Evolution of innate T cells

As a part of adaptive immunity, T cells identify and respond to products or antigens derived from pathogens. These antigens are seen by T cells in the form of short fragments or peptides presented by classical major histocompatibility (MHC) molecules. The selectivity of a T cell arises from the T cell receptor variant it displays at its surface, with an individual's T cell population containing a large number of different T cells each expressing a distinct T cell receptor variant. This results in an overall massive repertoire of different T cell receptor specificities. Besides these conventional T cells, there is a less well characterized subgroup of T cells that display limited or invariant sets of T cell receptors and that interact with different types of MHC or MHC-like molecules. These so called innate T cells (iT cells) are thought to be rapid responders to infections, recognizing via their invariant T cell receptors highly conserved pathogenic motifs presented by MHC-like molecules and providing defense in advance (or absence) of an adaptive immune response.

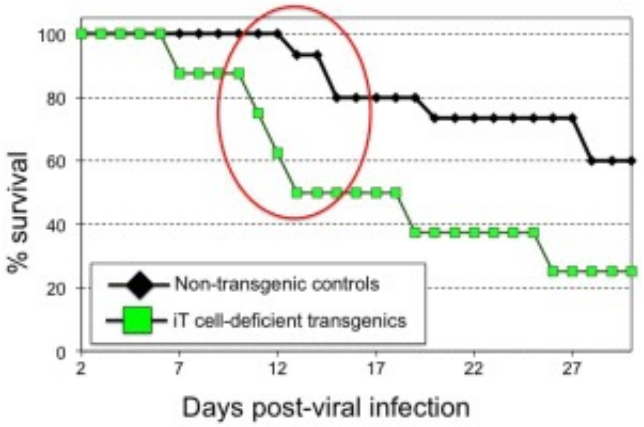

Fig. 1. Xenopus tadpoles lacking iT cells are more susceptible to viral infection. Transgenic tadpoles with silenced expression of the nonclassical MHC class I XNC10 preventing the development of the corresponding iT cell population (12 individuals) and non-transgenic siblings (15 individuals) were infected with the ranavirus FV3 (a natural amphibian pathogen). Survival was monitored daily for 30 days. The red circle emphasize the marked increase in mortality during early stages of infection by transgenic tadpoles deficient in iT cells.

Until recently, these iT cells were considered to be a minor specialized T cell populations confined to mammalian species. Our work has challenged this misconception, since we have shown that iT cells are present in the amphibian *Xenopus,* and thus are represented outside mammals. Focusing on one particular iT cell subset, we were able to show that as in mammals, iT cell development and function in *Xenopus* require interaction with specific MHC-like molecules. This was done by generating transgenic *Xenopus* tadpoles that had the MHC-like gene of interest specifically

silenced. As a result, these transgenic animals lacked the corresponding iT cell population. Importantly, these iT cell-deficient tadpoles were significantly more susceptible to viral infection, which provide evidence of the biological importance of these cells (Fig. 1).

Unlike mammalian embryos that develop in uterus and are protected by the maternal immune system, tadpoles develop outside of the maternal body in a pathogen rich environment and thus require the capacity to mount rapid immune responses to viruses and bacteria. However, the dilemma is that *Xenopus* tadpoles possess very few T cells and thus cannot generate a large repertoire of T cell receptor variants for specifically recognizing and responding to all potential pathogens.

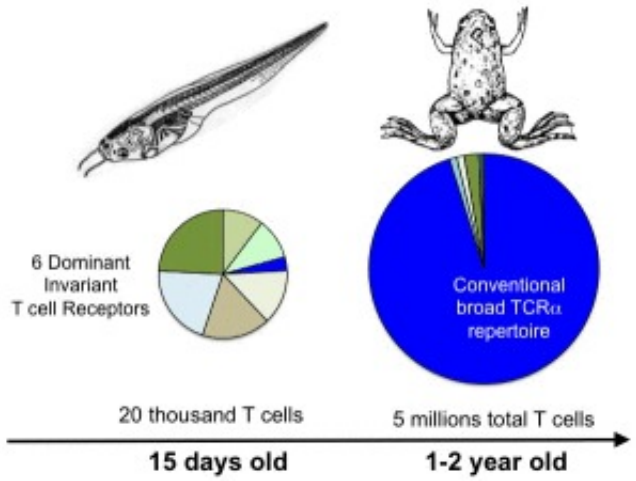

Fig. 2. Proposed preponderant iT cell-based immunity in Xenopus tadpoles compared to conventional T cell-based immunity in Xenopus adults. During early development in tadpole, MHC-like-mediated T cell differentiation is predominant resulting in a limited number of T cells (10–20,000 T cells) producing six unique overrepresented T cell receptor variants. After metamorphosis into adult frogs, conventional T cells expressing many different T cell receptor variants are becoming more numerous and replace the limited T cell receptor repertoire of iT cells.

As an adaptive alternative, we wondered whether tadpoles could overcome this obstacle by relying more heavily on distinct iT cell populations recognizing conserved pathogenic patterns and structures. To explore this possibility we sequenced a large number of T cell receptors from tadpoles. We expected to find a large repertoire of different T cell receptor variants. Surprisingly, the vast majority (80%) of the T cell receptor repertoire in tadpole was in fact dominated by only six T cell receptor variants, one of which being the invariant T cell receptor of the previously characterized iT cell population (Fig. 2).

This finding is of fundamental relevance because it suggests that tadpole *Xenopus*, in which there are very few T cells, different subsets of iT cells might recognize different groups or types of pathogens, and comprise the major arm of the T cell response. The predominance of iT cell expressing a few T cell receptor variants able to recognize distinct conserved or common pathogens would allow tadpoles to maximize the use of the small number of T cells they can differentiate and survive in a pathogen rich environment.

In summary, our work implies that iT cells are not ‘dead-end’ cells in mammals but rather are widely present in all vertebrates from shark to man; and that in animals with few lymphocytes, iT cells may provide the bulk of the protective T cell responses.

Publication

Nonclassical MHC-Restricted Invariant V?6 T Cells Are Critical for Efficient Early Innate Antiviral Immunity in the Amphibian Xenopus laevis.
Edholm ES, Grayfer L, De Jesús Andino F, Robert J
J Immunol. 2015 Jul 15