Immunoglobulin and T-Cell Receptor Gene Rearrangements in Hodgkin’s Disease

H. Daus, G. Schwarze, G. Kümel, P.G. Scheurlen

Medizinische Universitätsklinik I, Homburg; Institut für Mikrobiologie und Zentrum für Hygiene, Universität Frankfurt, FRG

Since it has been recognized as neoplastic element in Hodgkin’s disease (HD) the origin of Reed-Sternberg (RS) cells is still controversial. In the past morphological, histochemical, immunophenotyping and cell culture techniques were used to determine RS cell line derivations and the suggested origin included B and T lymphocytes, macrophages, interdigitating and dendritic reticulum cells [1]. The recognition that during lymphoid development a DNA rearrangement process assembles the components of immunoglobulin (IgH) and T-cell antigen receptor (TcR) genes has provided an additional tool to identify monoclonal B-and T-cell populations in lymphoid neoplasms [2, 3].

We report here our results of Southern blot analysis of tumor tissue DNA (11 lymph nodes, 1 pleura effusion, 1 bone marrow biopsy) obtained from patients with HD (1 lymphocyte predominant, 4 mixed cellularity, 8 nodular sclerosing). A 2.2-kb Sau 3A fragment of the immunoglobulin heavy chain joining region (kindly provided by Dr. P. Leder, Boston, Mass., USA) and a 440-bp fragment specific for the constant region of the TcR ß-chain gene (a gift from Dr. T. Mak, Toronto, Ont., Canada) were used as gene probes.

Three out of eight cases with nodular sclerosis and 1 out of 4 cases with mixed cellularity had a TcR gene rearrangement after Eco R I or Hind III digestions. In 1 case Cß1 and Cß2 genes were rearranged (fig. 1a, b). One HD showed two rearranged IgH alleles (fig. 1c). In 6 cases the intensity of the Eco RI 12-kb TcR-band was diminished according to the grade of polyclonality of the T-cell population. A summary of previously published genotypic analysis in HD is given in table 1.

In most studies no correlation was found between the proportion of RS cells and the intensity of rearranged fragments in the autoradiograms and cases with gene rearrangement were not restricted to a particular subtype. In our study except of one TcR rearrangement signals of rearranged bands were weak, not reaching the level found in non-Hodgkin’s lymphomas. Since the detection limit of mixing placenta DNA and Blast DNS was at the level of 2% clonal cells in a sample, clonal cell populations must be small in Hodgkin’s disease. In contrast to most mentioned studies, we detected 4 TcR and only 1 IgH rearrangement out of 13 Hodgkin samples. With an improved method of fixation, which sharply defined cell borders, Kadin et al. [12] could reveal T-cell antigens on RS cells in 8 out of 30 cases of HD. Our results also agreed with those
of Griesser et al. [10], who demonstrated 4 TcR and 2 IgH rearrangements in 22 HD. Six cases showed a decrease in the 12-kb TcR band after Eco RI digestion, which is a molecular sign for polyclonality of T cells. This would reflect the high percentage of T-cell populations in tissues involved by HD. Our findings indicate a heterogeneity of rearranged genes in HD. More cases need to be evaluated for correlation of IgH and TcR gene rearrangement findings with clinical outcome, and may eventually distinguish HD subsets with varying prognoses.

Immunoglobulin and T-Cell Receptor Gene Rearrangements in Hodgkin’s Disease

Table 1. Summary of gene rearrangement studies in HD

<table>
<thead>
<tr>
<th>References</th>
<th>Study Details</th>
</tr>
</thead>
</table>

Fig. 1. Examples of gene rearrangement in HD. 

(a) Hybridisation with the TcR gene probe after digestion with Eco RI: * = germline bands at 12 and 4 kb. 
(b) Hybridisation with the TcR gene probe after Hind III digestion; * = germline bands at 8, 6.5, 3 kb. 
(c) Hybridisation with JH probe after digestion with Bam HI; • = gene rearrangement. 
(d) Restriction map of the human TcR chain and IgH chain; B = Bam HI; E = Eco RI; H = Hind III.


Examined biopsies, n  Rearrangements of
Ref. No.
IgH light chain TcR
gene gene gene
4 5 6 7 8 9 10 11

In the study of Sundeen et al. [8] RS cells were enriched by cell separation techniques. Cases with high numbers of RS cells.