European Journal of Immunology

WILEY-VCH

European Journal of Immunology
Basic • Clinical • Translational

REVIEW

Highlights-reviews

Multifaceted Role of ILCs in Metabolic Adaptations: From Adult to Neonate

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Received: 25 May 2025 | **Revised:** 22 October 2025 | **Accepted:** 23 October 2025

Keywords: adult | innate lymphoid cells | metabolic adaptation | neonate | tissue function

ABSTRACT

In the almost two decades since their discovery, innate lymphoid cells (ILCs) have received considerable attention for their roles in immune defense and tissue repair. However, a growing body of evidence now highlights a broader functional spectrum, positioning ILCs as key integrators of environmental cues that support tissue-specific metabolic adaptation. These insights challenge traditional immune-centric paradigms, suggesting that ILCs also contribute to core physiological functions of tissues. In this review, we discuss emerging roles for ILCs in the regulation of energy homeostasis during adulthood, including nutrient sensing, uptake, storage, and utilization. We further examine how these functions may be shaped during the neonatal period, a critical window of developmental transitions that coincides with the establishment of ILC tissue residency. We suggest that ILCs may act as early regulators of postnatal metabolic adaptation, playing a fundamental role in the physiological maturation of tissues after birth.

1 | Introduction

Innate Lymphoid Cells (ILCs) are tissue-resident immune cells well known to participate in the organism's defense and repair mechanisms. As key players of the innate immune system, they lack rearranged adaptive antigen receptors and are characterized by a prompt reactivity to environmental signals released by neighboring cells, microbial- or food-derived products. They are essential actors of inflammatory responses, maintaining a balance between defense and tolerance. Different ILC subtypes, classified as group 1 ILCs, group 2 ILCs, and group 3 ILCs, have been described based on their main transcription factor (TF) expression and cytokine production. Group 1 ILCs, abundant in the liver, are mainly involved in intracellular pathogen defense and tumor immunosurveillance. Sentinels of the antiviral immune responses at the infection site, they comprise cytotoxic natural killer (NK) cells and ILC1s, characterized by T-BET expression and IFN-γ-production. ILC2s, specialized in extracellular parasite defense, are highly represented at mucosal sites like the intestine, the lung, and the skin. They are characterized by GATA-binding protein 3 (GATA3) expression and interleukin (IL)-5 and IL-13 production. Group 3 ILCs express RORγt as their master TF and produce IL-22, IL-17, and lymphotoxins (LTα1β2 or LTα3), key cytokines for gut barrier homeostasis, including lymphoid tissue organogenesis and microbiota balance.

Innate lymphoid cells contribute to immune defense and tissue homeostasis through distinct, subset-specific functions. ILC1s, although rare at steady state, can expand and produce IFN-γ as observed during the early phases of MCMV infection, aiding pathogen clearance [1]. While they serve as the main viral sentinels in their tissue of residency, their increased number under chronic inflammation can be detrimental for the host. In the intestine of Crohn's disease patients or in the adipose

tissue of patients with type 2 diabetes, ILC1s can drive fibrosis through TGF-β1-mediated pathways, resulting in tissue damage and dysfunction [2, 3]. ILC2s respond to epithelial cytokines like IL-25, IL-33, and TSLP by producing IL-5 and IL-13, promoting mucus secretion and epithelial regeneration [4–8]. These functions are regulated through reciprocal interactions with tuft cells, and further support eosinophil recruitment and type 2-mediated tissue repair [9, 10]. ILC3s play a key role in maintaining microbiota balance and epithelial barrier integrity via IL-22 production, enhancing antimicrobial defenses and stem cell repair [11, 12]. They also support immune tolerance and IgA responses, bridging innate and adaptive immunity [9–13].

In this review, we will not focus on the immune and repair functions of ILCs, but we will rather highlight recent findings on the involvement of ILCs in metabolic health during adult life. We explore how this expanding role is reshaping our understanding of innate lymphoid cells, not merely as defenders against external threats or keepers of tissue homeostasis, but as integral components of physiology that regulate key functions within the organs they inhabit. Finally, we discuss and speculate about the importance of ILCs in orchestrating metabolic adaptations during postnatal development, a critical period characterized by rapid physiological changes in response to a dynamic and novel environment.

2 | Part I: ILCs in Adult Metabolic Homeostasis

2.1 | I-a: ILC Functions are Regulated by Metabolic Cues and Nutritional Inputs

The capacity of ILCs to secrete effector cytokines is tightly regulated by their intrinsic metabolism. Similar to adaptive lymphocytes [14], ILC function requires metabolic adaptation that provides the energetic supply necessary for effector activity.

For example, ILC3s rely on mTOR signaling, which activates mitochondrial metabolism and drives the production of reactive oxygen species (ROS). These ROS stabilize HIF1α, enabling cells to extract energy from glycolysis. This metabolic program is required for the expression of IL-17 and IL-22 and, most importantly, for the induction of *Rorc*, the key transcription factor for ILC3 development and function. This phenotype has been confirmed in human ILC3s isolated from tonsils [15].

Human ILC2s are also under strong metabolic regulation. At steady state, circulating ILC2s show robust oxidative phosphorylation (OXPHOS) activity, which depends on their ability to upregulate transporters and absorb amino acids such as valine, isoleucine, and arginine. These processes regulate ILC2 proliferation as well as mTOR activation. Upon activation, however, ILC2s shift toward glycolysis to sustain their functions, a process associated with increased glucose uptake that supports IL-13 production [16].

In mice, such metabolic regulation of ILC2s plays a critical role in responses to pathological stimuli such as lung inflammation. Ablation of *Arg1* in ILC2s results in reduced allergic inflammation, showing that metabolic activation of ILC2s is required to drive tissue responses to external cues [17]. The importance of arginase in ILC2 biology is also reflected in their strong expression of the amino acid transporter *Slc7a8*, which allows the uptake of arginine and other large neutral amino acids [18].

Nutrient availability seems to be an important driver of ILC function and is required to support immune defense against bacteria, helminths, and viruses. ILCs express nutrient sensors for dietary metabolites such as vitamin A and tryptophan derivatives. In mice, vitamin A deficiency results in loss of ILC3s and reduced IL-22 expression, leading to increased susceptibility to bacterial infection. These findings demonstrate that retinoic acid (a vitamin A metabolite) is required for maintaining the intestinal barrier. In this context, ILC2s become activated and secrete higher levels of IL-5 and IL-13, suggesting a compensatory mechanism to sustain tissue integrity. Type 2 cytokines promote mucus secretion, IgA transport into the lumen, and helminth protection, thereby reinforcing barrier defenses [19].

The functional balance between ILC2s and ILC3s is also regulated by tryptophan metabolism. The aryl hydrocarbon receptor (AHR), which senses dietary tryptophan derivatives (e.g., glucosinolates), is required to maintain equilibrium between these subsets. Diets depleted of phytochemicals such as derivatives of glucosinolates lead to loss of ILC3s and increased susceptibility to bacterial infection [20]. Conversely, AHR activation in ILC2s downregulates IL-13 and IL-5 production through mechanisms involving Gfi1 and epigenetic regulation of type 2 cytokine loci [21]. ILC1s are likewise influenced by dietary AHR ligands. In mice, AHR deficiency results in reduced NK cell numbers in the liver and impaired immune memory in hapten-based models.

Together, these findings highlight that ILCs are tightly regulated by their nutritional environment, with dietary signals shaping their intrinsic metabolism. Further studies are even needed to complement the impact of metabolism on ILC plasticity, an area of research opening for new mechanistic insights with potential for clinical applications.

In the following section, we explore how ILC subsets, in turn, contribute to the regulation of nutrient availability and systemic metabolic homeostasis.

2.2 | I-b: ILCs in the Regulation of Nutrient Uptake and Feeding Responses

Growing evidence indicates that ILCs play roles beyond tissue defense and repair—they also support tissue adaptation to environmental changes such as dietary shifts and feeding patterns. Feeding is a life-sustaining process that requires coordinated responses from multiple organ systems. The gastrointestinal tract plays a central role, not only by absorbing nutrients but also by sensing nutrient intake and relaying this information to the brain, the enteric nervous system (ENS), and the liver. Recent evidence indicates that this complex physiological process is partly regulated by ILCs.

Following food intake, cholecystokinin rapidly induces the release of vasoactive intestinal peptide (VIP), which modulates

both ILC2s and ILC3s by stimulating IL-13 and IL-22 production, respectively. These cytokines recruit eosinophils and provide protection against *Trichuris muris* and *Citrobacter rodentium*, the latter of which is highly sensitive to ILC3-derived IL-22 [22–24]. Together, these findings suggest that feeding elicits immune responses that preemptively protect against foodborne pathogens, an evolutionarily efficient mechanism.

Conversely, another study revealed that VIP signaling can instead suppress IL-22 production upon feeding, thereby increasing susceptibility to pathogens while at the same time enhancing nutrient absorption by regulating expression of intestinal epithelial transporters for major macronutrients [25]. Indeed, ILC3-derived IL-22 has been shown to regulate lipid uptake in IECs through the control of CD36 (fatty acid transporter) and NPC1L1 (cholesterol transporter). Similarly, glucose transporters such as SLC2A2 and SLC5A1 appear to be regulated by IL-22. This reveals an overlapping pathway in which nutrient absorption and immune defense are co-regulated. These dual observations suggest a trade-off between feeding and immunity. Reconciling these two models will require further study, possibly accounting for additional regulatory factors that influence ILC3-mediated nutrient uptake, such as the circadian rhythm.

Both ILC2s and ILC3s are subjected to circadian regulation [26–28]. In the gut, IL-13 expression by ILC2s follows a day-night rhythm dictated by feeding patterns. As a result, eosinophil accumulation in the intestine also follows this temporal pattern. Eosinophils themselves support homeostasis by targeting bacteria and modulating local adaptive responses [29]. ILC3s undergo similar circadian regulation: studies show that IL-22 production oscillates with the day-night cycle, dictating rhythmic shifts in IEC transcriptional profiles. For example, CD36, the fatty acid transporter, is expressed in a circadian manner under ILC3 control. Since mouse feeding behaviors also follow circadian rhythms, these findings suggest ILC3s regulate IEC nutrient absorption daily. While the precise upstream signals remain incompletely defined, evidence suggests that the central nervous system and light-based entrainment may contribute. Local gut sentinel cells, such as tuft cells or enterochromaffin cells, may also fine-tune these ILC circadian responses [30].

Beyond acute feeding responses, ILCs also mediate adaptation to long-term dietary changes. In mice fed carbohydrate-rich versus protein-rich diets, ILC3-derived IL-22 drove large-scale transcriptional remodeling in IECs, enabling adaptation from one nutrient environment to another. For instance, under a protein-rich diet, IL-22 suppressed carbohydrate utilization programs in IECs, thereby modulating the uptake and metabolism of complex sugars by enterocytes [31]. A similar observation was made in mice receiving a high-fat diet for a short period of time, inhibiting IL-22 production by ILC3, resulting in loss of epithelial barrier function [32].

Overall, these findings emphasize that regulation of ILC2 and ILC3 activity is essential not only to maintain tissue and systemic homeostasis but also to ensure nutrient availability that meets the body's energetic demands [31, 32].

2.3 | I-c: Impact of ILC Function in Metabolic Health

ILCs appear to be essential for regulating digestive function in the intestinal tract, with significant implications for metabolic health. Several studies have demonstrated that impaired intestinal type 3 immunity, particularly involving ILC3s, is associated with metabolic dysregulation, including type 2 diabetes, in both murine models of obesity and human cohorts [33, 34]. The mechanisms at play are complex and involve, in part, IL-22-mediated maintenance of the local gut barrier and control of endotoxemia, which ultimately contribute to improved peripheral metabolic functions, including insulin sensitivity and lipid metabolism. Indeed, ILCs appear to play a key role in regulating glucose homeostasis during high-fat diet (HFD) conditions [32]. Mice lacking all lymphocytes require less insulin to regulate circulating glucose levels, whereas mice possessing only ILCs need higher insulin levels to achieve the same effect. In recombination activating gene (RAG)-deficient mice, lacking T and B cells, ILC3s are overactivated, suggesting that ILC activation influences glucose metabolism during HFD. Transfer experiments further demonstrated that both ILC2s and ILC3s can regulate glucose metabolism in an activation-dependent manner that requires IL-2 [35].

In the context of a normal diet, intestinal ILC2s appear to be central regulators of glucose homeostasis. During overnight fasting, ILC2s become activated and migrate to the pancreas. Their expression of IL-5 and IL-13 directly regulates glucagon secretion by pancreatic alpha cells. Intestinal ILC2s are regulated by the sympathetic enteric nervous system under these fasting conditions. In the absence of β-adrenergic receptors, ILC2s lose their ability to migrate to the pancreas, resulting in impaired regulation of glucose homeostasis [36]. In the liver, ILC2s also play a fundamental role in the regulation of blood glucose levels. Recent data show that IL-13-derived ILC2s secretion suppresses hepatocytes' neoglucogenesis to promote glucose release from hepatic glycogen stores upon IL-33 treatment [37].

Due to their antiviral capacity, resident ILC1s are more abundant in the liver than other ILCs. Recent single-cell sequencing data in mice and humans revealed a "liver-type-ILC1" with distinct phenotypic and functional features as compared with NK cells or other ILCs [38]. While liver ILC1-derived IFN-γ secretion is detrimental in an acute inflammatory context such as viral hepatitis, their chronic activation is linked with liver alcoholic steatosis and fibrosis [39]. In high-fat-diet-fed *Rag1*$^{-/-}$ mice, anti-IL-12-mediated inhibition of adipose tissue ILC1 proliferation improved insulin sensitivity and reduced hepatic steatosis [3]. The complex interplay between the immune system and metabolic processes extends beyond the inflammatory state.

Thus, in adults, ILCs appear to play a fundamental role in the body's adaptation to feeding, whether locally in the intestine after nutrient intake, or in response to long-term changes in diet and overall metabolic state. These recent discoveries highlight that ILCs, and more broadly the immune system, are essential players in the physiological regulation of body function Figure 1.

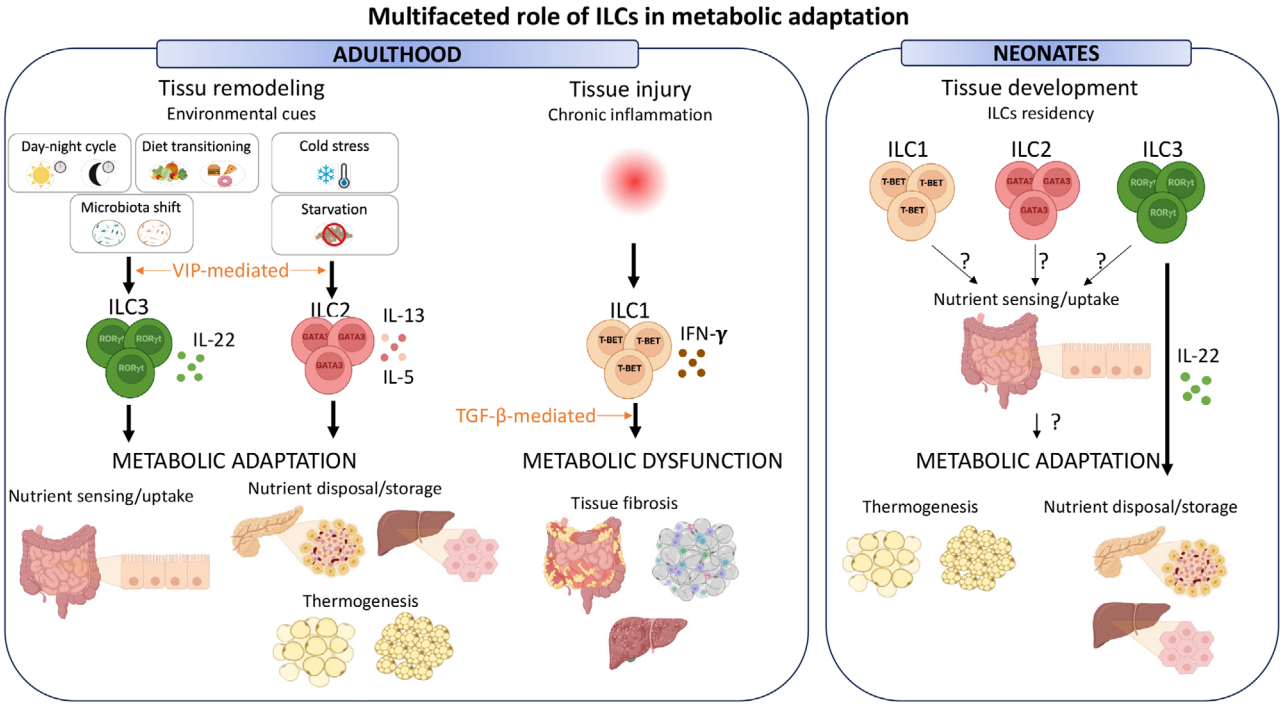

FIGURE 1 | Schematic representation illustrating the roles of ILCs in metabolic adaptation, both in the adult and neonatal period. In adulthood, ILC2s and ILC3s react to different environmental cues to sustain tissue remodeling in favor of metabolic adaptation, including key processes such as nutrient sensing, uptake or storage, and thermogenesis, with VIP signaling known as an upstream molecule driving their activation. Conversely, chronic ILC1s activity leads to tissue injury and metabolic dysfunction, with downstream TGF-ß-mediated signaling involved in tissue fibrosis. In neonates, a developmental period of intense changes, ILCs establish their niche of tissue residency. At this time, the neonatal intestine is known to be a central integrator of environmental signals, such as those derived from the sequential waves of food and microbiota diversification. The high energy demand of this period required the parallel establishment of the neonatal autonomous nutritional homeostasis. In line with what has already been explored in adults, we question the role of neonatal ILCs in the metabolic adaptation they participate in, opening toward future discoveries in the field.

3 | Part II: ILCs in Neonatal Metabolic Homeostasis

A deeper understanding of ILCs' role in tissue physiology is positioning tissue resident ILCs as pivotal players guiding tissue adaptation, with broader implications for metabolic homeostasis. In this context, research investigating ILC involvement during the neonatal period is of particular interest. This developmental window is characterized by high energy demands and rapid adaptation to the evolving environment, occurring in parallel with the establishment of ILC niches.

3.1 | II-a: Birth and Neonatal Metabolic Adaptation

Birth marks a profound physiological shift, triggering adaptations essential for neonatal survival. In mice, these adaptations continue throughout the neonatal period, a critical window characterized by rapid growth and metabolic transitions. As the newborn shifts from a stable intrauterine environment, where nutrients are continuously delivered via the placenta, to the external world, it faces fluctuating nutrient availability, temperature changes, and microbial colonization [40]. Navigating this transition requires precise metabolic regulation to fuel growth and maintain homeostasis.

Perinatal metabolism is shaped by intrinsic genetic and hormonal programs, such as glucocorticoids and thyroid hormones, which orchestrate tissue-specific development. It is also influenced by external factors, including diet, microbiota, and ambient temperature, collectively referred to as the exposome. In utero, the fetus relies on a continuous and tightly regulated nutrient supply: initially through uterine secretions (histiotrophic nutrition) that support organogenesis under low oxygen, and later via placental blood flow (hemotrophic nutrition) that enables oxidative metabolism [41]. At birth, this steady supply ends abruptly, and neonates must transition to an intermittent feeding pattern, requiring rapid metabolic adaptation to ensure energy homeostasis. In mice, the initial 3–4 h postbirth represents a fasting phase during which liver glycogenolysis provides glucose [40, 42]. Within 24 h, the intestine ramps up its absorptive capacity, allowing nutrient uptake from maternal milk and triggering a metabolic shift in the liver from gluconeogenesis to lipid utilization. This transition is accompanied by profound transcriptional reprogramming in hepatocytes, with early expression of genes involved in gluconeogenesis progressively replaced by those supporting β-oxidation and lipid metabolism [43].

In parallel, adipose tissue undergoes rapid postnatal remodeling. Neonatal fat expansion is primarily fueled by lipids from maternal milk and includes three types of adipose tissue: white (WAT), brown (BAT), and beige [44]. BAT, critical for thermogenesis,

compensates for environmental temperature fluctuations. Notably, WAT transiently expresses UCP1, a thermogenic marker, peaking at weaning before declining. This transient thermogenic phase is developmentally regulated and influenced by maternal diet, neonatal sex, and the IL-33/ST2 immune axis, with lasting impacts on adipose tissue function [45].

Among all organs, the small intestine emerges as a central regulator of neonatal metabolic adaptation. It coordinates nutrient absorption, shaping the development of distal metabolic tissues such as the liver and adipose tissue. At birth, intestinal epithelial cells express a milk-adapted transcriptional program driven by *Prdm1*. Loss of *Prdm1* leads to premature maturation, with reduced expression of milk-digesting enzymes and early activation of carbohydrate-processing genes, resulting in impaired growth and liver dysfunction [46, 48]. This highlights the essential role of intestinal maturation in systemic metabolic adaptation.

Microbial colonization further refines intestinal function. Early-life shifts in microbiota composition influence host nutrient processing and immune development [49]. Microbiota-derived metabolites, such as short-chain fatty acids (SCFAs), serve both as energy sources and regulatory signals for intestinal and immune cells. Disruption of this process, for example, by antibiotics, impairs epithelial cell survival and damages the intestinal stem cell niche [50]. The "weaning reaction", a transient immune activation in the small intestine, coincides with microbial maturation and helps establish long-term immune tolerance [51]. Interestingly, the liver contributes to microbiota selection through its metabolic output, creating a symbiotic loop with the intestine that is essential for proper postnatal development [52].

Together, these interconnected processes: metabolic reprogramming, epithelial maturation, microbiota colonization, and immune education, underscore the centrality of the small intestine in orchestrating neonatal adaptation in this developmental window. This raises an important question: are ILCs active players in coordinating these transitions, beyond their canonical immune roles?

3.2 | II-b: The Immune System and Neonatal Metabolic Adaptation: Focus on ILCs

The role of the immune system in regulating metabolic functions during the neonatal period, as well as its role in the newborn's adaptation to its environment, is not yet well understood. At birth, the immune system is highly dynamic, especially the innate immune system, which develops in distinct waves. Immune cells present during the neonatal period originate from embryonic and fetal stages and are gradually replaced or accompanied by newly bone marrow-derived immune cells that emerge after birth [53]. Innate lymphoid cells (ILCs) are no exception to this developmental pattern. Similar to macrophages, ILCs derive from different ontogenic waves, starting in the fetal liver, followed by the expansion of postnatal ILCs, which are eventually partially replaced by adult cells [40–54]. Thus, neonatal ILCs might have specialized functions required to sustain postnatal tissue adaptation.

3.2.1 | Role of ILCs in the Neonatal Period

The role of ILCs during the neonatal period is less studied than in adults, but evidence suggests they play a critical role in defense against pathogens and tissue remodeling. ILC1s are more abundant in the liver, but are also found in the intestine, salivary glands, and lungs. The role of ILC1 in the neonatal period has been associated with immune surveillance restricting early onset of viral infections, thus preserving the neonate from adverse outcomes and developmental sequelae [1, 54].

In the intestine, ILC2s reach their peak activation at weaning, marking the end of the postnatal developmental period [53, 55, 56]. Their activation is linked to the colonization of commensal parasites, which triggers IL-25 production by tuft cells, a process dependent on the transition from milk to solid food [57]. Activation during the preweaning period appears to be important for tissue development. In the lungs, neonatal ILC2 activation is also associated with tissue maturation, as IL-33 derived from bronchial branching drives this process. Functionally, neonatal ILC2s appear to be more active than their adult counterparts [58]. The expression of effector cytokines such as IL-13, IL-4, and IL-5 is higher in neonates compared with adults, and this is observed across all organs [55]. In vitro, neonatal ILC2s exhibit a greater capacity to produce these cytokines in response to IL-33. The activation of neonatal ILC2s during development is linked to morphological changes within the tissues they reside in [56]. Thus, given the key role of adult ILC2s in regulating metabolic adaptation, neonatal ILC2s might play an important role during this critical phase of life with lasting consequences. Indeed, overactivation of ILC2s results in increased length and thickness of intestinal tissue, which can be inhibited by antibiotic treatment from birth [57], indicating that ILC2s' activity must be tightly regulated. In models of infantile allergic inflammation, overactivation of neonatal ILC2s by IL-33 skews the lung's immune environment toward type 2 immunity, promoting allergic inflammation [57]. Similarly, during viral infections, activation of ILC2s via IL-25 leads to increased type 2 cytokine production, creating an environment prone to allergic inflammation later in life [58, 59].

Neonatal ILC3s are predominantly found in the intestine. At birth, ILC3s express low levels of IL-22, which gradually increase during postnatal development, peaking at weaning. This activation coincides with microbial colonization and is regulated by the colonization of particular bacteria, such as the segmented filamentous bacteria [60]. Neonatal ILC3s play a key role in protecting tissues from inflammatory insults. For example, in a model of necrotizing enterocolitis, IL-22 derived from neonatal ILC3s is essential for protecting tissues from bacterial overgrowth [61], in a process that is regulated by FXR in intestinal epithelial cells [62]. Similarly, in cases of infantile rotavirus infection, IL-22 from ILC3s, in synergy with interferon lambda, promotes a robust antiviral response in the intestinal epithelium [63]. Thus, high ILC3 activity early in life prevents microbial damage by pathogenic agents, a function that persists into adulthood.

3.2.2 | 2 Do Neonatal ILCs Play a Role in Metabolic Adaptation?

The role of neonatal ILCs in the metabolic adaptation of tissues during the postnatal period remains unclear. However, given the significant role of adult ILCs in regulating the physiological functions of the tissues they inhabit, it is likely that ILCs also participate in the metabolic adaptation of neonates.

After birth, the neonatal liver transitions from glycogenolysis to fatty acid oxidation and gluconeogenesis after milk suckling [42]. Glucose homeostasis impairment at this period represents a significant risk, especially regarding brain development. How neonatal ILC1s, the predominant ILC subtype found in the liver, contribute to this functional adaptation is currently not understood.

In adipose tissue, the physiological browning of fat during ontogeny depends on the IL-33/ST2 axis, but unlike in adults, this process is independent of ILC2s [45]. Although neonatal ILC2s produce higher levels of cytokines than adult ILC2s, their role in regulating UCP1 in adipose tissue during postnatal development appears to differ. This suggests that the physiological roles of neonatal and adult ILC2s in adipose tissue are distinct. In adults, ILC2s have been shown to regulate glucose metabolism during fasting by migrating from the small intestine to the pancreas and regulating glucagon production [36]. Neonates undergo a significant metabolic transition after birth, which kickstarts physiological processes in metabolic organs. While the role of ILC2s in this transition remains unclear, it is not yet known whether fetal-derived or newly expanded neonatal ILC2s contribute to glucose regulation during this critical window.

In contrast, ILC3s appear to play a more prominent role in neonatal glucose metabolism. In a mouse model overexpressing IL-23, a myeloid-derived cytokine that activates ILC3s, mice exhibited a stunting phenotype culminating in early death, underscoring the impact of dysregulated ILC3 activity on metabolic homeostasis. This phenotype was associated with heightened ILC3 activation and shown to be IL-22-dependent, suggesting a mechanistic link between ILC3-derived cytokines and impaired neonatal growth [64]. In IL-22 knockout mice, digestive and absorptive functions in the intestine were disrupted, leading to increased fat in the stool of suckling mice. In the pancreas, IL-22 appears to regulate the expression of key enzymes required for lipid digestion from maternal milk. Further in vitro studies showed that IL-22 can regulate gene expression in neonatal pancreatic cells [64]. In adults, IL-22 regulates lipid absorption and overall metabolism, raising the question of whether ILC3s are important for the metabolic transition that occurs during the postnatal period. In adults, IL22-expression by ILC3s is regulated by $\gamma\delta$ T cells, controlling the transcriptional programming of intestinal epithelial cells (IECs), including the expression of digestive enzymes [31]. The role of ILC3s in shaping the intestinal transcriptome during development and its impact on body metabolism remains poorly understood.

4 | Conclusion

The intestine is a central organ driving the metabolic adaptation of the body. By regulating nutrient intake and microbial composition, intestinal cells have a major systemic impact on the liver, the pancreas, and the adipose tissue. ILCs, along with macrophages, are the primary immune cells present in the intestine at birth, raising the question of their role in postnatal adaptation. In recent years, new experimental models for specifically depleting ILCs have been developed, and datasets comparing neonatal and adult ILCs have been generated. It will be fascinating to see how these tools and data are used to further understand the physiological functions of ILCs during postnatal development. In the era of spatial transcriptomics and proteomics, it will be particularly interesting to study how the absence of ILCs affects the tissue niches they inhabit and how this impacts the metabolic adaptation of neonates and their health later in life.

Author Contributions

Fabian Guendel and Emelyne Lécuyer contributed equally to this work.

Acknowledgments

We thank the Microenvironment & Immunity Unit lab and the Physiopathology of Nutritional Adaptations lab. This work was supported by a Walter Benjamin fellowship from the Deutsche Forschungsgemeinschaft (F. Guendel) and the Division for Human Nutrition and Food Safety of the French National Research Institute for Agriculture, Food and Environment (INRAE) (E. Lécuyer), as well as the "Région Pays de la Loire" in the frame of "PULSAR" and "Étoiles Montantes" programs (E. Lécuyer).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No new data were generated or analyzed in this review.

Peer Review

The peer review history for this article is available at https://doi.org/10.1002/eji.70088.

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