Available online at www.sciencedirect.com
SCIENCE DIRECT®
Microbes and Infection 7 (2005) 503–509
Microbes and Infection
www.elsevier.com/locate/micinf

Forum in immunology

# Sensing cell stress and transformation through Vγ9Vδ2 T cell-mediated recognition of the isoprenoid pathway metabolites

Marc Bonneville [a], Jean-Jacques Fournié [b,*]

[a] *Inserm U601, Institut de Biologie, 9 quai Moncousu, 44035 Nantes cedex 1, France*
[b] *Inserm U563, BP 3028 CHU de Purpan, 31024 Toulouse, France*

Available online 21 March 2005

**Abstract**

Vγ9Vδ2 cells, a major peripheral blood γδ T cell subset in adults, recognize non-peptidic phosphorylated metabolites referred to as phosphoantigens (phosphoAg), which are produced by a broad array of prokaryotic and eukaryotic organisms. We will review here the biosynthetic pathways leading to production of phosphoAg and our current understanding of the mode of activation of Vγ9Vδ2 cells by these compounds. We will also discuss the physiological relevance of this immune recognition process and show how it can enable discrimination by Vγ9Vδ2 lymphocytes of infected and/or transformed cells.


*Keywords:* Immunology; T lymphocytes; Gamma/delta T cell receptor; Isoprenoid biosynthesis

## 1. Vγ9Vδ2 cells respond to widespread non-peptide ligands, the phosphoantigens

At the time of their first description 15 years ago, human Vγ9Vδ2 T lymphocytes were found to respond to mycobacteria and to human tumor cells [1]. Early analyses of the *Mycobacterium tuberculosis* compounds stimulating Vγ9Vδ2 cells led to the identification of four structurally related phosphoesters (so-called TUBag 1–4), with thymidine or uridine nucleotide conjugates together with their non-nucleotidic pyrophosphoester moieties [2–4]). In *Mycobacterium smegmatis*, isopentenyl pyrophosphate (IPP) and its dimethylallyl pyrophosphate (DMAPP) isomer were also identified [5,6]. Although these findings were confirmed later, at that time, they did not account for the Vγ9Vδ2 cell reactivity to distinct histotypes of human tumor cells, encompassing lymphoma and carcinoma. It has become clear since then that a broad set of natural compounds with a phosphate part as the major determinant of bioactivity was produced by microorganisms and mammalian cells and selectively stimulated the human γδ T cell population expressing Vγ9Vδ2 T cell receptor (TCR) [7]. These were defined as phosphoantigens (phosphoAg) on this basis [3]. Natural phosphoAg such as IPP, DMAPP [8], or also *Escherichia coli*-derived 3-formyl-butyl-pyrophosphate [9] and 4-hydroxy-3-dimethylallyl pyrophosphate (HDMAPP) [10] were identified in many microorganisms [3,11] and plants [12], implying that these organisms share a biosynthetic route for these phosphorylated metabolites, leading to more complex isoprenoids [13]. Also, non-phosphorylated non-peptide molecules that stimulate in a cross-reactive fashion the same Vγ9Vδ2 T lymphocytes are now known, including natural and synthetic alkylamines [14] and therapeutic aminobisphosphonates (ABP) such as pamidronate [15,16]. Since the Vγ9Vδ2-stimulating compounds from human cancer cells have recently been identified as the IPP and DMAPP metabolites of the human mevalonate (MVA) pathway to cholesterol [17,18], and since ABP inhibit the MVA pathway after IPP/DMAPP biosynthesis [19], the ability of ABP to activate human γδ T cells reflects their pharmacological ability to induce IPP accumulation by treated cells, instead of acting directly, like phosphoAg themselves. Accordingly, ABP concentrations required to stimulate γδ T

*Abbreviations:* ABP, aminobiphosphonate; Ag, antigen; ApoA1, apolipoprotein A1; AS, ATP synthase; DC, dendritic cell; DMAPP, dimethylallyl pyrophosphate; DOXP, 1-deoxy-D-xylulose-5-phosphate; HDMAPP, 4-hydroxy-3-dimethylallyl pyrophosphate; HMGR, HMG-CoA reductase; HSP, heat shock protein; IPP, isopentenyl pyrophosphate; MAb, monoclonal antibody; MVA, mevalonate; PhosphoAg, phosphoantigen; TCR, T cell receptor.

* Corresponding author. Tel.: +33 5 62 74 83 64; fax: +33 5 61 31 97 52.
*E-mail address:* fournie@purpan.inserm.fr (J.-J. Fournié).

1286-4579/$ - see front matter © 2005 Elsevier SAS. All rights reserved.
doi:10.1016/j.micinf.2005.03.004

cell clones in vitro are 3 to 4 log higher than those needed to induce γδ T cell expansion in vivo [20,21]. Furthermore, upstream MVA inhibitors such as statins are able to abrogate the γδ T cell activation, presumably through blockade of production of downstream metabolites such as IPP [17,18].

## 2. Biosynthesis of phosphoantigens by MVA and DOXP pathways to isoprenoids

All living organisms produce isoprenoids, essential metabolites of their cellular and intercellular biology, but share a metabolic bottleneck at isomerization of the two IPP and DMAPP C5 isomers. On the one hand, archaebacteria and most eukaryotes synthesize IPP from acetyl-CoA through the lipid MVA pathway. In all of these cells, both statins and ABP may prove useful to probe this MVA route, which appears mostly distributed in the mitochondriates (Fig. 1). On the other hand, cyanobacteria, most eubacteria, algae and plastids make IPP differently, through a carbohydrate-based route referred to as 1-deoxy-D-xylulose-5-phosphate (DOXP) after its first intermediate [22]. The DOXP pathway starts from pyruvate plus D-glyceraldehyde-3-phosphate substrates, and after several steps with oxygen-free conditions, produces HDMAPP [23] followed by IPP and DMAPP. Multicellular algae and higher plants cumulate the MVA pathway in the cytosol and in mitochondria, together with, in their chloroplasts, a functional DOXP pathway whose genes remain encoded in the

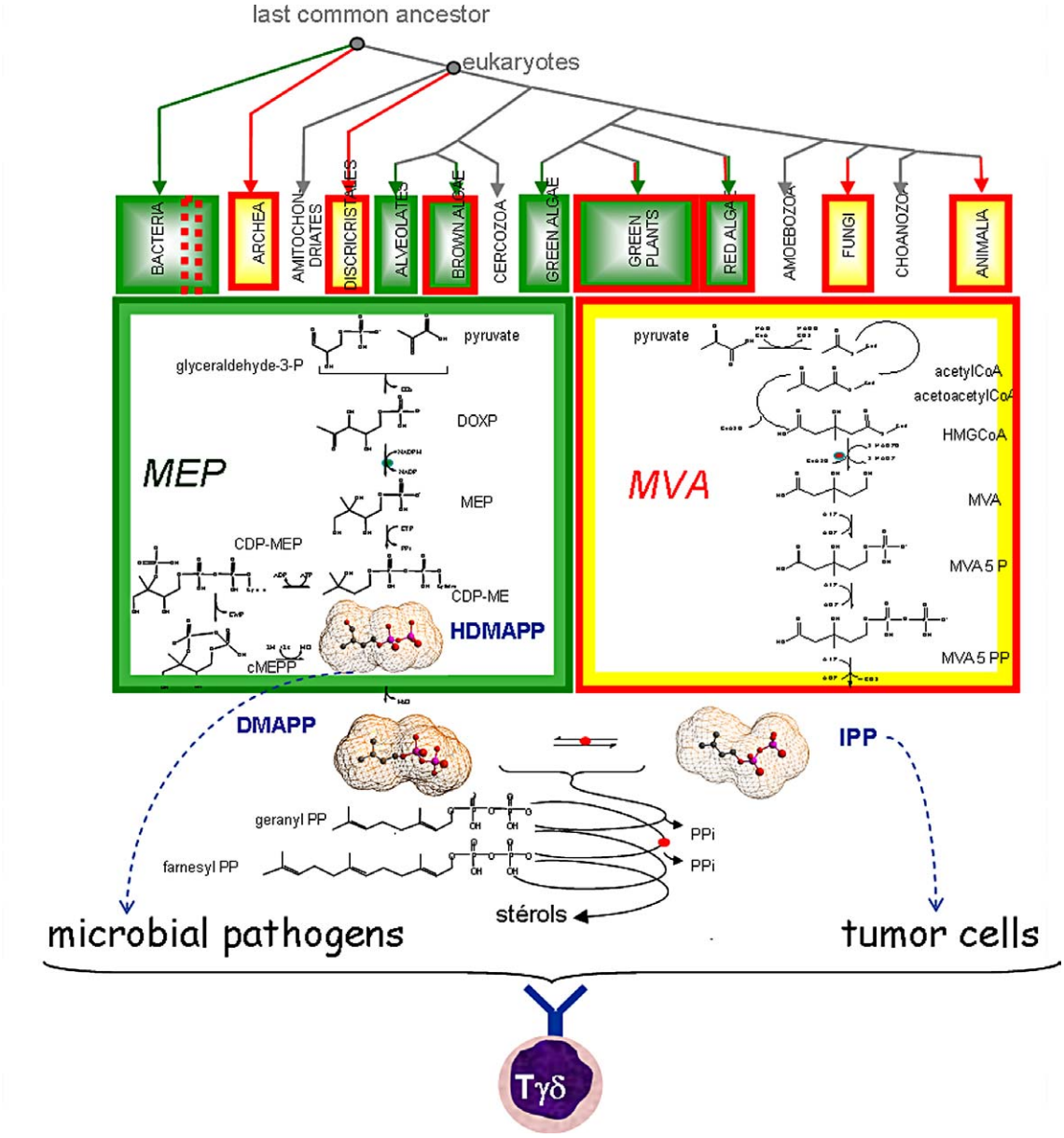


Fig. 1. The DOXP and MVA metabolic paths of cholesterol biosynthesis involve phosphoAg intermediates. Top panel, phylogenetic distribution of DOXP (green boxes) and MVA (yellow boxes) pathways in a simplified tree of life. Bottom panels, DOXP and MVA pathways, with phosphoAg intermediates shown with green molecular surfaces. Grey boxes indicate inhibitors.