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Biology and Therapy of Hodgkin's Disease

J. Wolf and V. Diehl

No convincing model exists either to define the cell of origin of Hodgkin's Disease (HD) or to explain the interaction between the putative malignant Hodgkin/Reed-Sternberg (HD/RS) cells and the surrounding bystander cells.

Lymphocyte predominant HD seems to be an exception, since in this histological subtype as a rule, the HD/RS cells express a B-cell phenotype [1]. Immunophenotyping of HD/RS cells in the other subtypes of HD, as well as on the few established cell lines, revealed that some antigens are consistently expressed including the activation markers Ki 1 (CD30) and the interleukin-2 receptor (CD25). In contrast, no homogeneous pattern is found for lineage specific antigen expression: the HD/RS cells may express B- or T-cell specific surface antigens or none of these (0-phenotype) [2]. By analogy, the HD derived cell lines show either (complete or incomplete) Ig- or TCR-rearrangements which might point to an immature lymphoid origin of these cells [3]. In Hodgkin's lymph nodes, clonal Ig- or TCR-rearrangements have also been described, although the interpretation of these studies is complicated by the scarcity of tumour cells in the biopsy specimens.

Similarly, karyotype analysis of HD has revealed a quite heterogeneous pattern. In a recently published review, only 40 well documented cases of complete karyotype banding studies in HD were found [4]. In these studies, the proportion of abnormalities varied from 22 to 83% including a broad spectrum of numerical and structural abnormalities. No specific chromosomal marker, such as the translocation (9/22) in chronic myelogenous leukaemia or (8.14) in Burkitt's lymphoma, was detected.

In addition, karyotype abnormalities in HD might not be restricted to the HD/RS cells. We have shown that after transplantation of HD derived lymph node biopsies into immunodeficient SCID mice, EBV-positive tumours of B-cell origin grow preferentially in lymphatic tissue(s). After short-term recultivation of these B-cell tumours, both structural and numerical chromosomal aberrations were detected at a high frequency. The SCID mouse tumours obtained after transplantation of HD tissue might, therefore, derive from EBV-positive bystander cells which differ significantly from normal EBV-infected B cells owing to an inherent genetic instability, and which might be amplified in SCID mice. Whether these bystander cells represent a (semi-) malignant cell popoulation present in HD lymph nodes in addition to HD/RS cells remains to be clarified [5].

EBV genomes could be demonstrated in HD/RS cells in approximately 50% of the HD cases in industrialised countries and even in approximately 90% in developing countries. In 50–60% of EBV-positive HD cases, the viral latent membrane protein (LMP1) is expressed in HD/RS cells, whereas the EBV nuclear protein 2 (EBNA2) is not expressed [6]. The biological function of LMP1 expression in HD is still not understood. It has a transforming potential, as was shown by tumorigenic transformation of epithelial cells after transfection of the *LMP1* gene. Furthermore, via upregulation of the *BCL2* gene, *LMP1* might protect B-lymphocytes from apoptosis.

The lack of understanding of the pathogenetic events leading to Hodgkin's Disease is contrasted with the impressive success in treatment. The aim of initial treatment of patients with HD is cure, which is now possible in 75% of patients by radio- and/or chemotherapy. Disease stage is the principal factor in selecting treatment strategy. In addition, several clinical parameters such as mediastinal bulk, extranodal disease, elevated ESR, and number of involved lymph node areas have been well documented as being prognostically significant.

Radiotherapy is still considered as the treatment of choice for patients in the localised stages CS/PS I–IIA. With extended field irradiation, a long-term survival rate of approximately 90% can be achieved [7]. Newer treatment approaches aim at avoiding staging laparotomy which is associated with a morbidity of 10–20%, and at reducing the high risk of relapse after radio-

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therapy alone by introducing additional less toxic chemotherapy up front.

Combined modality therapy is the standard therapy for patients in localised stages with one or more of the aforementioned adverse factors. However, the optimal duration of the chemotherapy regimen as well as the right dose and extent of radiotherapy of such combined modality programmes are ill defined. A special risk for patients treated with combined modality are second neoplasias [8]. Current strategies aim at reducing treatment-related toxicity without compromising efficacy. The HD1 trial of the German Hodgkin's Lymphoma Study Group (GHSG) compared 40 Gy extended field versus 20 Gy extended field plus 20 Gy bulk irradiation after 2 cycles COPP–ABVD. Survival and time to treatment failure were identical after a median follow-up time of 48 months. These data suggest that 20 Gy irradiation may be sufficient in the extended field after chemotherapy to control subclinical disease. The ongoing HD8 trial is now comparing extended versus involved field radiation after 2 double-cycles COPP–ABVD.

The treatment of choice for patients in advanced stages IIIB and IV is combination chemotherapy. Several chemotherapy regimens are capable of inducing complete remissions in over 80% of patients. However, as patients are followed, up to 30% relapse. Thus, the primary treatment regimen should only result in the cure of approximately 50% of advanced stage patients [9]. One approach to improve treatment results is intensification of chemotherapy by support of haemopoietic growth factors.

The optimal salvage therapy for patients relapsing after polychemotherapy depends on the primary chemotherapy regimen used and the duration of the response. Accumulating data suggest that high-dose chemotherapy (HDC) followed by stem cell transplantation can improve the treatment results for patients with relapsed HD. In order to better define the role of HDC in patients with relapsed HD, the ongoing HDR-1 trial of the GHSG compares HDC plus stem cell support with repeated courses of a dose escalated salvage chemotherapy (DexaBEAM) Plus G-CSF support.

HD may be an ideal target for immunotherapy. Current experimental strategies involve bispecific monoclonal antibodies, anti-idiotypic antibodies and immunotoxins. Immunotoxins are currently being evaluated in clinical phase-I trials in patients with refractory Hodgkin's Disease [10].

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Breast Cancer Angiogenesis: Therapy Target and Prognostic Factor

A.L. Harris, S. Fox, R. Leek, H. Zhang, P. Scott, R. Bicknell and K. Gatter

BREAST CANCER is the commonest cancer in women in Europe. Improvement in current treatments and the development of new approaches to breast cancer therapy are most likely to come from advances in the basic understanding of breast biology. Angiogenesis is essential for tumour growth and metastasis [1]. It is a complex multistep process involving extracellular matrix remodelling, endothelial cell migration and proliferation, capillary differentiation and anastamosis which is regulated by angiogenic peptides [2]. However, the relative importance of each of these key events or their regulating factors in tumour angiogenesis is unknown. Similarly, although there is increasing evidence that endothelial cell adhesion molecules play a significant role in angiogenesis [3] and tumour-endothelial cell adhesion [2, 4], their role in breast cancer is unknown.

PROGNOSTIC ROLE OF ANGIOGENESIS

Weidner *et al.* [5] first demonstrated the association of angiogenesis, assessed by factor VIII associated antigen, with metastasis