cells (Tregs), which strengthen tolerance to the malignant clone and further inhibit immunological responses. The Gal-9/TIM-3 axis is a key mechanism that shifts the immunological balance from anti-tumor immunity toward immunosuppression in the setting of CLL, where immune surveillance is naturally compromised (6).

2. Cytotoxic Immune Cell (CD8 T and NK Cell) Suppression:

Cytotoxic immune cell suppression is directly aided by Gal-9. When Gal-9 engages TIM-3 on NK cells, it reduces degranulation processes including granzyme B release and perforin, which lessens the cytotoxicity of the cells. This leads to a reduction in the innate immune system's ability to eradicate leukemic B cells in CLL. Similar to this, Gal-9 suppresses the cytotoxic activity and cytokine release of $CD8^+$ T-cell effectors, which together lead to the severe immunological dysfunction characteristic of advanced CLL (8).

3. Encouragement of Leukemic Cell Survival and Drug Resistance: Gal-9 directly affects CLL cells in addition to regulating the immune system. Pro-survival signaling pathways, especially those involving BCL-2 family proteins, are activated by Gal-9 through its attachment to glycoprotein ligands on leukemic B cells. This process leads to decreased therapeutic sensitivity and resistance to apoptosis. Reduced reactivity to specific medicines, such as venetoclax (a BCL-2 inhibitor) and ibrutinib (a BTK inhibitor), has been associated with elevated Gal-9 expression. By improving anti-apoptotic signaling and mitochondrial integrity, Gal-9 mechanistically enables CLL cells to tolerate treatment stress (10).

4. Induction of an Immuno-suppressive but Pro-Inflammatory Microenvironment: The tumor microenvironment (TME) plays a key role in CLL pathogenesis, and Gal-9 is an essential facilitator of its remodeling. Gal-9 triggers the release of pro-inflammatory cytokines by stimulating monocytes and myeloid-derived suppressor cells (MDSCs), which ironically maintain tumor-promoting inflammation while increasing immune suppression. In addition to maintaining stromal and nurse-like cell contacts with CLL clones, this persistent inflammatory environment prolongs T-cell activation and exhaustion. Together, Gal-9 strengthens leukemic cell survival in lymphoid niches by bridging the gap between inflammation and immunological dysfunction (8).

5. Synergistic Exhaustion and Checkpoint Crosstalk: Gal-9 also interacts with other immune checkpoint pathways, including PD-Ligand 1 (PD-L1) and Programmed Cell Death Protein 1 (PD-1). Gal-9/TIM-3 signaling enhances the suppressive effects of PD-1 engagement, and TIM-3 and PD-1 are often co-expressed on fatigued T cells in CLL. The effectiveness of PD-1/PD-L1 inhibition as a monotherapy is limited by this cooperative

checkpoint interaction, which intensifies immune fatigue. In order to overcome immune escape in CLL and restore functional T-cell responses, simultaneous inhibition of the Gal-9/TIM-3 and PD-1/PD-L1 pathways is being studied (11).

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