

IMMUNOGENETICS

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SELECTED PUBLICATIONS

Fichtner AS, Karunakaran MM, Gu S, Boughter CT, Borowska MT, Starick L, Nöhren A, Gobel TW, Adams EJ, Herrmann T (2020) *Alpaca (Vicugna pacos), the first nonprimate species with a phosphoantigen-reactive Vγ9Vδ2 T cell subset.*

PNAS 117(12):6697-6707

Karunakaran MM, Willcox CR, Salim M, Paletta D, Fichtner AS, Noll A, Starick L, Nöhren A, Begley CR, Berwick KA, Chaleil RAG, Pitard V, Déchanet-Merville J, Bates PA, Kimmel B, Knowles TJ, Kunzmann V, Walter L, Jeeves M, Mohammed F, Willcox BE, Herrmann T (2020) *Butyrophilin-2A1 Directly Binds Germline-Encoded Regions of the Vγ9Vδ2 TCR and Is Essential for Phosphoantigen Sensing.*

Immunity 52(3):487-498.e6

Fichtner AS, Karunakaran MM, Starick L, Truman RW, Herrmann T (2018) *The Armadillo (Dasypus novemcinctus): A Witness but Not a Functional Example for the Emergence of the Butyrophilin 3/Vγ9Vδ2 System in Placental Mammals.*

Frontiers in Immunology 9:265

RESEARCH INTERESTS

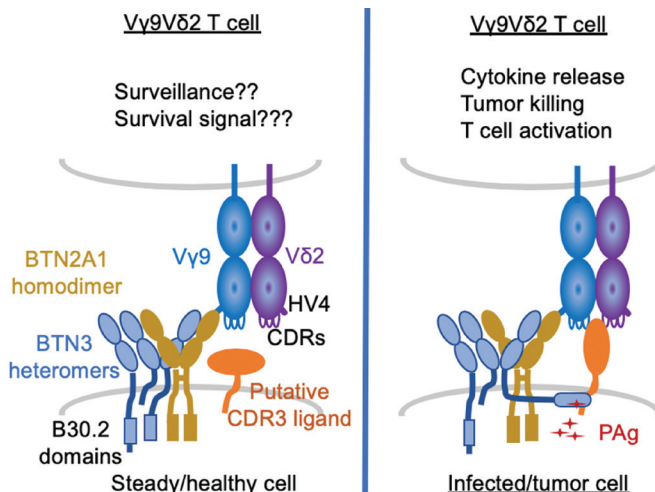
Vγ9Vδ2 T cells are effectors with anti-microbial and anti-tumor activity. Their eponymous Vγ9Vδ2 T-cell antigen-receptor recognizes phosphoantigens (PAG) sensing tumor or host cells. The PAG (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP) is found in many eubacteria and in apicomplexa such as *Plasmodium* spp. and leads to expansion of Vγ9Vδ2 T cells in infections. The ubiquitous but very weak PAG isopentenyl pyrophosphate (IPP) is increased in tumors, especially after administration of aminobisphosphonates (e.g. zoledronate) and triggers anti-tumor activity. We aim to understand the molecular basis of recognition of PAGs in infections and to harness the anti-tumor effector potential of Vγ9Vδ2 T cells.

HIGHLIGHTS & OUTLOOK

A key player in Vγ9Vδ2 T cell-activation is the cell surface molecule butyrophilin (BTN)3A1. Its extracellular domain is very similar to members of the B7

family (e.g. CD80/86). Binding of PAGs to the intracellular B30.2 domain of BTN3A1 leads to a conformational change of the entire molecule, and finally to Vγ9Vδ2 T-cell activation by the BTN3A1-expressing cell. This requires cooperation with the BTN3A1 paralogues BTN3A2 and BTN3A3. Until recently, Vγ9Vδ2 T cells were found only in primates. We identified and characterized key genes of PAG-recognition (Vγ9, Vδ2, and BTN3) and their products in other mammalian species (Fichtner *et al.*, 2018) and newly generated reagents allowed us to identify the alpaca (*Vicugna pacos*) as the first non-primate species with functional Vγ9Vδ2 T cells. Interestingly, alpaca possess only one BTN3, which merges the functions of the three human BTN3s (Fichtner *et al.*, 2020).

We also identified the human BTN2A1 molecule as a new player in PAG-presentation by screening human-rodent radiation hybrids for their capacity of PAG-presentation (Karunakaran *et al.*, 2020). In cooperation with the Willcox group in Birmingham, UK, BTN2A1 binding was shown to the Vγ9 gene product and the V-domain of BTN3A1. BTN2A1 and BTN3A1 transferred the capacity of PAG presentation to rodent cells and is aimed to be used for creation of a transgenic mouse model for PAG-reactive Vγ9Vδ2 T cells, which so far can only be studied in primates. The study of the molecular basis of interaction between the butyrophilins and of ligands binding to the Vγ9Vδ2 TCR will also be continued.



Model of Vγ9Vδ2 T cell activation. BTN2A1 binds to Vγ9 and PAG binding to BTN3A1 induces a conformation of the BTN-complex exposing an unknown ligand(s) to the CDR3s of Vγ9Vδ2 TCR.

Figure from: An Update on the Molecular Basis of Phosphoantigen Recognition by Vγ9Vδ2 T Cells. Herrmann T, Fichtner AS, Karunakaran MM. *Cells*. 2020 Jun 9;9(6):E1433. doi: 10.3390/cells9061433.

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