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Opinion Article

Inborn Errors: Managing Malignancies in the Context of Primary Immunodeficiencies

Zephyrin Thal*

Department of Immunology, Cornell University, Ithaca, United States

DESCRIPTION

The study of Primary Immunodeficiencies (PI) has traditionally focused on a "lack" of defense patients are perpetually vulnerable to pneumonia, sepsis, or rare fungal infections. However, in the clinical landscape of 2025, identified a much more complex "root" of these disorders: the paradoxical link between an underactive immune system and an overactive risk of malignancy. These "inborn errors of immunity" are now understood not just as a failure to fight germs, but as a fundamental failure of "immunological surveillance." When the body cannot recognize a pathogen, it often simultaneously loses the ability to recognize a pre-cancerous cell.

This realization has fundamentally altered the "remedy" strategy for PI patients. We are no longer simply looking to prevent infections; we are engaged in a high-stakes race to restore the body's internal "police force" before a malignancy can take root.

The biological roots of cancer in patients with Inborn Errors of Immunity lie in the specific genes that govern T-cell and Natural Killer (NK) cell function. In a healthy individual, the immune system acts as a constant gardener, weeding out cells that have acquired dangerous mutations. This is "immune surveillance." In patients with PI such as those with wiskott-aldrich syndrome or Common Variable Immunodeficiency (CVID) the genetic "wiring" of these "gardener" cells is broken.

Specifically, mutations in genes like *WAS* or *ATM* prevent immune cells from physically interacting with other cells to "check" their health status. This creates a "blind spot" in the body's defenses. Within this blind spot, cells that have acquired random mutations are allowed to multiply without interference. Furthermore, because these patients often suffer from chronic, unresolved viral infections, their immune systems are kept in a state of constant, ineffective "exhaustion." This chronic inflammation actually promotes genomic instability, acting as a fertilizer for cancer cells. The "root" is therefore a dual tragedy: the immune system is too weak to kill the cancer, but the chronic struggle against infection makes the cancer more likely to form.

Cell-based gene correction and targeted biologics

The remedy in 2025 is moving toward "cell-based gene correction." Rather than relying on bone marrow transplants from donors which carry a high risk of rejection clinicians are now using molecular-scissors to fix the patient's own stem cells. By correct the *WAS* or *ATM* gene in the lab and then re-infusing the cells, we can restore the body's ability to perform surveillance. This is the ultimate "root" remedy; it provides a permanent, genetic fix that allows the patient to hunt both viruses and cancer cells for the rest of their life.

For patients are not candidates for gene therapy, clinical precision involves the use of "targeted biologics" that mimic the missing immune signals. For instance, if a patient lacks a specific "kill signal" for tumor cells, we can use bispecific antibodies to manually bridge the gap between the weak T-cell and the cancer cell. Additionally, 2025 protocols emphasize "Proactive Surveillance" using liquid biopsies to detect "cancer DNA" in the blood years before a tumor would appear on a scan. This integrated approach ensures that the "lived experience" of a PI patient is no longer defined by the fear of an invisible tumor, but by a scientifically rigorous plan for long-term survival.

CONCLUSION

Inborn errors of immunity provide a unique window into the link between defense and surveillance. By addressing the biological roots of genetic failure and applying remedies like ex-vivo gene correction, we are transforming "primary immunodeficiency" from a life-threatening vulnerability into a manageable genetic condition. We are giving these patients back their "internal police force," ensuring they are protected against both the world of germs and the world of cancer.

Correspondence to: Zephyrin Thal, Department of Immunology, Cornell University, Ithaca, United States, Email: thal@gmail.com

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