

# Gamma Delta ( $\gamma\delta$ ) T Cells



Matthias Eberl, Cardiff University, UK  
Adrian Hayday, King's College London, UK

Gamma delta ( $\gamma\delta$ ) T cells are the prototype of 'unconventional' **T cells** and represent a relatively small subset of T cells in peripheral blood. They are defined by expression of heterodimeric **T-cell receptors (TCRs)** composed of  $\gamma$  and  $\delta$  chains. This sets them apart from the classical and much better known CD4+ **helper T cells** and CD8+ **cytotoxic T cells** that express  $\alpha\beta$  TCRs. The mechanism of (thymic) selection of  $\gamma\delta$  T cells is still largely unknown.

## Tissue-associated $\gamma\delta$ T cell populations

$\gamma\delta$  T cells often show tissue-specific localisation of oligoclonal subpopulations sharing the same TCR chains. For instance, human peripheral blood  $\gamma\delta$  T cells are largely V $\gamma$ 9/V $\delta$ 2+, and murine skin  $\gamma\delta$  T cells, so-called **dendritic epidermal T cells (DETCs)**, are largely V $\gamma$ 5/V $\delta$ 1+. In general,  $\gamma\delta$  T cells are enriched in epithelial and mucosal tissues where they are thought to serve as the first line of defense against pathogenic challenge.

## Recognition of target cells by $\gamma\delta$ T cells

The majority of  $\gamma\delta$  T cells are activated in an MHC-independent manner, in striking contrast to MHC-restricted  $\alpha\beta$  T cells. The antigens recognised by most  $\gamma\delta$  T cells are still unknown. A small proportion of murine  $\gamma\delta$  T cells (<1%) bind the MHC-I-related proteins T10 and T22 that are expressed by highly activated cells. Human V $\gamma$ 9/V $\delta$ 2+ T cells show TCR-dependent activation by certain phosphorylated metabolites such as microbial HMB-PP or eukaryotic isoprenoid precursor IPP. Due to metabolic dysregulation IPP is often accumulated by cancer cells. Some  $\gamma\delta$  T cells also recognise markers of cellular stress, resulting from infection or tumorigenesis. Stress surveillance performed by  $\gamma\delta$  T cells is thought to depend not only on their TCRs but also on co-stimulatory signals from, for instance, NK-type receptors. Finally,  $\gamma\delta$  TCRs have been shown to recognise lipid antigens presented by CD1 molecules, in particular CD1d.

## $\gamma\delta$ T cell-mediated immune responses

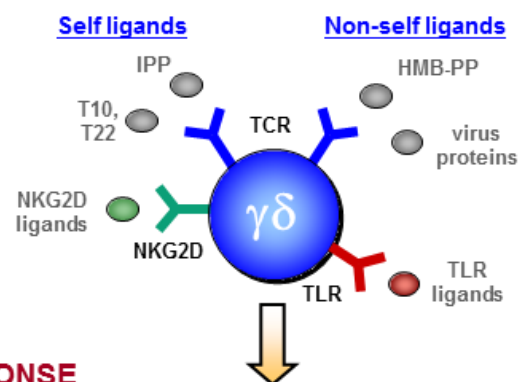
$\gamma\delta$  T cells display broad functional plasticity following recognition of infected/transformed cells by production of **cytokines** (IFN- $\gamma$ , TNF- $\alpha$ , IL-17) and **chemokines** (RANTES, IP-10, lymphotactin), **cytolysis** of infected or transformed target cells (perforin, granzymes, TRAIL), and interaction with other cells including **epithelial cells, monocytes, dendritic cells, neutrophils, and B cells**. In particular, human V $\gamma$ 9/V $\delta$ 2+ T cells are capable of serving as professional antigen presenting cells.

Certain infections (e.g. human cytomegalovirus) have been shown to drive clonal expansion of peripheral  $\gamma\delta$  T cells bearing person-specific TCRs, indicating the adaptive nature of  $\gamma\delta$  T cell-mediated immune response.

## $\gamma\delta$ T cells for immunotherapy

$\gamma\delta$  T cells are capable of recognising and lysing diverse cancers in an MHC-unrestricted manner, highlighting their potential for pan-population immunotherapy, in contrast to MHC-restricted  $\alpha\beta$  T-cell mediated immunotherapy. Past clinical trials, which focused on V $\gamma$ 9/V $\delta$ 2+ T cells expanded using phosphorylated metabolites, showed an overall good safety profile but the clinical efficacy was generally underwhelming. The potential of  $\gamma\delta$  T cells for pan-population immunotherapy will be evaluated in upcoming clinical trials using different subsets of  $\gamma\delta$  T cells or specific  $\gamma\delta$  TCRs.

## RECOGNITION



## RESPONSE

Cytokine production	Inflammation	B cell help
Chemokine production	Epithelial growth	DC maturation
Cytotoxicity	Wound healing	Antigen presentation