the first week of life that cannot be predicted from cord blood samples.

Topological data analysis also confirmed that cord blood and postnatal peripheral blood immune samples fall into distinct clusters. The immune systems of term and preterm infants also fell into two distinct branches in the first week of life; strikingly, the immune systems began to converge after birth and an intermixed group was observed by 3 months. The authors found that the relative abundances of 10 key immune cell populations in cord blood were completely heterogeneous but then began to show a stereotypic change in composition, characterized by a gradual reduction in neutrophils after birth and a concomitant increase in $CD4^+$ and $CD8^+$ T cell proportions. This convergence occurred even though some preterm children remained in hospital for the entire study period, and the immune systems of children born by vaginal or caesarean delivery were also found to converge by 3 months.

Further analyses suggested a key role for microbes in driving these stereotypic changes in the immune system. Therefore, the authors conducted ribosomal RNA profiling of faecal samples from children in the cohort to better understand these host–microbe interactions. They found that the diversity of the faecal microbiome increased over time after birth but was extremely low in some children, indicating dysbiosis. Notably, the children with early gut dysbiosis showed more inter-individual immune diversity compared with the children with a diverse microbiota. Therefore, interactions with microbes during the first few weeks of life seem to be crucial for driving stereotypic immune system development.

This study offers important new insights into the infant immune system and adds to our growing understanding of how the developing immune system is shaped by early-life microbial exposures.

Yvonne Bordon

ORIGINAL ARTICLE Olin, A. Stereotypic immune system development in newborn children. *Cell* **174**, 1277–1292 (2018)

but held in a poised state. It is therefore expected that TCR-mediated stimulation of mechanistic target of rapamycin complex 1 (mTORC1) leads to 4E-BP phosphorylation and activation of eIF4E-dependent translation.

Naive $CD4^+$ T cells stimulated in vitro accumulated GLUT1 and ACC1 proteins, associated with the recruitment of pre-existing *GLUT1* and *ACC1* mRNAs to actively translating polysomes. Furthermore, GLUT1 and ACC1 protein levels were affected to a greater extent by blocking translation than by blocking transcription. The results indicate that metabolic reprogramming during T cell activation is regulated by translation and that naive T cells repress the translation of key metabolic enzymes, such as ACC1.

In other cell types, the activity of ACC1 is inhibited by AMP-activated protein kinase (AMPK), which is activated by a high ATP to AMP ratio. However, the authors showed that the ATP to AMP ratio remains almost constant during T cell activation. Instead, translational derepression of ACC1 was shown to be regulated by the assembly of the eIF4F translation initiation complex downstream of TCR-mediated mTORC1 activation. Pharmacological inhibition of ACC1 reduced the activation-driven changes to glycolysis and respiration, as well as FAS, which suggests that ACC1 functions at an important metabolic node that regulates full metabolic reprogramming during T cell activation.

This study shows how the translation of pre-existing mRNAs enables the rapid metabolic switch required for activation of naive T cells. The authors suggest that this emphasis on translational control of FAS and associated pathways, rather than regulation through AMPK, should enable the rapid activation of mTORC1 that is required for full T cell activation, which would otherwise also be negatively regulated by AMPK.

Kirsty Minton

ORIGINAL ARTICLE Ricciardi, S. et al. The translational machinery of human $CD4^+$ T cells is poised for activation and controls the switch from quiescence to metabolic remodeling. *Cell Metab.* https://doi.org/10.1016/j.cmet.2018.08.009 (2018)

Journal club

AN AVIAN FOUNDATION FOR DOMINANT TOLERANCE

The discovery of regulatory T (T_{reg}) cells has transformed immunology. In the pre-T_{reg} cell era, our concept of immune tolerance was that it largely involved a developmental purge of autoreactivity. Today, we understand that immune tolerance is a dynamic and ongoing process.

Evidence for tolerogenic T cells dates back nearly 50 years. Unfortunately for the field, many of the early insights were tossed away together with the suppressor T cell model in the 1980s, a concept that collapsed under the weight of experimental artifacts. It took the labour of Shimon Sakaguchi and Fiona Powrie in the 1990s to bring T_{reg} cells back into a sceptical field; the concept did not gain full acceptance until landmark publications in 2003 from the labs of Sakaguchi, Alexander Rudensky and Fred Ramsdell that linked forkhead box protein P3 (FOXP3) expression to T_{reg} cell differentiation and function. Here, I would like to highlight a forgotten gem of the 1980s — two studies by Nicole Le Douarin and colleagues.

These landmark papers in 1987 and 1988 used an elegant microsurgical system of grafting the wing buds of quail onto embryonic chickens. The grafted quail wing bud would grow into a normal quail wing as the chick developed, but was quickly rejected after hatching. If, however, proto-thymus from the same quail was simultaneously grafted into the chick embryo, the adult chicken could survive for months with intact quail wings. These results clearly demonstrated the power of the thymic epithelium to induce cross-species tolerance in the developing T cells, even if only part of the thymic epithelium was of quail origin. The chick–quail marker system that had earlier been developed by Le Douarin, together with the unique structure of the chicken thymus, with 10–16 anatomically separated thymic lobes, was used to prove dominant tolerance: chicken T cells that developed in a chicken thymic lobe could be controlled by chicken T cells that developed in a quail thymic lobe.

These papers are a must read for students starting a career in T_{reg} cells. They show the virtue of patience in tool development and of understanding developmental biology. The studies showed the existence of a key cell type that took another 15 years to conclusively identify, and Le Douarin did so at a time when the work of many of her colleagues was sinking into the quagmire of the putative I–J suppressor region of the MHC.

Adrian Liston
VIB and University of Leuven, Leuven 3000, Belgium
e-mail: adrian.liston@vib.be

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ORIGINAL ARTICLES Ohki, H. et al. Tolerance induced by thymic epithelial grafts in birds. *Science* **237**, 1032–1035 (1987) | Ohki, H. et al. Implants of quail thymic epithelium generate permanent tolerance in embryonically constructed quail/chick chimeras. *Development* **104**, 619–630 (1988)
FURTHER READING Le Douarin, N. et al. Evidence for a thymus-dependent form of tolerance that is not based on elimination or anergy of reactive T cells. *Immunol. Rev.* **149**, 35–53 (1996)