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EXPLORING THE COMPLEXITIES OF THE IMMUNE SYSTEM

DECODING THE DYSFUNCTION

RSV IN INFANCY

UNDERSTANDING NEW EVIDENCE FOR A DIRECT VIRAL EFFECTOF TIME

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Ruby Thomas, Mathematics Department, Bahrain Teachers College, University of Bahrain, Sakir, Bahrain. https://www.interesjournals.org/articles/immunology-exploring-the-complexities-of-the-immune-system.pdf

"Deciphering T-cell exhaustion in the tumor microenvironment: paving the way for innovative solid tumor therapies" Authors: Reshmi Nair, Veena Somasundaram, Anshu Kuriakose, Shiv Ram Krishn, David Raben, Rachel Salazar, Pradip Nair.

De Leeuw et al., (2025, November 28). Maternal allergy and neonatal RSV infection synergize via FcR-mediated allergen uptake to promote the development of asthma in early life. ScienceImmunology. https://www.science.org/doi/10.1126/sciimmunol.adz4626

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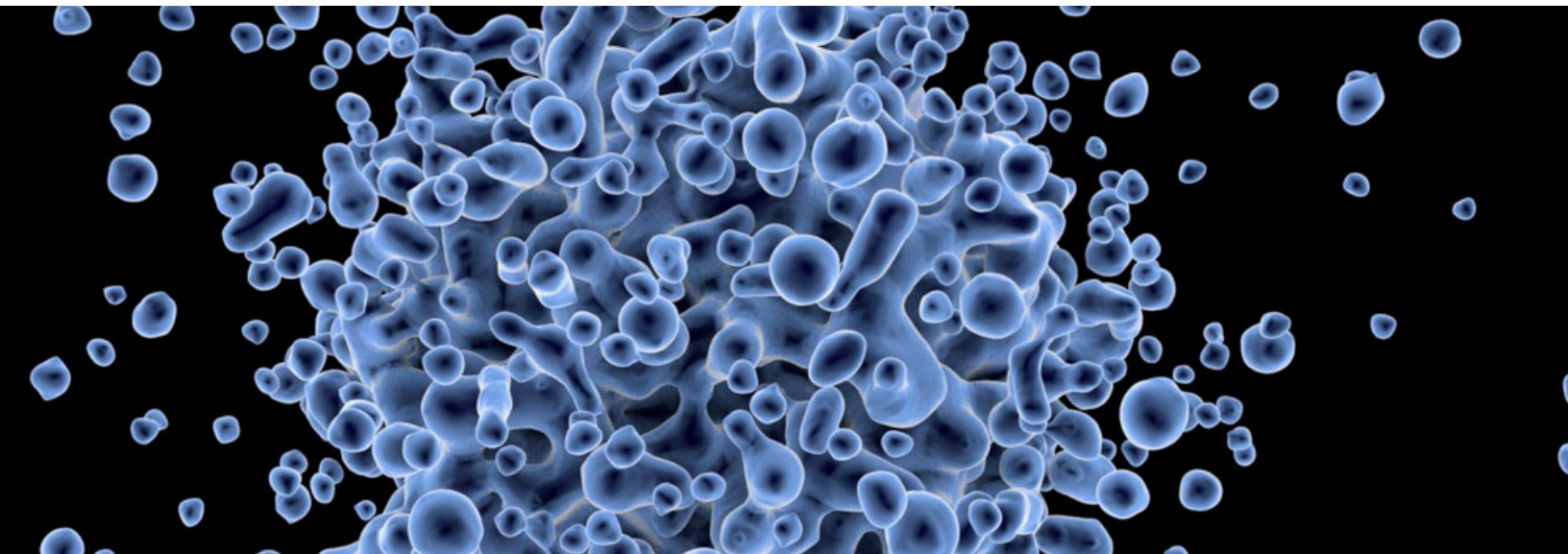
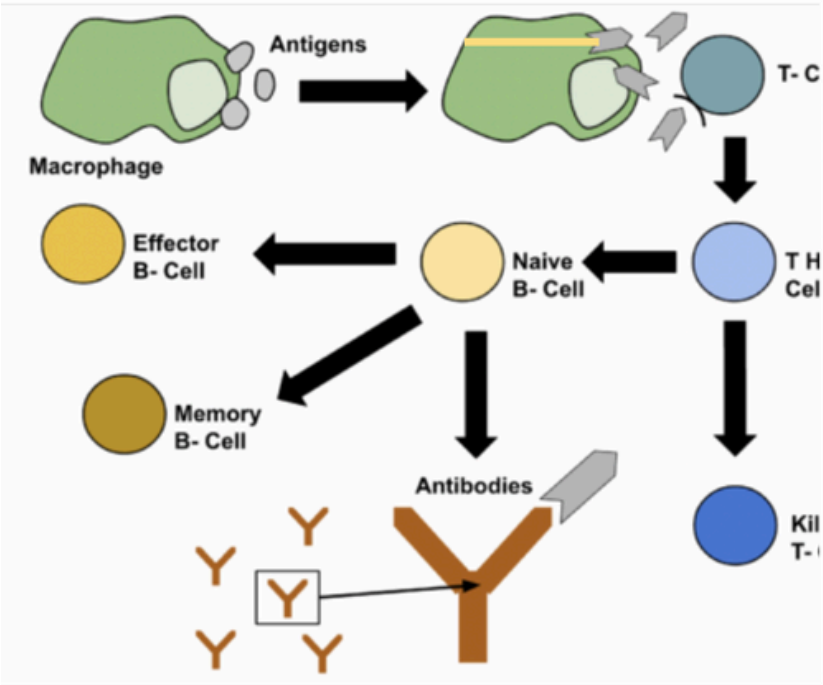


Immunology: Exploring the Complexities of the Immune System

Original Article by: R. Thomas | Digest by: Nicole Ekanem

The immune system has two main ways to defend the body:
the innate and adaptive immune responses. The first defense acts right away and is not specific, using barriers like skin and mucous membranes, along with immune cells such as macrophages and neutrophils that find and destroy germs. The innate response is important because it can recognize and fight infections even if the body has never seen them before.In contrast, the adaptive immune response develops over time, involving B cells and T cells that specifically target pathogens. B cells are responsible for producing antibodies that target specific antigens, and T cells coordinate the immune response and directly kill infected cells. Acquiring adaptive immunity can occur naturally through exposure to antigens or artificially



through vaccination, which prompts the production of memory cells, which will offer long-term protection against future infections. In addition, temporary immunity can result from the transfer of preformed antibodies.

Various types of immune cells play distinct roles in defense against pathogens. Neutrophils are phagocytic cells that eat and destroy bacteria, while macrophages also engage in phagocytosis and present antigens to activate other immune cells. Natural Killer (NK) cells eliminate infected or abnormal cells. Dendritic cells capture antigens and present them to initiate an immune response.

The immune system can sometimes overreact to non-threatening substances, resulting in allergies such as hay fever, food allergies, and asthma.

Diagnosis and treatment often involve allergy testing and immunotherapy. Autoimmune diseases occur when the immune system mistakenly targets healthy cells. To manage these, it may require medications.

Immunization is a preventive measure that causes an immune response without causing the disease itself. Vaccines have weakened or inactivated pathogens or their components, providing immunity against specific diseases and reducing their severity. Additionally, advancements in immunotherapy use the immune system to target and eliminate cancer cells, including treatments like immune checkpoint inhibitors and CAR-T cell therapy. Immunology is an interesting and quickly developing field that dives into the complexities of the immune system, the body's primary defense against infections, diseases, and foreign substances.

Key to immunology is the understanding of the immune response, which is the detailed interplay of various cell types and molecules—both innate and adaptive. Understanding these mechanisms is essential for the making of effective disease treatments and vaccines.

Immunologists categorize immunity into two primary types: active and passive. Active immunity is from exposure to antigens, either through natural infection or vaccination, offering long-lasting protective effects. On the other hand, passive immunity is gained through the transfer of preformed antibodies, providing immediate but temporary protection against infections.

Vaccination has changed public health, reducing the impact of infectious diseases significantly. As immunological research progresses, it promises to reveal new methods and approaches to effectively using the immune system's capabilities to foster improved health outcomes. By diving into these concepts, we gain insights into the defence mechanisms that protect our bodies and contribute to a healthier future through increased immunological knowledge and advancements. Vaccination represents a major achievement in immunology, made to prevent and control infectious diseases. By prompting the immune system to respond to specific pathogens, vaccines provide immunity and protect against severe disease manifestations.

Their impact is seen through diseases being eliminated, like smallpox, and the number of sick cases being drastically reduced in others, including polio and measles.

Moreover, immunotherapy is revolutionizing cancer treatment, employing the immune system's capabilities to target and eliminate cancer cells through therapies like immune checkpoint inhibitors and CAR-T cell therapy, which have shown efficiency and potential for increasing survival rates across various cancers.

Immunology, the study of the immune system, is foundational to understanding how white blood cells—neutrophils, macrophages, natural killer cells, B cells, and T cells—detect, combat, and eliminate pathogens and infected cells. Antigen-presenting cells (APCs), are key in activating immune responses by showing antigens to other immune components. The significance of this field becomes clear when we consider immunological disorders like allergies and autoimmune diseases. Allergies are an overreaction of the immune system to non-harmful substances, leading to different symptoms, while autoimmune diseases occur when the immune system targets healthy cells and tissues. Managing these conditions often involves immunotherapy and immunosuppressive medications, highlighting the need for specific therapeutic approaches.

Looking forward, the future of immunology is portrayed by significant advancements in techniques such as high-throughput sequencing and single-cell analysis, which deepen our understanding of the immune system's complexity. This developing knowledge base is essential for the expansion of personalized medicine—which is where treatments are tailored to a person's unique immune profile, which can lead to more effective therapies with reduced side effects.

In summary, immunology is a dynamic and essential field that has profoundly shaped our understanding of immune system functions and their implications for health. Researchers and practitioners in this field continue to drive progress in disease prevention through vaccines and innovative therapies, especially immunotherapy for cancer treatment. As we advance our comprehension of immune mechanisms, the likelihood for developing targeted, precise medical interventions becomes increasingly practical, promising enhanced healthcare outcomes and healthier populations.

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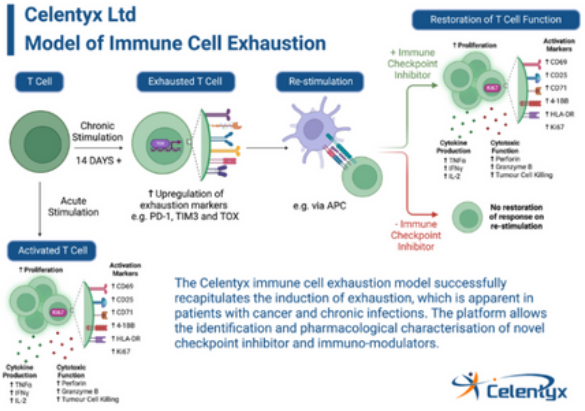
DECODING THE DYSFUNCTION: THE MOLECULAR MECHANISMS AND THERAPEUTIC TARGETING OF T CELL EXHAUSTION IN THE TUMOUR MICROENVIRONMENT

Original Article by: R. Nair, V. Somasundaram, A. Kuriakose, S. Ram Krishn, D. Raben, R. Salazar, P. Nair

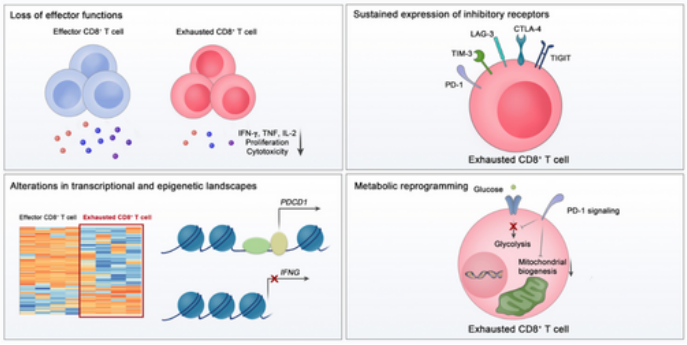
Digest by: Nathan Zhuang

I. The Immunological Dilemma: T Cell Exhaustion in Cancer

The rise of cancer immunotherapy, particularly Immune Checkpoint Inhibitors (ICIs) targeting molecules like PD-1 and CTLA-4, has dramatically shifted the oncology landscape. However, the efficacy of these treatments is often limited, especially in solid tumours, due to a phenomenon known as T cell exhaustion (Tex). T cell exhaustion is an acquired state of cellular dysfunction characterized by a progressive loss of effector functions (such as producing IFN-γ and IL-2) and the sustained high expression of multiple inhibitory receptors (immune checkpoints).



Originally identified in the context of chronic viral infections, Tex is now recognized as a major mechanism of immune evasion utilized by tumors. When cytotoxic CD8+T cells are chronically stimulated by tumor-associated antigens within the hostile Tumor Microenvironment (TME), they undergo a profound transcriptional and epigenetic reprogramming that locks them into this dysfunctional state. Understanding and reversing Tex is therefore paramount for improving clinical outcomes in cancer patients.



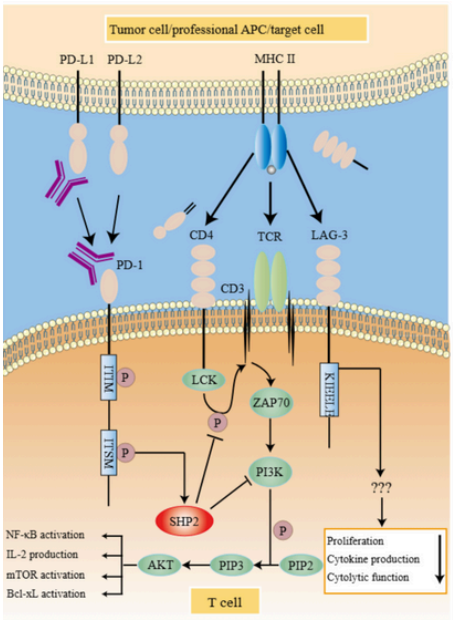
II. The Hostile Environment: TME Factors Driving T Cell Exhaustion

The complexity of Tex stems from the myriad of immunosuppressive cues within the TME. The paper highlights several key factors that cooperate to drive T cell dysfunction:

A. Chronic Antigenic Stimulation and Immune Checkpoints:

The continuous presence of tumor-specific antigens, which the immune system fails to clear, is the foundational trigger for Tex. This chronic signalling through the T cell receptor (TCR) leads to the sustained upregulation of inhibitory receptors.

- Programmed Cell Death Protein 1 (PD-1): Perhaps the most famous, its interaction with its ligand PD-L1 (often highly expressed on tumor cells) dampens T cell signaling, a mechanism successfully targeted by ICIs.



- Lymphocyte Activation Gene 3 (LAG-3) and T Cell Immunoglobulin and Mucin-Domain Containing-3 (TIM-3): These and other co-inhibitory receptors are co-expressed with PD-1 on terminally exhausted T cells. Targeting these in combination with PD-1 blockade is a major avenue of current clinical research, as combination blockade can overcome resistance to monotherapy.

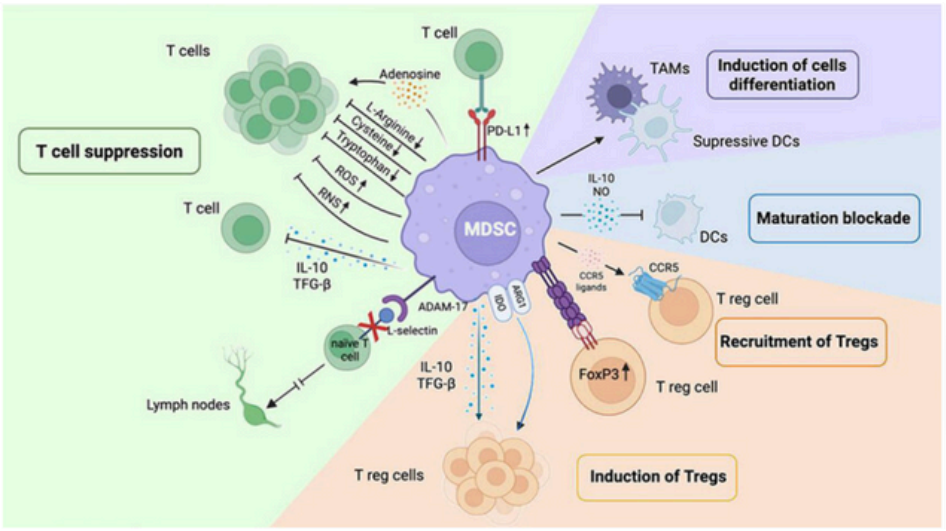
B. Immunosuppressive Cell Populations:

The TME is populated by various immune cells that actively suppress the function of T cells:

- Myeloid-Derived Suppressor Cells (MDSCs): These immature myeloid cells accumulate in the TME and exert potent suppressive effects through mechanisms like the production of reactive oxygen species (ROS) and the depletion of essential amino acids.

- Tumor-Associated Macrophages (TAMs): Specifically, the M2 polarization state of TAMs promotes tumor growth, tissue remodeling, and immunosuppression, contributing to the poor TME quality that fatigues T cells.

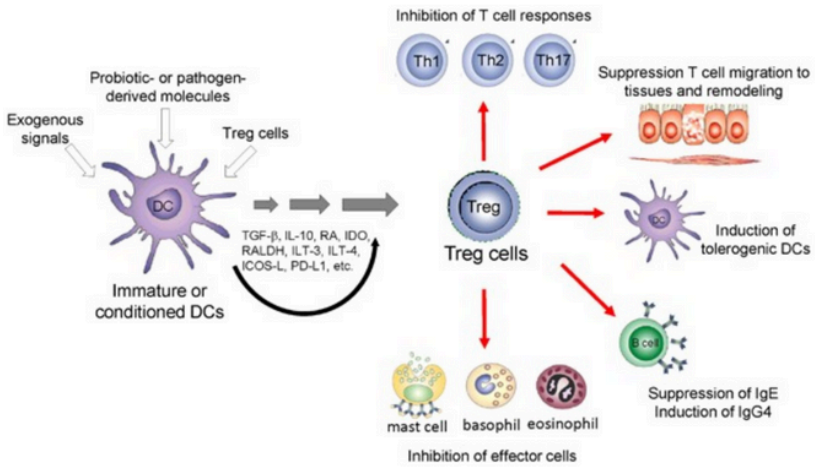
- Regulatory T Cells (Tregs): These cells are specialized in maintaining immune tolerance. Their enrichment in the TME suppresses CD8+T cell responses via IL-10, TGF-β, and the CTLA-4 pathway.



C. Soluble Cytokines and Metabolites

The TME is a soup of signaling molecules that impede T cell activation:

- Immunosuppressive Cytokines: TGF-β and IL-10 directly inhibit T cell proliferation and effector function.

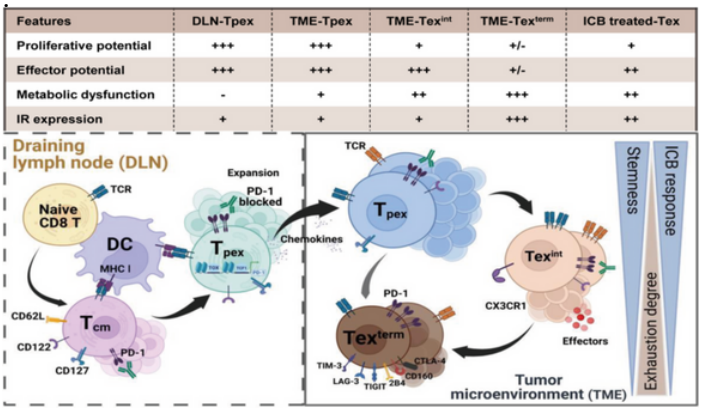


- Metabolic Deprivation: Rapidly proliferating tumour cells often create a local environment depleted of essential nutrients like glucose and amino acids, particularly L-Arginine. T cells require high metabolic activity to function, and this resource deprivation leads to a state of metabolic dysfunction characteristic of exhaustion. The article emphasizes how metabolic reprogramming—such as shifting from glycolysis to oxidative phosphorylation—is essential for T cell survival but often restricts their maximal effector capacity

III. The Tex Spectrum: T Cell Heterogeneity and Stemness

A crucial insight from recent single-cell RNA sequencing (scRNA-seq) studies, as summarized in the paper, is that T cell exhaustion is not a uniform state but a spectrum of differentiation with distinct subsets.

Tpex (T cell Progenitor Exhausted): These are the precursor exhausted T cells, often marked by the expression of the transcription factor TCF1. These cells are proliferative, reside mainly in the tumor-draining lymph nodes, and are the primary cells responsible for the therapeutic effect of PD-1 blockade. They represent the "stem-like" population capable of self-renewal and generating terminally exhausted cells.



Tint (T cell Intermediate Exhausted): A transitional population, exhibiting reduced proliferation and intermediate effector function.

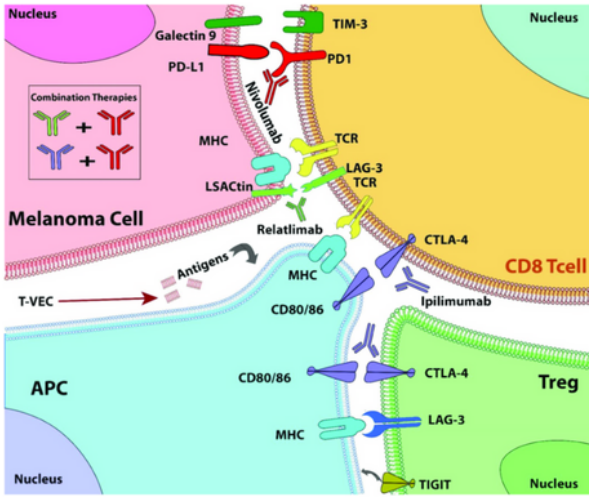
Tterm (T cell Terminally Exhausted): These cells are highly dysfunctional, express the maximum number of inhibitory receptors, are non-proliferative, and lack robust effector function. They are generally refractory to current ICIs.

The paper stresses that the success of immunotherapy hinges on expanding the Tpex population and preventing their differentiation into the terminally exhausted state. The presence and location of these different Tex subsets in a patient's tumor are increasingly being used as biomarkers to predict response to treatment.

IV. Paving the Way for Innovative Therapies

The comprehensive understanding of Tex mechanics and subsets has opened several innovative therapeutic pathways beyond traditional single-target ICIs:

A. Combination Checkpoint Blockade
The co-expression of multiple inhibitory receptors (PD-1,LAG-3,TIM-3,CTLA-4) on



Tterm cells suggests that combinatorial blockade might be necessary to fully lift the brakes on the immune system. The clinical success of the PD-1 and LAG-3 dual-blockade (e.g., Relatlimab/Nivolumab) in certain cancers validates this approach

B. Metabolic Reprogramming

By targeting the T cell metabolism, researchers aim to restore the energy required for sustained effector function. Strategies include:

- Inhibiting the IDO1 enzyme, which starves T cells by breaking down the essential amino acid Tryptophan.
- Providing small molecules that can help T cells overcome glucose and oxygen deprivation in the hostile TME.

C. Transcriptional/Epigenetic Rewiring

Since Tex is fundamentally a state of epigenetic change, therapeutic strategies are being developed to "rewire" the T cell's identity away from exhaustion. Targeting key transcription factors like TOX and Blimp1—which drive the exhaustion program—or promoting those associated with the Tpex stemness (like TCF1) holds immense promise for generating more persistent and potent anti-tumor T cells.

D. Enhancing Adoptive T Cell Therapy (ACT)

For ACT approaches like CAR-T cell therapy in solid tumors, the TME still induces exhaustion in the transferred cells. Novel strategies are being developed to engineer CAR-T cells to be intrinsically resistant to Tex by knocking down exhaustion-associated genes or overexpressing stimulatory signals, thereby improving their persistence and effectiveness against solid tumors.

V. Conclusion

The paper by Nair et al. synthesizes the current understanding of T cell exhaustion, emphasizing its multifaceted nature driven by chronic stimulation, multiple inhibitory pathways, and the suppressive TME.

The key takeaway is the critical distinction between the responsive Tpex and the refractory Tterm cells. Future solid tumor immunotherapies will likely revolve around sophisticated multi-modal strategies that not only block immune checkpoints but also metabolically and epigenetically reprogram T cells while simultaneously modifying the immunosuppressive components of the TME to sustain T cell function.

This integrated approach is essential to transform non-responsive tumors into immunologically "hot" tumors and realize the full potential of cancer immunotherapy.

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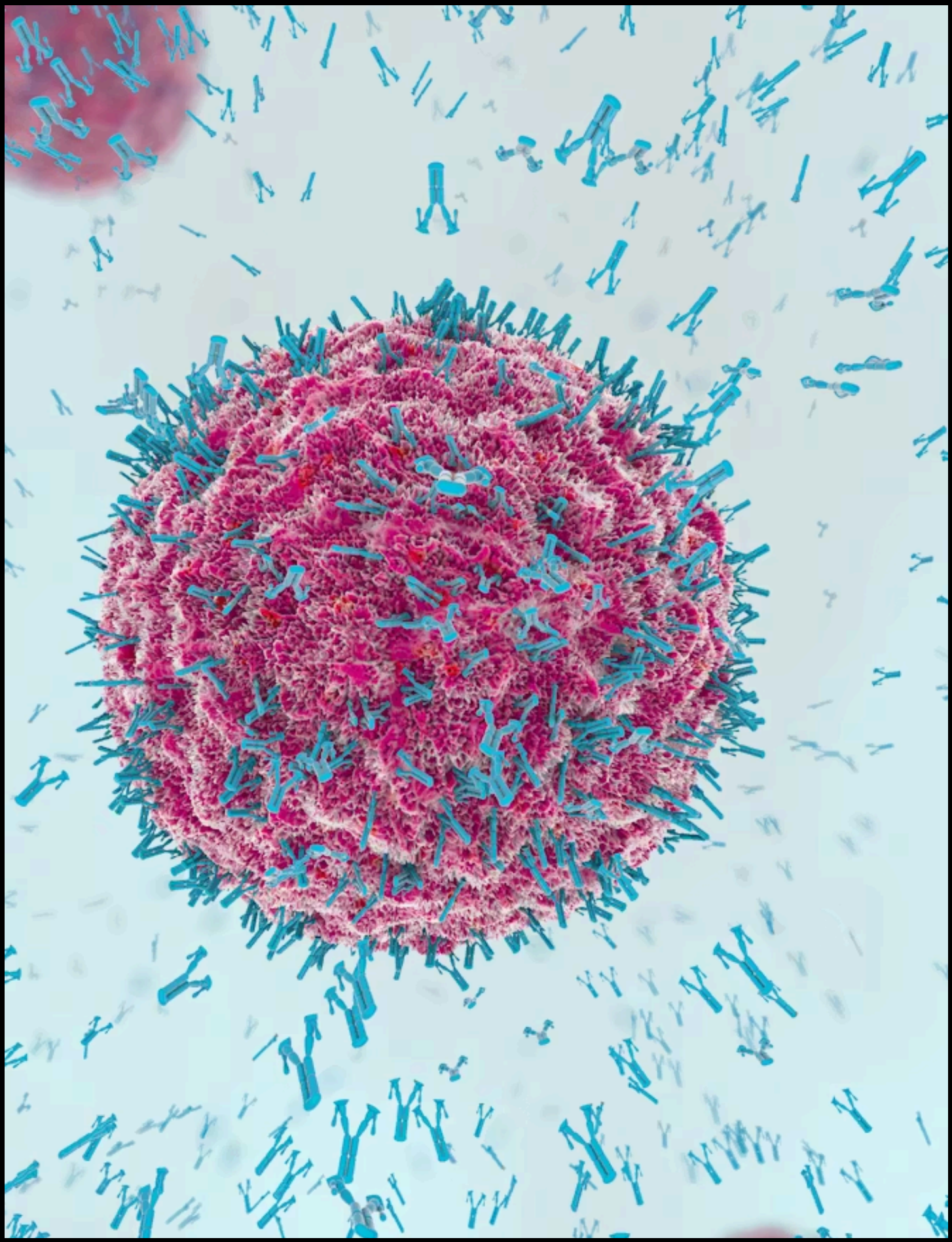

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RSV IN INFANCY

Original Article by: E. De Leeuw Digest by: Jessice Lu

Allergic asthma develops through complex interactions between genes and the environment, involving strong type 2 immune responses to inhaled allergens. This leads to eosinophilic airway inflammation, mucus overproduction, and bronchial hyperreactivity (BHR). Many young children become sensitized to common airborne allergens such as house dust mite (HDM), animal dander, pollen, or fungal spores. Allergic asthma usually develops in early childhood and is influenced by factors such as birth mode, maternal diet, and air pollution. Early-life respiratory syncytial virus (RSV) infection and parental asthma, are considered major risk factors for later asthma development.

Using the Danish National Patient Registry, De Leeuw et al. analyzed close to 1.5 million children. They identified children hospitalized with RSV bronchiolitis in the first 6 months of life, from 1994 to 2018, and linked this data to parental asthma. They found that children hospitalized with RSV bronchiolitis in early childhood had a three times higher risk of asthma, while having a parent with asthma doubled the risk. Children who had both of these risk factors had the highest overall asthma incidence.

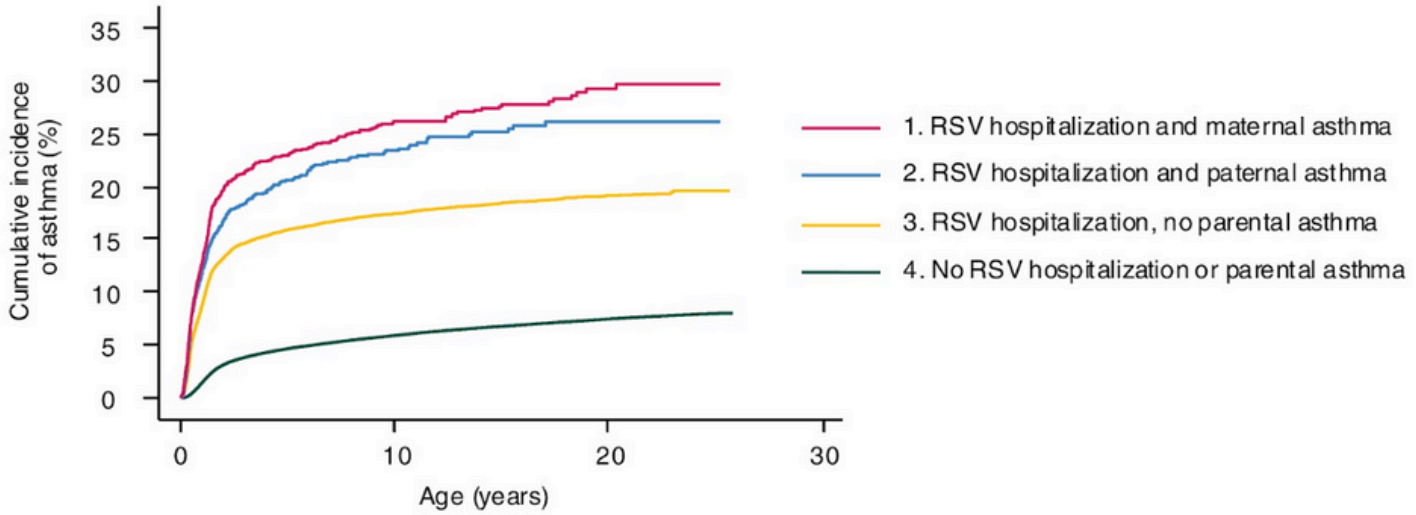


Fig. 1. Cumulative incidence of asthma according to RSV hospitalization during infancy and parental asthma status.

To test whether early RSV-like infection causes asthma susceptibility, the researchers developed a mouse model combining maternal or paternal HDM-induced asthma, induced by HDM with neonatal infection with PVM (a virus similar to RSV). They found that neonatal PVM infection significantly worsened later HDM-induced asthma features. This effect was strongest in pups born to allergic dams, but not those born to allergic sires.

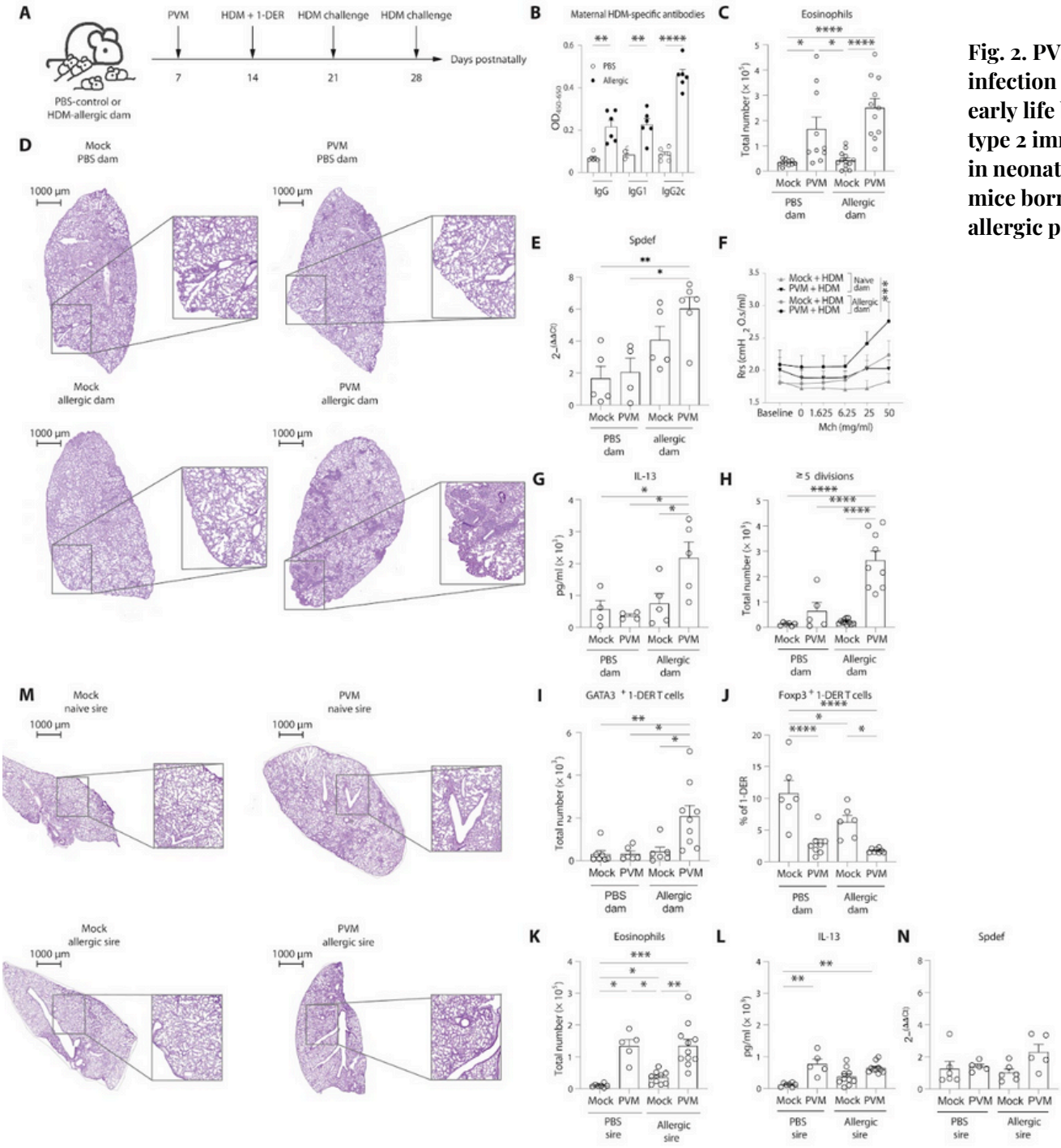
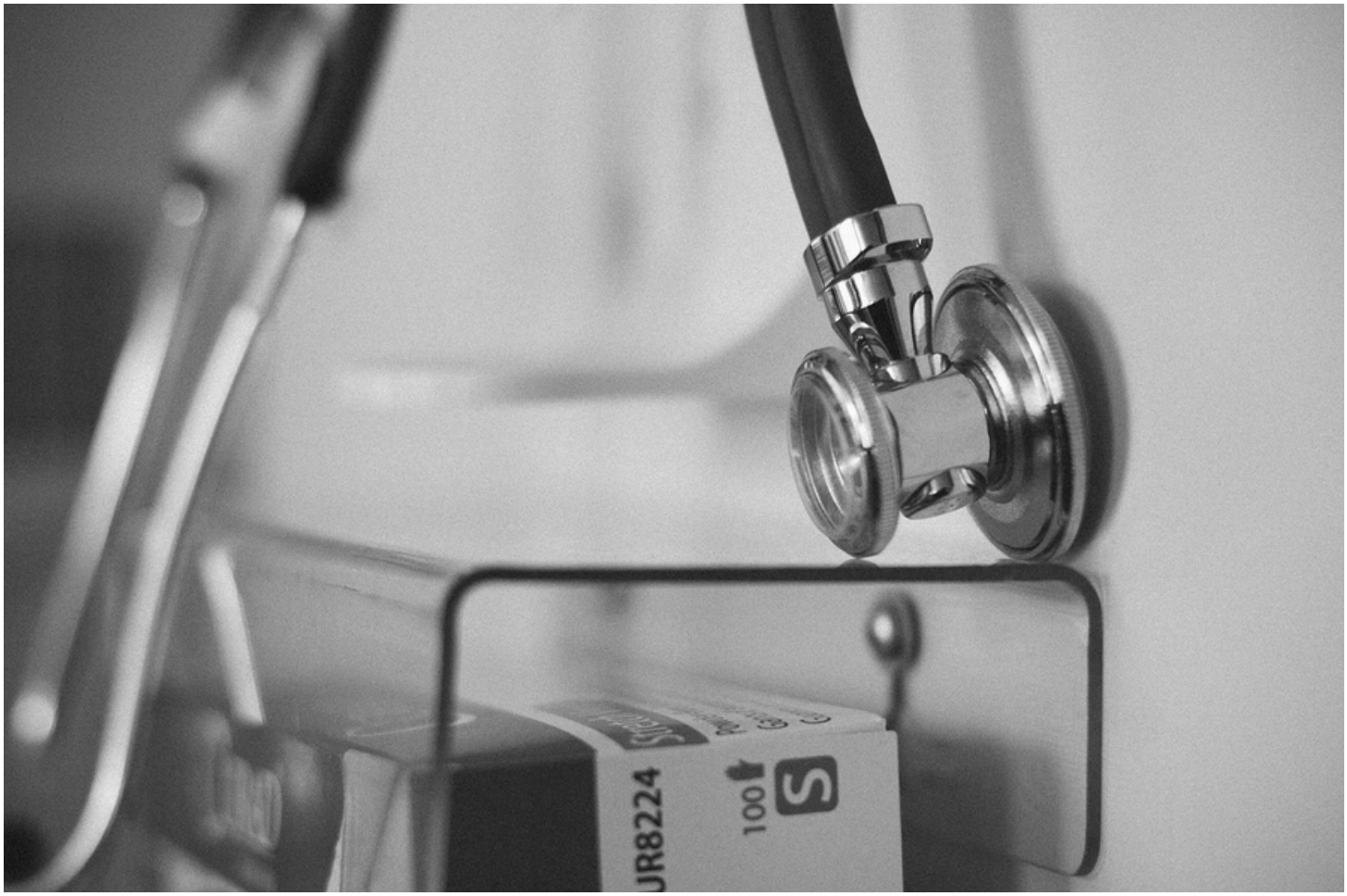


Fig. 2. PVM infection in early life boosts type 2 immunity in neonatal mice born to an allergic parents.

Finally, the researchers tested whether preventing neonatal RSV infection could prevent asthma risk. They administered MPE8, an antibody that protects against PVM, to lactating dams. MPE8 inhibited PVM's asthma-enhancing effects, suppressing airway hyperreactivity, mucus hyperproduction, and airway eosinophilia, eliminating the added asthma risk caused by early-life infection. Importantly, these protective effects in mice suggest that preventing severe RSV infections in infancy could also reduce long-term asthma development in humans. This highlights the potential for maternal vaccination or long-acting RSV antibodies to provide both immediate protection against bronchiolitis and lasting benefits for respiratory health.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Understanding New Evidence for a Direct Viral Effect of Time

Original Article by: S. Klingenstein, N. Ruetalo, P. Helmut Neckel, A. Kleger, M. Schindler, S. Liebau, M. Klingenstein

Digest by: Daniella Ling

When COVID-19 first emerged, attention naturally focused on its respiratory consequences. As the pandemic continued, clinicians documented a wide spectrum of symptoms involving nearly every organ system. Hair loss, particularly telogen effluvium (TE), soon became one of the most widely reported post-COVID complaints. TE is a form of diffuse hair shedding caused by a synchronized shift of many hair follicles from the growth phase into the resting phase. Traditionally, this shift is attributed to triggers such as high fever, severe infection, major stress, surgery, childbirth, nutritional deficiencies, or systemic inflammation. At first, COVID-19–related shedding was assumed to follow the same logic: a stressful illness leading to delayed-onset TE a few months later.

Yet case reports quickly revealed something unusual. Many COVID-19 patients were experiencing hair shedding far earlier than the classic three- to four-month window. In some cases, shedding began as soon as two to four weeks after infection. This accelerated pattern prompted scientists to ask whether SARS-CoV-2 might have more direct effects on the hair follicle itself. The study summarized and interpreted here explores that possibility by investigating whether the virus—or its structural proteins—interact with human hair follicles in ways that could influence their health, cellular stability, or cycling.

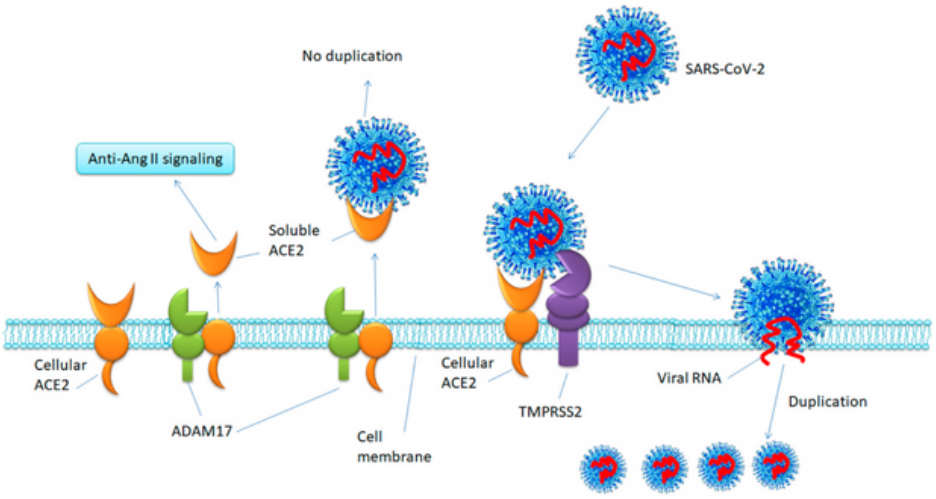
Hair Follicles and Their Vulnerability

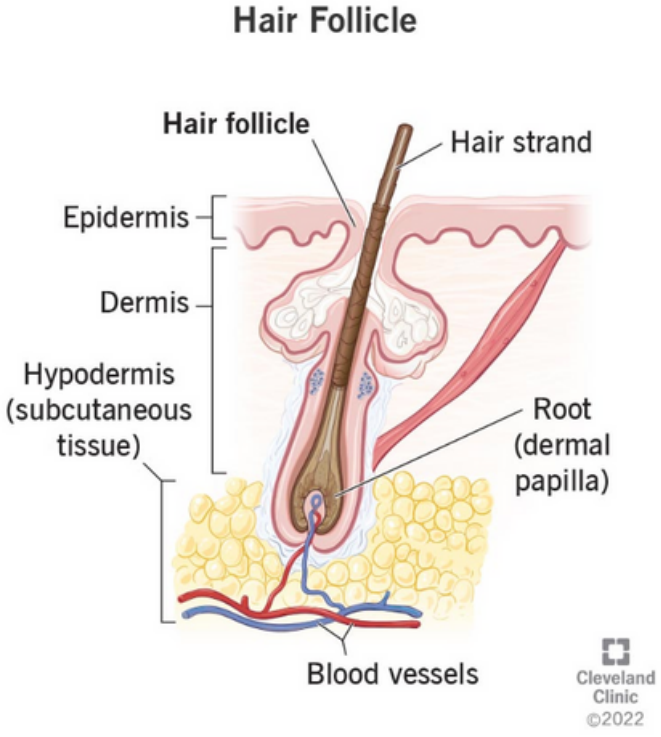
Human hair follicles are complex mini-organs composed of multiple specialized layers. Among these, the outer root sheath (ORS) plays a central role in anchoring the hair and supporting follicular growth. The ORS contains keratinocytes that express characteristic proteins such as keratin-15 (KRT15) in the basal layer and keratin-6 or keratin-75 in the suprabasal and companion layers. These keratinocytes interact closely with surrounding blood vessels and the dermal sheath, making them potentially exposed to circulating viral particles or inflammatory mediators.

Because SARS-CoV-2 enters human cells through ACE2 and is activated by TMPRSS2, identifying the presence and distribution of these proteins within hair follicles is crucial for determining whether the follicle is biologically capable of responding to the virus.

ACE2 and TMPRSS2 in the Human Hair Follicle

The researchers first examined both skin-embedded scalp tissue and freshly plucked follicles to map where ACE2 and TMPRSS2 are expressed. They found that ACE2 is consistently present in the basal layer of the ORS—the same region enriched in progenitor-like keratinocytes. This layer sits in continuity with the epidermis and lies just above the upper follicular stem cell niche. ACE2 was also detected in sebaceous and sweat glands, structures already known to express high levels of this receptor.





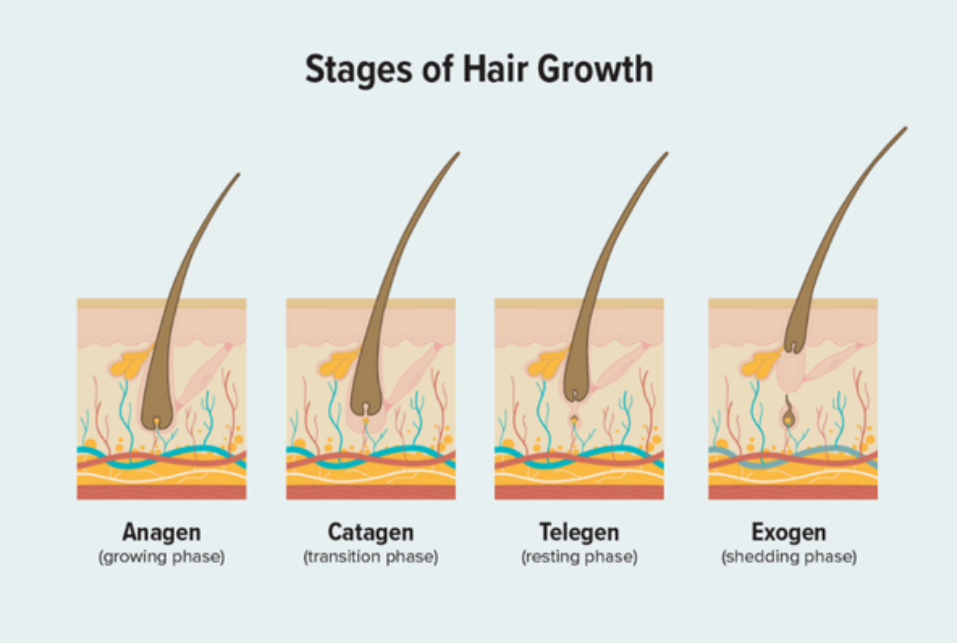
TMPRSS2, while present in the ORS, showed an even broader distribution. It appeared strongly in the outermost layers of the follicle, including Henle's layer of the inner root sheath. These findings confirm that hair follicles contain the molecular machinery required for SARS-CoV-2 attachment and entry, at least theoretically. Importantly, ACE2 expression in the follicle is not widespread but concentrated in a specific set of basal ORS cells, suggesting that any viral interaction would likely be localized rather than diffuse.

Ex Vivo Infection of Plucked Hair Follicles

To explore whether these entry factors translate into meaningful viral interactions, the authors exposed freshly plucked human follicles to live SARS-CoV-2 under controlled laboratory conditions. Because plucked follicles retain their ORS but not the deeper bulb, this model selectively tests the susceptibility of ORS keratinocytes—precisely the cells that express ACE2 and TMPRSS2.

After 96 hours of exposure, the follicles were examined for signs of viral presence and cellular response. The researchers detected SARS-CoV-2 nucleocapsid protein within ORS cells, indicating that viral material had entered or accumulated inside these keratinocytes. Although the study did not establish whether the virus replicated inside the cells, the presence of nucleocapsid protein alone suggests that ORS cells can internalize viral components.

Most strikingly, the infected follicles displayed markers of apoptosis within the ORS. Apoptosis, or programmed cell death, is a known driver of premature follicular regression. In vivo, an accumulation of apoptotic cells in the ORS could theoretically hasten the transition from anagen (growth) to catagen (regression), setting the stage for TE.



Connecting Viral Exposure to Telogen Effluvium

By linking ACE2 and TMPRSS2 expression, ex vivo viral entry, and ORS apoptosis, the study offers a plausible mechanistic bridge between SARS-CoV-2 infection and TE. Traditionally, TE develops when the follicle is pushed into a stress-response state—either from circulating inflammatory signals or from direct cellular injury. If SARS-CoV-2 can induce apoptosis locally within the ORS, even without replicating robustly, this injury might serve as a direct trigger for early catagen induction.

Such a mechanism could help explain why post-COVID TE often occurs earlier than TE caused by other febrile illnesses.

Rather than waiting for systemic inflammatory cascades to provoke a delayed follicular response, the follicle may itself detect viral components and initiate stress signaling. Supporting this idea, previous ultrastructural studies have reported SARS-CoV-2-like particles in ORS cells of patients with COVID-related hair shedding, aligning with the present findings.

Interpretation and Limitations of the Evidence

This study's conclusions require careful contextualization. Ex vivo follicle infection does not perfectly replicate the environment of living tissue. The absence of immune cells, vascular flow, and systemic cytokine responses limits the model.

Additionally, while the presence of viral nucleocapsid protein within ORS cells is significant, it does not prove productive viral replication. It remains possible that viral particles enter these cells transiently during short-lived viremia without establishing ongoing infection.

Similarly, although apoptosis was observed after prolonged viral exposure in vitro, whether the same degree of apoptosis occurs in vivo—and at physiologically relevant viral concentrations—remains uncertain. Nonetheless, the fact that ORS cells are capable of internalizing viral protein and responding with measurable cellular stress provides conceptual support for a follicle-intrinsic contribution to COVID-associated TE.

Broader Implications

The idea that SARS-CoV-2 may exert direct effects on skin appendages adds nuance to our understanding of post-COVID sequelae. Hair follicles, as dynamic structures dependent on precise control of cell proliferation and survival, are particularly sensitive to disruptions. The identification of ACE2 and TMPRSS2 in specific follicular compartments highlights the follicle as a potential—if limited—target for viral interaction. Combined with known systemic triggers such as fever, cytokine production, and psychological stress, direct follicular involvement may help explain the variability in timing and severity of hair shedding observed among patients.

Conclusion

Mounting clinical evidence shows that telogen effluvium is a common consequence of COVID-19, often appearing earlier than expected. The study reviewed here provides a biological framework supporting the possibility that SARS-CoV-2 interacts directly with ORS keratinocytes through ACE2 and TMPRSS2, allowing viral proteins to enter these cells and induce apoptosis. While further in vivo studies are needed to determine the extent of this interaction and its clinical relevance, this work adds a new dimension to our understanding of COVID-related hair loss. It suggests that TE following SARS-CoV-2 infection may result not only from systemic stress but also from localized cellular responses within the hair follicle itself.

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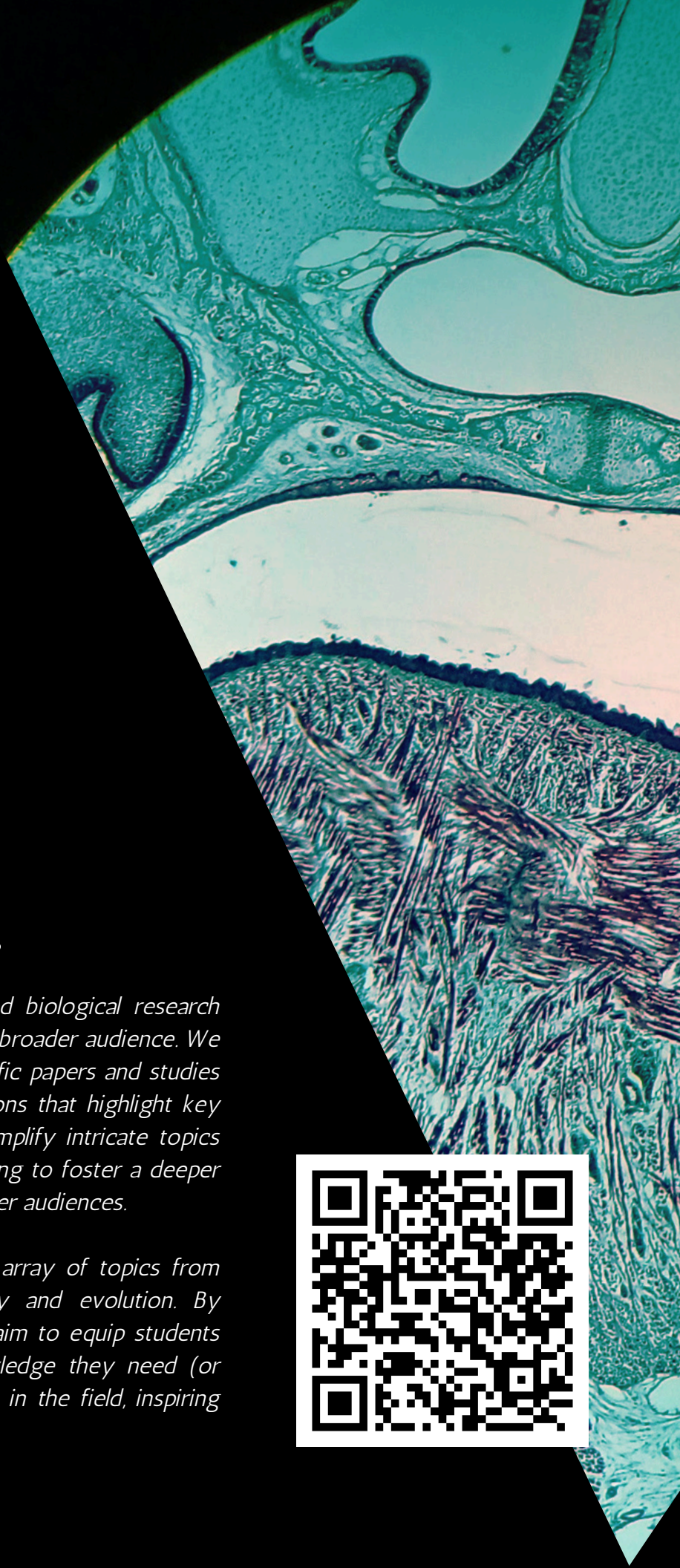

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