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INSIGHTS

Staying IgD positive in a challenging environment

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The nasopharyngeal tissues provide a frontline defense against airborne exposure to viruses, bacteria, and allergens. In this issue of *JEM*, Tachó-Piñot et al. (https://doi.org/10.1084/jem.20251752) show that mutated IgD$^+$ B cell subsets populate epithelial areas of nasopharyngeal mucosa, ready to tackle a multitude of antigenic targets.

The mucosal immune system is the body's largest immune compartment, responsible for host defense while maintaining immune tolerance amid constant exposure to commensal and environmental antigens (Zhou et al., 2025). It spans multiple barrier tissues, including the respiratory, urogenital, and gastrointestinal tracts, each with distinct structural and immunological features. Within these sites, mucosa-associated lymphoid tissues (MALTs) house immune cell populations specialized for sensing and responding to local antigenic cues (Zhou et al., 2025). Local B cell responses and antibody production are central to immunity in the respiratory tract, particularly in the upper airways, where antigen encounter is frequent and diverse. Interest in the nasopharyngeal mucosa has intensified in recent years, driven in part by the SARS-CoV-2 pandemic (Ramirez et al., 2024), which underscored the importance of advancing mucosal vaccination strategies that prime local immune responses and establish protection in the respiratory tract (Kwon et al., 2025; Oh et al., 2021). The tonsils, as antigen-rich lymphoid structures at the interface of the respiratory and alimentary tracts, are thus a critical site for interrogating human B cell immunity. Yet, studies of mucosal antibody responses in the respiratory tract have traditionally focused on IgA (Chen et al., 2020; Liu et al., 2024), potentially overlooking contributions from other antibody isotypes in shaping humoral responses to food antigens and commensal microbes in this environment.

Following antigen engagement through the B cell receptor, B cells undergo multiple layers of specialization, including affinity maturation, Fc glycosylation, and class-switch recombination (Polmear and Good-Jacobson, 2021; Victora and Nussenzweig, 2012). Collectively, these processes generate B cells and antibodies that are functionally adapted to distinct classes of antigens, such as viruses, bacteria, parasites, and allergens. While mature naive B cells co-express IgM and IgD, B cells downregulate IgD upon activation and either retain IgM expression or class-switch to downstream isotypes IgG, IgA, or IgE. As a result, IgD has often been relegated to the role of the "forgotten middle child" of antibody isotypes. This bias is particularly evident in the memory B cell field, where IgM and IgD memory B cells are frequently analyzed together, if IgD memory is considered at all. Emerging evidence, however, indicates that IgD$^+$IgM^{lo} B cells serve distinct roles in the immune response. This subset has historically been known for their enrichment for autoreactive specificities and anergic properties; however, they can participate in germinal centers (GCs) and hypermutate away from autoreactivity (Burnett et al., 2019; Koelsch et al., 2007; Sabouri et al., 2014). Additionally, IgD$^+$IgM^{lo} memory B cells have been shown to contribute to the stable long-lived memory population formed in response to parasitic infection (Krishnamurty et al., 2016). Given that the tonsils are continuously exposed to a broad spectrum of inhaled and ingested antigens, they offer a unique context in which antibody isotypes specialized for immune balance and tolerance, such as IgD, may be selectively favored. Yet, an in-depth understanding of IgD$^+$IgM$^-$ B cell subsets in the tonsils has been lacking.

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Tachó-Piñot et al. (2026) addressed this gap by undertaking a comprehensive analysis of IgD$^+$ B cell populations in human tonsils. Using spectral flow cytometry combined with RNA sequencing, they resolved four major IgD-expressing populations: anergic naive B cells, GC B cells, memory B cells, and plasma cells. IgD$^+$IgM$^-$ memory (IgD-ME) B cells were transcriptionally distinct from naive B cells and were enriched in tonsils relative to spleen, indicating tissue-specific specialization within the tonsil, rather than a subset present in the tonsil due to recirculation. Further interrogation of the data revealed further IgD-ME

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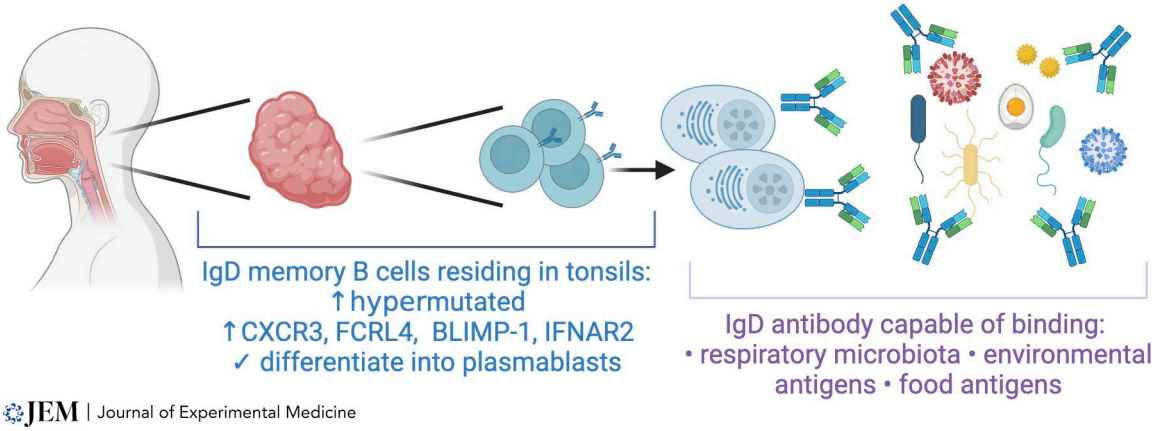

Within the upper respiratory tract, tonsillar IgD$^+$IgM$^-$ memory B cells adopt an activated profile and are hypermutated. Increased expression of plasma cell genes and downregulation of CD21 suggest that they are poised to differentiate into antibody-secreting cells. IgD antibody in the mucosa is capable of binding commensal bacteria, viruses, and food antigens, suggesting that IgD plays a frontline role in both homeostasis and respiratory lymphoid responses to foreign antigen.

subsets, with transcriptomes suggesting different lineages and functions. Histological analysis, together with utilization of published spatial transcriptomic datasets, further revealed that IgD-ME B cells preferentially localized to epithelial and interfollicular regions of the tonsil. This positioning places IgD-ME at sites of frequent antigen encounter, consistent with a role in sampling and responding to diverse inhaled and ingested antigens.

A central comparison within the study was between IgD-ME and transcriptional programs associated with so-called age-associated or atypical memory B cells (ABCs). ABCs are typically characterized by expression of CD11c, T-bet, CXCR3, and FCRL4 together with downregulation of CD21, features often linked to viral infections and/or inflammatory environments (Cooper and Good-Jacobson, 2020). One of the first reports of memory B cells with some features now commonly associated with ABCs was performed on tonsillar B cells; at the time, this newly defined phenotype was used to denote a tissue-based memory B cell subset (Ehrhardt et al., 2005). While the majority of this memory subset had downregulated IgD, the authors did find a small fraction of this memory B cell subset had retained IgD expression (Ehrhardt et al., 2005). In line with this early observation, Tachó-Piñot et al. observed partial overlap between IgD-ME B cells and ABC memory gene signatures, including reduced CD21 expression and increased interferon receptors (see figure). Accordingly, IgD-ME B cells appeared transcriptionally poised to differentiate into antibody-secreting cells, a property shared with but not exclusive to ABCs. Notably, however, IgD-ME B cells lacked expression of Zeb2, a transcription factor that drives ABC differentiation (Dai et al., 2024), and several overlapping genes reflected general activation states rather than lineage-defining features. These findings suggest that while IgD$^+$ memory B cells may adopt select features associated with ABCs, this overlap does not necessarily imply equivalence, and it remains unclear whether the acquisition of these traits is driven by inflammatory cues, local tissue context, or antigenic burden.

Previous studies have demonstrated that IgD$^+$ B cell populations can be enriched for autoreactive specificities (Koelsch et al., 2007). In line with this, the authors found that IgD$^+$ GC B cells, IgD-ME B cells, and IgD$^+$ plasma cells preferentially utilized the IGHJ6 segment (associated with B cells that are self-reactive) and could bind self-antigens. Importantly, similar reactivity was also observed among IgG-expressing memory B cells, indicating that autoreactive potential was not exclusive to the IgD lineage. Beyond self-recognition, IgD-derived antibodies displayed specificity for airborne and food antigens, as well as respiratory microbiota, consistent with the antigenic milieu of the tonsils and upper respiratory tract. These findings suggest that IgD$^+$ B cell subsets occupy a functional role at the interface of tolerance and immunity, although future studies could further elucidate putative functional capabilities depending on the specificity of IgD-ME B cells.

Together, the study by Tachó-Piñot et al. reveals the phenotype, transcriptome, and localization of hypermutated IgD$^+$ memory B cells in human tonsils, demonstrating that these cells can efficiently differentiate into antibody-secreting cells with specificity for a wide array of self, microbial, and environmental antigens. While IgD has traditionally been viewed as an isotype downregulated upon activation by foreign antigens, its persistence through affinity maturation and terminal differentiation in this antigen-rich tissue suggest a specialized contribution to mucosal immunity. In particular, the generation of IgD$^+$ memory and plasma cells may represent a strategy to sense and adapt to diverse antigens while restraining responses to commensal bacteria and food antigens.

These findings raise several important questions. The longevity of tonsillar IgD-ME remains unclear: are these cells sustained by continuous antigen exposure, or can they persist independently as a stable memory compartment? How do IgD-ME contribute to tolerance toward food antigens and commensal microbes in the upper respiratory tract, and do they differ from IgG-expressing tonsillar counterparts in their propensity to promote or restrain self-reactivity? Finally, elucidating whether IgD$^+$ memory and plasma cells are restricted to the tonsils or can seed other MALTs will be critical for understanding their broader

relevance to barrier immunity. Defining the distinct functional roles of IgD-ME subsets and IgD$^+$ plasma cells will be essential to reveal how humoral immunity is tuned to the unique demands of mucosal environments and whether this can be harnessed in mucosal vaccination strategies.

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