Circulating human γδ T lymphocytes comprise a unique lymphoid cell subset exerting strong cytolytic activity against cancer cells. In healthy adults, around 1% of peripheral blood mononuclear cells are γδ T lymphocytes, most of which harbour a CD3+ CD4+ CD8- NKG2D+ phenotype and express the same TCR Vγ9/Vδ2 gene-encoded receptor for antigens. These lymphocytes often referred to as Vγ9/Vδ2+ T cells do respond to both human cancer cells and tuberculosis infection, by the selective recognition of HLA-unrestricted antigens with non-peptide phosphoesters structures, the phosphoantigens.

Natural phosphoantigens are thus produced by both mycobacteria and by human cancer cells, although the metabolic pathways to produce phosphoantigens differ in both types of producing cells. While mammalian cells and notably human tumours produce the phosphoantigens isopentenyl pyrophosphate and dimethylallylpyrophosphate through the mevalonate pathway for cholesterol biosynthesis, bacteria produce structurally related phosphoantigens like hydroxyl-dimethylallylpyrophosphate through a non-mevalonate pathway unique to the eukaryotic world. Since therapeutic amino-phosphonates like Aredia™ or Zometa™ target the farnesylpyrophosphate synthase enzyme from the mammalian mevalonate pathway, this drug induces bioaccumulation of endogenous phosphoantigens in treated cells. Thus as recently discovered by Kunzmann and colleagues, Vγ9/Vδ2+ T cells are strongly activated in cancer patients with multiple myeloma receiving Zometa™ or Aredia™ treatment for their bone-metastasis, and induced myeloma reductions. Activating Vγ9/Vδ2+ T cells in vivo in cancer patients either through Phosphostim™ or Zomet™ thus provides a novel means for anticancer immunotherapy. It is therefore of interest to identify other types of malignant diseases which may be targeted by Vγ9/Vδ2+ T cell recognition and cytolytic activity.

Like other cytotoxic lymphocytes, human γδ T cells expressing Vγ9/Vδ2+ encoded TCR cells bind to antigen cells through immunological synapses, acquire patches of their plasma membrane (trogocytosis) and eventually kill these targets. Although the process of trogocytosis mediated at the lytic synapse by cytolytic lymphocytes has recently been described, there is of as yet no clear understanding of how the delivery of cytolytic granules to target cells is associated to their trogocytosis, nor of their temporal relationship. Here using flow cytometry and time-lapse confocal video microscopy, we analyzed at the single cell level both features between human Vγ9/Vδ2+ T lymphocytes preactivated with synthetic phosphoantigens or with zometa and anaplastic large cell lymphoma (ALCL) cell lines. We found that both trogocytosis and perforin release were simultaneously initiated by formation of the immunological synapses. However, the target cell death stopped trogocytosis while the release of lytic granules at the synapse continued. Since nibbling of the target depended upon its viability, this demonstrated that the target cells controlled its trogocytosis together with the effector lymphocytes. In the reverse direction, the target cell also mediated a weak trogocytosis of its effector, in which case however the delivery of lytic granules from the ALCL cancer cells (contre-attaque) was unadjusted, and missed its objective. This first report for a dissociation of trogocytosis and cytotoxic response at the single cell level of lytic synapses (Figure 1) suggests that in this context, the purpose of trogocytosis could be to polarize the secretion of cytotoxic granules.

Thus the strong reactivity of human Vγ9/Vδ2+ T lymphocytes to anaplastic large cell lymphoma triggers their specific lysis. These in vitro findings evidence the potential of activating γδ T cells for...
immunotherapies of ALCL, a recently classified hematological malignancy and broadens their possible therapeutic use.

References