| PublisherInfo | | |
|---|---|---|
| PublisherName | : | BioMed Central |
| PublisherLocation | : | London |
| PublisherImprintName | : | BioMed Central |

# HLA, killer cell inhibitory receptors and autoimmune anemia

| ArticleInfo | | |
|---|---|---|
| ArticleID | : | 1 |
| ArticleDOI | : | 10.1186/ar-1999-66736 |
| ArticleCitationID | : | 66736 |
| ArticleSequenceNumber | : | 1 |
| ArticleCategory | : | Paper Report |
| ArticleFirstPage | : | 1 |
| ArticleLastPage | : | 4 |
| ArticleHistory | : | RegistrationDate : 1999–10–18<br>OnlineDate : 1999–10–18 |
| ArticleCopyright | : | Current Science Ltd1999 |
| ArticleGrants | : | |
| ArticleContext | : | 130751111 |

Martin Rudwaleit

## Keywords

HLA class I, killer inhibitory receptors, large granular lymphocytes, pure red-cell aplasia

# Context

Pure red-cell aplasia (PRCA) is characterized by anemia, reticulocytopenia, and severe erythroid hypoplasia of the bone marrow associated with normal maturation of myeloid and megakaryocytic cell lines. Its pathogenesis is considered to be heterogeneous with various autoimmune mechanisms (autoantibodies and T cell mediated) and secondary forms (following parvovirus B19 infection) playing a causal role. A notable feature of PRCA is the ability of eythropoietic cells to proliferate *in vitro* but not *in vivo* suggesting that there maybe an inhibitor *in vivo*that blocks erythropoiesis. Most patients respond to immunosuppresive therapy such as cyclosporin. A proportion of PRCA is associated with T cell large granular lymphocytic leukemia, chronic lymphocytic leukemia or thymoma. A combination of large granular lymphocyte (LGL) expansion with PRCA may also occur in association with rheumatoid arthritis or Felty?s syndrome. The role of expansion of large granular lymphocytes (LGLs), some of which may have a natural killer cell or T cell phenotype, in PRCA is not clear. To demonstrate, in a patient with PRCA and expansion of LGLs, that the LGLs are directly involved in the lysis of erythropoietic precursors.

# Significant findings

Of the circulating lymphocytes, 96% were T cells and of these, 78% expressed Î³/Î´ receptors. The Î³/Î´ T cells were positive for CD2, CD5, and CD7 and negative for CD16 and CD56 (both of which are markers of natural killer cells), CD57 and CD4. They expressed the rearranged VÎ³4 and V Î´1 genes in a clonal fashion and expressed the killer-cell inhibitory receptors p58.1, p70, p140, and CD94. The Î³/Î´ cells were also found in the bone marrow. Erythropoiesis was normal *in vitro* and the patient's serum did not induce lysis of erythropoietic precursors, which excludes a stem cell defect and autoantibodies. The patient's lymphocytes exhibited strong MHC unrestricted cytotoxicity in *vitro* against Daudi (Burkitt's lymphoma) and K562 (erythroleukemia) cells, both of which lack human leukocyte antigen (HLA) class I expression. Lysis of Daudi cells was greatly diminished by pretreatment with anti-Î´1 mAbs or antibodies against p58.1 (strongest inhibition), CD94 and p70, but not against other killer cell inhibitory receptors, such as p58.2, which were not expressed on the patient's lymphocytes. After restoration of HLA class I expression in transfected Daudi cells, the lysis of these transfectants was strongly reduced, whereas preincubation of transfected Daudi cells with HLA class I antibodies restored lysis.

Furthermore, autologous and allogeneic $CD34^+$ hematopoietic stem cells (expressing relatively high levels of HLA class I molecules) were made susceptible to lysis by preincubation with antibodies against HLA class I antigens. Therefore, erythroblasts (showing low levels of HLA class I) from bone marrow of normal donors were lysed by the patient's lymphocytes without preincubation.

# Comments

*The expansion of LGLs in patients with PRCA is not uncommon but the expression of Î³/Î´ receptors and, particularly, the expression of VÎ³/4 and VÎ´1 is unusual. Thus, it is unlikely that the same mechanism occurs precisely in other patients with PRCA as well. Nonetheless, this case report is interesting because it clearly demonstrates that, in a very special situation, low level expression of HLA class I antigens can lead to autoimmunity. This finding may stimulate more research into the role of killer inhibitory receptors in other autoimmune conditions.*

# Methods

Flow cytometry applying various monoclonal antibodies (mAbs) against surface molecules, was used to define the phenotype of the LGLs. Clonality of Î³/Î´ cells was demonstrated by hybridization of the rearranged T cell receptor Î³ chain to the $^{32}$p labeled probe M13H60. $CD34^+$ hematopoietic stem cells and glycophorin A+ erythroid precursors were obtained from bone marrow and purified with magnetic beads. Cytotoxic lysis of tumor cells (Daudi and K562 cells) was assessed by chromium-release assay and an assay based on a fluorescence-enhancing ligand that is released from dying target cells.

# Additional information

In an excellent accompanying editorial (*N Engl J Med* 1999, **340**:314-315), David Rautlet presents a concise summary of the various killing mechanisms of the immune system, and the various receptors involved in the regulation of killing is given. To be killed, a target cell must have two properties relating to natural killer cells: the inability to inhibit them and the capacity to stimulate them. Thus, two important questions are raised: first, if the Î³/Î´ lymphoctes, which behave like natural killer cells, are not inhibited by erythroblasts because of low HLA class I antigen expression, what is the antigen that stimulates them and through which receptor? Second, why do the patient's lymphocytes lyse erythroblasts *in vivo* (and Daudi cells and K562 cells *in vitro*) but apparently spare other cells (such as hepatocytes) which also have a low level of HLA class I surface expression? These intriguing questions remain to be answered.

# References

1. Handgretinger R, Geiselhart A, Moris A, Grau R, Teuffel O, Bethge W, Kanz L, Fisch P: Pure red-cell aplasia associated with clonal expansion of granular lymphocytes expressing killer-cell inhibitory receptors. N Engl J Med. 1999, 340: 278-284.