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Targeting haematopoietic-specific minor histocompatibility antigens to distinguish graft-versus-tumour effects from graft-versus-host disease

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Allogeneic stem cell transplantation (allo-SCT) and donor lymphocyte infusions can induce durable remission in patients with haematological malignancies through a graft-versus-tumour (GvT) effect. In human leukocyte antigen (HLA)-matched settings, this powerful immunotherapeutic effect is predominantly mediated by donor T cells directed at the recipient's minor histocompatibility antigens (mHags) presented on malignant cells. The mHags are short peptides excised from polymorphic regions of intracellular proteins, and are presented by HLA molecules to donor T cells. Several ubiquitously expressed mHags are involved not only in GvT but also in graft-versus-host disease (GvHD). However, a specific set of mHags is expressed exclusively by haematopoietic cells and their malignant counterparts. Targeting these haematopoietic mHags is an attractive strategy to induce specific GvT effects without increasing the risk of GvHD. This chapter will summarize the current efforts to identify therapeutically relevant haematopoietic mHags, and outline the strategies to apply mHag-based cellular immunotherapy to treat recurrent malignancies after allo-SCT.

Key words: minor histocompatibility antigens; graft-versus-tumour effect; graft-versus-host disease; adoptive immunotherapy; dendritic cell vaccination.

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GRAFT-VERSUS-TUMOUR EFFECT OF ALLOGENEIC STEM CELL TRANSPLANTATION

Allogeneic stem cell transplantation (allo-SCT) represents a powerful immunotherapeutic approach in the battle against several haematological malignancies.[1,2] Early transplantation studies demonstrated that allo-SCT mediated a significant therapeutic effect, which was not observed after autologous or syngeneic transplantation.[1,2] The price paid for this potentially curative graft-versus-tumour (GvT) effect was the development of life-threatening graft-versus-host disease (GvHD), which remains a major source of morbidity and mortality following allo-SCT. Removal of donor T cells from a haematopoietic graft has been shown to prevent GvHD, but also abrogates the therapeutic GvT effect[3], confirming the important role for alloreactive T cells in GvHD as well as in GvT. Finally, treatment with donor lymphocytes induces sustained remission in a subset of patients who relapse following allogeneic transplantation.[4] Although the most powerful GvT effects are observed in patients with chronic myeloid leukaemia, clear GvT effects have also been demonstrated in several other types of acute and chronic leukaemia, lymphoma and in multiple myeloma.[4–13]

MINOR HISTOCOMPATIBILITY ANTIGENS: MAJOR TARGETS OF THE GVT EFFECT

Starting from the earliest transplantation studies, it was obvious that elimination of GvHD, while preserving the GvT effect, would be the most important task towards safe and effective allo-SCT. Although the risk of GvHD is reduced significantly by matching the recipient and the donor for human leukocyte antigens (HLA)[2], even after genotypically HLA-matched SCT, 20–50% of the recipients develop GvHD, which is also the most predictive factor for GvT.[2] Of note, patients with mild GvHD demonstrate the best outcomes due to a lower risk of relapse while minimizing the toxicity associated with more advanced GvHD. Thus, even in fully HLA-matched transplant settings, the 'alloreactivity' towards recipient cells is the key factor for the development of GvHD and GvT effects. In an HLA-identical setting, alloreactive donor T cells are directed at non-HLA-encoded polymorphic antigens expressed by the recipient cells. These polymorphic antigens were originally discovered by Barth et al in mice and were designated as 'weak (minor) histocompatibility antigens' (mHags).[14] However, current knowledge on the immunobiology of mHags indicates that the 'minor' designation is misplaced since these antigens can induce very potent $CD4^+$ and $CD8^+$ T cell responses after HLA-matched, mHag-mismatched transplantation.[15]

BIOCHEMICAL NATURE OF MHAGS

As mHags are considered to be the key targets of GvHD and GvT, unravelling their biochemical nature has been a major focus of research. Early studies showed that human mHags were inherited as a Mendelian trait.[16] Thus, it seemed that mHags were immunological reflections of genetic variation between HLA-identical individuals. Indeed, the identification of the first series of human mHags demonstrated that they are HLA-bound polymorphic peptides derived from intracellular proteins.[17–21] In most cases, the difference between these polymorphic peptides is encoded by a single nucleotide polymorphisms (SNPs) in diallelic genes.[17–27] The mHag difference between the donor and recipient can also be generated by a gene deletion in the donor[28], by