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INSIGHTS

Allergic airway reactions rewired by PI3Kδ mutation

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In this issue of *JEM*, Golec et al. (https://doi.org/10.1084/jem.20252154) report that a mutation of PI-3 kinase underlying activated PI3K δ syndrome (APDS) impairs type 2 immunity. Surprisingly, mice with this mutation have disordered responses to allergic insults, with enhanced production of IFN-γ and a decrease in Th2 cytokines.

The report by Golec et al. in this issue of *JEM* (Golec et al., 2026) examines the impact of a gain-of-function mutation in the signaling protein phosphatidylinositol 3-kinase δ (PI3Kδ) on T helper 2 (Th2) biology *in vivo*. PI3Ks are enzymes that generate second messengers that regulate cellular proliferation, survival, and differentiation, among other functions (Vanhaesebroeck et al., 2012; Madsen and Vanhaesebroeck, 2020). One of these second messengers, phosphatidylinositol trisphosphate, can regulate downstream signaling targets like Akt and Itk via the pleckstrin homology (PH) domains in these proteins. There are different classes of PI3K that have diverse means of regulation, determined in part by what types of receptors lead to their activation (Vanhaesebroeck et al., 2012). The class IA PI3Ks are heterodimers, comprising a catalytic subunit (p110α, p110β, or p110δ) and a regulatory subunit. Antigen receptors on T and B lymphocytes are primarily coupled to class IA PI3Kδ, so named because it includes the δ catalytic isoform (Okkenhaug and Fruman, 2010; Murter and Kane, 2020). PI3Kδ can also be activated by other receptors that are important for lymphocyte activation and proliferation, such as the costimulatory receptors CD28 and CD19, and the receptor for IL-2.

Previous studies demonstrated that the PI3Kδ mutation studied here results in enhanced kinase activity. This mutation and several other activating mutations in PI3Kδ were initially described in patients with the disorder known as type 1 activated PI3K δ syndrome (APDS) or p110δ-activating mutation causing senescent T cells, lymphadenopathy, and immunodeficiency (Angulo et al., 2013; Lucas et al., 2014). APDS presentation commonly includes hyperplasia of the spleen and lymph nodes, along with recurrent respiratory infections and bronchiectasis (Tangye et al., 2019; Ijspeert et al., 2024). The current study of Golec et al. takes advantage of a mouse model, developed by this group and others in parallel, in which the most common p110δ mutation associated with APDS ($p110\delta^{E1020K}$) is engineered into the genome of C57BL/6 mice (Avery et al., 2018; Preite et al., 2018; Stark et al., 2018; Wray-Dutra et al., 2018). This model has been shown to recapitulate most features of APDS, with one advantage being that immune phenotypes can be studied in a uniform genetic background and in the absence of the chronic infections commonly seen in patients.

Several groups previously studied the effects of the $p110\delta^{E1020K}$ allele on T cell function, both *in vitro* and *in vivo*, demonstrating that it leads to enhanced activation and differentiation of $CD4^+$ and $CD8^+$ T cells (Preite et al., 2019; Tangye et al., 2019; Cannons et al., 2021; Ijspeert et al., 2024). Although these effects are associated with splenomegaly, lymphadenopathy, and autoimmunity, they somewhat paradoxically also lead to compromised T cell–mediated immunity, due at least in part to senescence and/or exhaustion of T cells. B cell development and function are also altered in patients with APDS-causing p110δ mutations, with increased levels of IgM, decreased IgG and IgA, and susceptibility to some infections. Much less is known about how activating mutations in p110δ affect type 2 immunity and Th2 ($CD4^+$) T cells, especially *in vivo*, although it has been shown that production of Th2 cytokines like IL-4 is enhanced in Th2-polarized APDS T cells, at least *in vitro* (Bier et al., 2019; Preite et al., 2019).

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To determine how $p110\delta^{E1020K}$ affects Th2 biology *in vivo*, Golec et al. started with a well-established house dust mite (HDM) model of allergic asthma (and confirmed some of their findings with another type 2 airway inflammation model) (Golec et al., 2026). Thus, they found that type 2 immunity and differentiation of $CD4^+$ T cells to a Th2 lineage are seriously impaired in $p110\delta^{E1020K}$ mice, leading to reductions in airway hyperreactivity and production of type 2–associated cytokines (IL-4, etc.) and antibodies (IgE), relative to WT mice exposed to HDM. Interestingly, however, there

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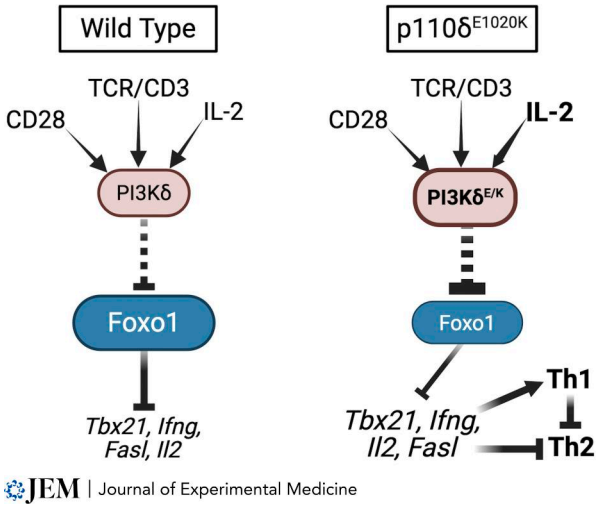

Simplified model for pathways controlling dysregulated Th2 differentiation in p110δ^{E1020K} CD4^{+} T cells. Created in BioRender. Kane, L. (2025) https://BioRender.com/i3can49.

was still significant inflammation in the lungs of the p110δ^{E1020K} mice, with greater numbers of CD4^{+} T cells and neutrophils but fewer eosinophils. The authors were able to determine that this shift was due, at least in part, to enhanced production of IFN-γ and IL-2 under otherwise Th2-inducing conditions *in vivo*. Looking further at the underlying mechanisms with transcriptional and epigenetic approaches, they determined that the transcription factor Foxo1 is a key linchpin for the altered cytokine production. Thus, PI3K, via the serine/threonine kinase Akt, leads to phosphorylation of the transcription factor Foxo1, leading to its exclusion from the nucleus and degradation in the cytoplasm. Foxo1 is a key enforcer of quiescence and an inhibitor of differentiation in the T cell lineage. The authors show, through enforced expression of phosphorylation-resistant (i.e., constitutively active) Foxo1 and Crispr/Cas9-mediated knockout of Foxo1 in WT and p110δ^{E1020K} CD4^{+} T cells, that phosphorylation and inhibition of Foxo1 activity are critical for the shift in CD4^{+} T cell phenotype under conditions that would normally favor Th2 differentiation.

Another interesting mechanistic finding of Golec et al. is that increased Akt-mediated phosphorylation and inhibition of Foxo1 in activated p110δ^{E1020K} CD4^{+} T cells leads to enhanced expression of *Fasl*, which encodes FasL, the ligand for the Fas receptor. Although signaling through Fas is most commonly associated with apoptosis, under some circumstances, Fas can transduce signals that support T cell differentiation, at least in part via Akt activation (Klebanoff et al., 2016). Thus, Golec et al. show that knockdown of either Fas or FasL is sufficient to dampen the enhanced IFN-γ production of p110δ^{E1020K} CD4^{+} T cells, suggesting that this acts as an important feed-forward loop in APDS. It remains to be determined how this pathway contributes to the APDS phenotype *in vivo*, and whether interference with it could help to ameliorate the effects of APDS.

Although APDS is characterized by dysregulated inflammation, it is not typically associated with asthma (Tangye et al., 2019; Ijspeert et al., 2024). Interestingly, the study of Golec et al. suggests that conditions that lead to higher levels of PI3K activity may either predispose to Th2-low asthmatic endotypes or even be protective. Conversely, it is possible that hypomorphic alleles of PI3K (or downstream effectors like Akt) predispose to Th2-high asthma. This is potentially important because different asthma endotypes respond to different treatments. For example, the shift in p110δ^{E1020K} mice to a more neutrophilic type of T cell–driven lung inflammation is reminiscent of some similar clinical presentations of asthma that are more resistant to treatment with corticosteroids (Lambrecht et al., 2025). One factor limiting the utility of such comparisons is the nature of the mouse models of asthma. Thus, while these models can reproduce many aspects of the disease, including the roles of various immune cell types in the type 2 immune response, they are less reliable at capturing the more chronic physiological changes that occur in the lung, such as airway hyper-responsiveness (Aun et al., 2017). Given the findings of Golec et al., it will be interesting to determine whether the p110δ^{E1020K} allele impacts the development of disease in other models for type 2 inflammation in other tissues, such as the gut and skin.

Despite the dramatic shift to a more neutrophilic infiltration, Golec et al. actually observed a decrease in IL-17A production by lung-infiltrating CD4^{+} T cells from the p110δ^{E1020K} mice. Although another previous *in vitro* study from this group suggested that there was no difference in IL-17A production by murine p110δ^{E1020K} CD4^{+} T cells (Preite et al., 2019), a separate study showed that IL-17A was reduced in both mouse and human T cells expressing gain-of-function PI3K (Bier et al., 2019). Another important factor for neutrophil recruitment, IL-8/CXCL8, was not examined by Golec et al., although they did find that the mutant CD4^{+} T cells produced more TNF. It is thus still unclear what factors are responsible for the increased neutrophilic infiltrations observed in the lungs of p110δ^{E1020K} mice.

This study clearly demonstrates a cell-intrinsic function for PI3Kδ in regulating helper T cell differentiation toward Th1 vs. Th2 cell fates. Nonetheless, it is important to keep in mind that the mutated isoform of PI3K is expressed in multiple other hematopoietic lineage cells, including B cells, innate-like lymphoid cells, and innate myeloid lineage cells. Indeed, a previous study by Bier et al. demonstrated, using bone marrow chimeras, that there are some cell-extrinsic effects of PI3K gain-of-function on CD4^{+} T cell differentiation (Bier et al., 2019). In this vein, the p110δ^{E1020K} mutation is present throughout lymphocyte development, so some effects of the mutation during priming and/or recall responses may be obscured by compensatory mechanisms during lymphocyte selection in the bone marrow or thymus. To further address these issues, future studies could leverage a Cre-inducible version of the p110δ^{E1020K} allele previously described by Rawlings and colleagues (Wray-Dutra et al., 2018).

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