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Murine γδ T cells in infections: beneficial or deleterious?

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Abstract

Although the importance of γδ T cells in pathogen-induced immune responses is becoming increasingly apparent, it is not clear that their involvement is always of benefit to the host. Here we review evidence for the protective and damaging roles of γδ T cells in infection and discuss how these disparate findings might be resolved by considering the nature and properties of the pathogen, the sites of infection and conditions under which γδ T cell responses are initiated, and the involvement of different subsets of γδ T cells.

Keywords: T cells; Infections; T cell receptors; Inflammation

1. Introduction

The effective control and removal of infection requires a coordinated response by both lymphocytes and inflammatory cells, via molecular mediators and the direct killing of the pathogens themselves or the cells they infect. A defect in any component of this complex network can result in ineffective clearance and/or inappropriate pathology. Of particular importance is the regulation of the inflammatory cells themselves, the majority of which are not antigen-specific and, while activated, can damage surrounding tissue. Their response must therefore be modulated, and once the pathogen has been cleared it must be switched off. Failure to do so may result in chronic inflammation leading to scarring and tissue damage.

In a primary infection, the early stages are dominated by the inflammatory response, which is necessary for early pathogen containment and for the recruitment of lymphocytes to sites of infection. The subsequent eradication of the infection is mediated by antigen-specific B cells and αβ T cells and results in the establishment of long-term protective immunity. The role of γδ T cells in this process was first indicated by observations that their numbers increased at sites of inflammation and that a peak γδ T cell response could occur early after infection, suggesting their involvement during the initiation phase of the immune response. In addition, in their absence not only were mice more susceptible, and less able to clear infection, but they also developed accelerated and exacerbated inflammatory responses that were slow to resolve (reviewed in [1]). This preliminary evidence suggested that γδ T cells have a protective role in infection, but confusingly, this has not always been substantiated, with reports that the presence of γδ T cells in some infections actually makes the pathology more severe.

Here we review the evidence for the protective and damaging roles of γδ T cells in infection, and set out to explain how these apparently disparate findings can be resolved by an understanding of the function of γδ T cells and, in particular, the roles different γδ T cell subsets, as defined by the differential expression of variable (V) Vγ gene-encoded T cell receptors (TCRs), play in complex inflammatory immune responses. We will argue that responding γδ T cells show functional plasticity and heterogeneity dependent on the location and magnitude of the infection, the nature of individual pathogen-host interactions and the microenvironments in which they operate.

2. The role of γδ T cells in infection

In mice, γδ T cells constitute a small proportion (1–5%) of T cells in the blood and lymphoid tissues, but they are a major T cell population in epithelial tissues of the skin and intestinal mucosa, which as the first portal of entry of many infections, are important sites for initiating rapid responses by resident cells such as $\gamma\delta^+$ intraepithelial lymphocytes in

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Table 1
Evidence for protective role of γδ T cells in infection

Pathogen	Organism	Route of infection	Site of infection	Outcome in γδ T cell-deficient mice[a]
Bacteria	*L. monocytogenes*	Intraperitoneal, intravenous	Spleen, liver, peritoneal cavity	Increased bacterial load early in infection [12], necrotic liver lesions with large PMN infiltrates [13], increased mortality [12,13]
	M. tuberculosis	Aerosol, intravenous	Spleen, liver, lung	Increased mortality at high doses, large PMN infiltrates [14]
	Yersinia pseudotuberculosis	Oral	Gut, spleen, liver	Less resistant to dissemination of enteric bacteria to liver and spleen [15]
	Nocardia asteroides	Intranasal	Lung	Large inflammatory foci of PMNs, reduced pathogen clearance [16]
Viruses	West Nile virus	Intraperitoneal	Spleen, blood, brain	Increased viral load and mortality [17]
	Herpes simplex virus type 2	Intravaginal	Vagina	Increased susceptibility to infection, impaired Th1 response [18]
	Vaccinia virus	Intraperitoneal	Spleen, fat pads, liver	Increased mortality at high dose, increased viral load early in infection [19]
	Cytomegalovirus	Intraperitoneal	Spleen, liver, peritoneal cavity	Increased viral load early in infection [20]
Parasites	*P. yoelii*	Mosquito bite	Liver, blood, brain	Reduced sporozoite replication in liver [21]
	P. chabaudi	Intraperitoneal	Liver, blood, brain	Reduced blood-stage clearance increased antibody production increased Th2, decreased Th1 response [22]
	Eimeria vermiformes	Oral	Small intestine	Decreased resistance to infection in young mice [23]
	Encephalitozoon cuniculi	Intraperitoneal	Spleen, liver, peritoneal cavity	Dose-dependent increase in mortality, decreased $CD8^+$ CTL response [24]

[a] Compared with wt mice.

the small intestine (iIELs), $V\gamma5^+$ dendritic epidermal T cells (DETCs) in the skin and $V\gamma4^+$ T cells in the lung. In the spleen, γδ T cells appear to be constitutively activated and they have an activated or memory T cell phenotype [2]. Unlike naive αβ T cells, splenic γδ T cells constitutively express IL-12 receptors, indicating that they are poised for IL-12-dependent IFNγ secretion [3]. This allows them to respond rapidly, concurrent with, or before, the mobilization of resident innate immune cells such as NK cells and prior to the development of the adaptive αβ T cell response, indicative of their being able to bridge or link the innate and adaptive immune responses [4].

Although γδ T cells accumulate at sites of infection, there is very little evidence for pathogen specificity among responding γδ T cells. They have been shown to proliferate in vitro to antigen-presenting cells activated by pathogen-derived antigens [5], and hybridomas reactive to mycobacterial heat-shock proteins (e.g. HSP60) and to herpes simplex virus glycoprotein have been generated, although the majority of γδ hybridomas and clones react to (unknown) autologous antigens (reviewed in [1]). However, whether or not responding γδ T cells are pathogen-specific, they can promote or suppress inflammation, often at different stages of the disease, both by producing pro-inflammatory Th1 type cytokines such as IFNγ, or anti-inflammatory Th2 type cytokines such as IL-4 or IL-10, and also by cytolytic activity. During infection with coxsackievirus B3 (CVB3), γδ T cells promote a Th1 response by killing IL-4-producing virus-specific $CD4^+$ T cells [6], and in listeriosis, they down-modulate the response to *Listeria monocytogenes* once it has been cleared by killing populations of remaining activated macrophages [7]. In the absence of αβ T cells they are able to provide help for protective antibody production [8,9], although this is restricted in isotype and antibody specificity [10]. Pro-inflammatory γδ T cells have also been shown to promote NK cell IFNγ-dependent innate immunity against *L. monocytogenes* [11]. Overall, the type of response mounted by γδ T cells to infection includes both Th1 and Th2 elements as well as cytotoxicity.

Studies of mice deficient in γδ T cells by TCRδ gene disruption or antibody-mediated depletion have shown γδ T cells to be protective against infection by many bacteria, viruses and parasites (Table 1). Irrespective of the site of infection or the type of pathogen, the absence of γδ T cells in these infections leads to increased pathogen load, often with abnormal inflammatory responses. Studies that have examined the effect of γδ T cell deficiency on the overall Th1/Th2 phenotype of the response have found Th1 responses to be impaired and Th2 responses increased, highlighting the importance of the pro-inflammatory role of γδ T cells in containment of the infection [18,22].

2.1. The γδ T cell response to infection is staged

The progressive or staged involvement of γδ T cells and their accumulation at sites of infection during different phases of the immune response are a feature of many microbial and parasite infections.

2.1.1. The early γδ T cell response is pro-inflammatory

In sites of infection and initial pathogen replication, γδ T cells accumulate early, often within hours of infection, prior to αβ T cells, and are thought to have a pro-inflammatory role and to contribute to the fast-acting local innate response [4]. These early-responding γδ T cells have been shown to produce IFNγ to bacteria [12,25], viruses [17,19,26], and