Oct-2 and Bob-1 Deficiency in Hodgkin and Reed Sternberg Cells

Daniel Re, Markus Müsenhauser, Tahamtan Ahmadi, Claudia Wickenhauser, Andrea Staratschek-Jox, Udo Höllick, Volker Diehl, and Jürgen Wolf

Department of Internal Medicine I [D. R., M. M., T. A., A. S.-J., U. H., V. D., J. W.], Institute of Pathology [C. W.], and Institute for Genetics, Department of Immunology [M. M.], University of Cologne, 50931 Cologne, Germany

ABSTRACT

Hodgkin and Reed Sternberg (H-RS) cells represent the malignant cells in classical Hodgkin's disease. Although derived from germinal center B cells, they do not express surface immunoglobulin. This has been explained by the presence of crippling mutations within the immunoglobulin genes in numerous cases of Hodgkin's disease. As immunoglobulin gene expression in B cells requires an interaction between octamer sites and the transactivating factors Oct-2 and Bob-1, this study addresses the expression of the transcription factors Oct-2 and Bob-1 in H-RS cells. In Hodgkin's disease-derived cell lines, low levels of Oct-2 transcripts but no Oct-2 protein were detected. Transcripts of Bob-1, a B-cell-specific cofactor of Oct-2, could not be observed in these cell lines. Absence of Oct-2 and Bob-1 protein expression in primary H-RS cells was demonstrated by performing immunohistochemistry in 20 cases of classical Hodgkin's disease. H-RS cells stained negative for both proteins in all of the cases analyzed. In conclusion, absence of functional Oct-2 and Bob-1 represents a novel mechanism for immunoglobulin gene deregulation in H-RS cells. Lack of Oct-2 and Bob-1 points to a defect in transcription machinery in H-RS cells and is associated with lack of immunoglobulin gene expression in these cells.

INTRODUCTION

H-RS cells represent the malignant cells in classical HD. In most cases, the H-RS cells are derived from GC B cells because they harbor somatically mutated immunoglobulin-V region genes (1–3), whereas derivation from T cells is rare (4). Notably, in a substantial proportion of classical HD cases, the H-RS cells had lost their capacity to express a functional B-cell receptor because of obviously destructive somatic mutations, rendering potentially functional immunoglobulin gene rearrangements nonfunctional (2). However, in other cases potentially functional immunoglobulin gene rearrangements were detected in H-RS cells (3, 5), indicating that in these cases, immunoglobulin gene expression might be possible in the lymphoma cells. However, in situ hybridization experiments failed to show detectable amounts of IgL and IgH mRNA in these cases. From these data, it was concluded that in these cases the immunoglobulin gene transcription is deregulated in H-RS cells (3).

Expression of rearranged IgH and IgL genes is critical for B-cell differentiation and is regulated by a complex interaction between regulatory DNA elements and transcription factors (6). Among the regulatory DNA elements necessary for B-cell-specific transcription, the octamer motif is an important transcriptional regulatory site that is part of promoters and enhancers of ubiquitously expressed genes.

Furthermore, this octamer motif is found in all of the IgH and IgL promoters and in the heavy chain and κ light chain enhancer elements (7). It has been shown to be essential for B-cell specificity and activity of the immunoglobulin promoter and enhancer (8, 9). The octamer site interacts with transcription factors belonging to the POU family of homeodomain-proteins binding specifically to this octamer motif via their POU domain (10).

Oct-1 was identified as a ubiquitous protein, whereas Oct-2 expression is restricted to B cells and neuronal cells (11). In B cells and neuronal cells, alternative splicing of Oct-2 generates several proteins (12, 13). On the basis of transfection experiments, for Oct-2 a critical role for immunoglobulin promoter transactivation was shown (12). Recent studies (14) demonstrated that in addition to Oct-2, a B-cell-specific cofactor, namely Bob-1, is required. Thus, B-cell specificity of immunoglobulin promoter activity is mediated by the expression of Bob-1 (OCA-B or OBF-1). Bob-1 associates with the POU domain of octamer proteins Oct-1 and Oct-2 and alters their recognition specificity (10). In a Bob-1-deficient mouse model, GC formation was drastically impaired, and class switch recombination was reduced substantially (15).

Because H-RS cells derive from GC B cells (16) but lack immunoglobulin gene expression, we now address the role of Oct-2 and Bob-1 for immunoglobulin gene transcription in classical HD. In this study, we discuss whether a disturbed expression of transcription factors is involved in the deregulation of immunoglobulin gene transcription in classical HD.

MATERIALS AND METHODS

Cell Lines. The characteristics of the seven HD-derived cell lines are summarized by Drexler (17) and Wolf et al. (18). IARC277 is an EBV-immortalized lymphoblastoid cell line (19), and BJA-B is an EBV-negative B-cell lymphoma cell line established from the biopsy of a five-year-old patient suffering from an EBV-negative African Burkitt lymphoma (20). The adherent fibroblastic cell line NIH3T3 and the human T-lymphoblastic leukemia cell line Jurkat were obtained from the American Type Culture Collection (Manassas, VA). All of the cell lines were grown according to standard procedures.

Pathological Specimen. Twenty primary cases of classical HD and one nonneoplastic lymph node sample were analyzed by immunohistochemistry. Characteristics are listed in Table 1. Pathological specimens were classified according to the WHO classification (21). All of the diagnoses have been reviewed by the pathologist reference panel of the German Hodgkin’s Lymphoma Study Group.

Cell Separation and Flow Cytometry. B-cell subsets were purified from a reactive tonsil of a child and from peripheral blood of an unrelated donor. CD38<sup>−</sup>CD27<sup>−</sup>GC B cells were isolated according to Goossens et al. (22). After two cycles of magnetic cell sorting enrichment of CD77<sup>−</sup>CD27<sup>−</sup>CD20<sup>−</sup>CD19<sup>−</sup>CD56<sup>−</sup>CD8<sup>−</sup>CD3<sup>−</sup>CD16<sup>−</sup>CD25<sup>−</sup> CD123<sup>−</sup>CD5<sup>−</sup> and CD38<sup>−</sup>CD27<sup>−</sup>CD20<sup>−</sup>CD19<sup>−</sup>CD56<sup>−</sup>CD8<sup>−</sup>CD3<sup>−</sup>CD16<sup>−</sup>CD25<sup>−</sup>CD123<sup>−</sup>CD5<sup>−</sup>and CD38<sup>−</sup>CD27<sup>−</sup>CD20<sup>−</sup>CD19<sup>−</sup>CD56<sup>−</sup>CD8<sup>−</sup>CD3<sup>−</sup>CD16<sup>−</sup>CD25<sup>−</sup>CD123<sup>−</sup>CD5<sup>−</sup>cells were isolated from the biopsies of a five-year-old patient suffering from a EBV-negative African Burkitt lymphoma (20). The adherent fibroblastic cell line NIH3T3 and the human T-lymphoblastic leukemia cell line Jurkat were obtained from the American Type Culture Collection (Manassas, VA). All of the cell lines were grown according to standard procedures.

Received 6/8/00; accepted 1/18/01.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 Supported by the Deutsche Forschungsgemeinschaft through SFB502. D. R. is supported by the Friedrich and Maria Sophie Moritz’sche Stiftung (Cologne, Germany). M. M. holds a postdoctoral fellowship from the Cancer Research Institute (Tumor Immunology Program, New York, NY).

2 To whom requests for reprints should be addressed, at University of Cologne, Department of Internal Medicine I, Joseph-Stelzmann-Str. 9, 50924 Cologne, Germany. Phone: 49-221-478-3410; Fax: 49-221-478-6733; E-mail: juergen.wolf@medizin.uni-koeln.de.

3 The abbreviations used are: H-RS, Hodgkin and Reed Sternberg; HD, Hodgkin’s disease; GC, germinal center; RT-PCR, reverse transcriptase PCR.
Table 1 Description of primary cases of classical HD and results of immunohistochemistry for Oct-2 and Bob-1

<table>
<thead>
<tr>
<th>Case</th>
<th>HD-subtype</th>
<th>Age</th>
<th>Presentation</th>
<th>Localization</th>
<th>EBV*</th>
<th>Bob-1</th>
<th>Oct-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>NS</td>
<td>13</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>NS</td>
<td>13</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>NS</td>
<td>35</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>NS</td>
<td>28</td>
<td>First</td>
<td>Supraclavicular</td>
<td>-</td>
<td>m</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>NS</td>
<td>16</td>
<td>First</td>
<td>Intraclavicular</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>NS</td>
<td>32</td>
<td>First</td>
<td>Supraclavicular</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>NS</td>
<td>19</td>
<td>First</td>
<td>Cervical</td>
<td>+</td>
<td>ni</td>
<td>-</td>
</tr>
<tr>
<td>20</td>
<td>NS</td>
<td>66</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>NS</td>
<td>22</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>MC/LD</td>
<td>46</td>
<td>First</td>
<td>Paraclavicular</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>1</td>
<td>MC</td>
<td>38</td>
<td>First</td>
<td>Supraclavicular</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>NS</td>
<td>79</td>
<td>First</td>
<td>Axillary</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>MC</td>
<td>58</td>
<td>First</td>
<td>Axillary</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>MC</td>
<td>36</td>
<td>First</td>
<td>Axillary</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>MC</td>
<td>62</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>18</td>
<td>MC</td>
<td>61</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>LR</td>
<td>32</td>
<td>First</td>
<td>Parasternal</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>LR</td>
<td>69</td>
<td>First</td>
<td>Cervical</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>LD</td>
<td>40</td>
<td>First</td>
<td>Axillary</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>LD</td>
<td>na</td>
<td>First</td>
<td>Axillary</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>Reactive</td>
<td>na</td>
<td>na</td>
<td>Axillary</td>
<td>na</td>
<td>nd</td>
<td>+</td>
</tr>
</tbody>
</table>

* EBV infection was assessed by staining for LMP1; +, strong reactivity; (+), weak reactivity; --, no reactivity; nd, not done.

** NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depleted; LR, lymphocyte rich classical HD; na, not assessed/not applicable.

Western Blot. Cellular protein extracts were prepared in Laemmli buffer, boiled for 10 min, and chilled on ice. Protein extract (20 µg) was separated on a discontinuous denaturating SDS-PAGE containing 7.5 or 10% acrylamide. The gel was blotted onto nitrocellulose filters (Hybond C extra; Amersham-Pharmacia, Freiburg, Germany). Equal loading of the gel was verified by Ponceau S staining. Unspecific binding of the antibody was inhibited by incubating the blot for 1 h with blocking buffer. Subsequently, blots were incubated overnight at 4°C either with a rabbit polyclonal antibody (dilution 1:10,000) recognized against a peptide mapping at the COOH terminus of Oct-2 (clone C-20; Santa Cruz, Heidelberg, Germany) or with a mouse monoclonal antibodies (clone PT1; Oncogene) and anti-Bob-1 antibodies (sc955; Santa Cruz) were used for these experiments. Sections (6 µm) were mounted on standard slides, deparaffinized in xylene, rehydrated in graded alcohol, and washed in water. Staining was performed according to standard procedures. Antibody reactions were detected with avidin-biotin-coupled alkaline phosphatase (DAKO) and FastRed as chromogen (DAKO). Subsequently, slides were counterstained with hemalaun (Merck, Darmstadt, Germany). The percentage of Oct-2 and Bob-1 positive H-RS cells of a given case was evaluated, and staining was classified in four categories: strong (+), weak (+/-), absent (-), or not informative.

RESULTS

Detection of Oct-2 Transcripts in HD-derived Cell Lines. To amplify human Oct-2 isoforms differing at their COOH terminus, we used two sets of oligonucleotides hybridizing to the different isoforms. We detected transcripts for Oct-2A and Oct-2B in all of the H-RS cell lines as well as in the BJA-B cell line. The amount of amplified products was similar in all of the HD-derived cell lines but much lower than in the B-cell line BJA-B. Because cell lines L1236, L428, KM-H2, and L591 harbor rearrangements of immunoglobulin genes and cell line DEV expresses IgA2, these cell lines are considered to derive from B cells. By comparison, cell lines L540 and Hdm-2 harbor clonal rearrangements of the T-cell receptor genes and, thus, are considered to derive from T cells. Because both the B-cellular and the T-cellular HD-derived cell lines express the same low level of the B-cell-specific Oct-2 transcripts, this indicates a non-B-cell-specific transcription background in H-RS cell lines (Fig. 1).

Lack of Oct-2 Expression in HD-derived Cell Lines. Using a polyclonal antibody raised against a peptide mapping at the COOH terminus of Oct-2A, we analyzed the expression of this protein in the three EBV negative B-cellular HD-derived cell lines L1236, L428, and KM-H2. Western blot analysis showed a strong signal for BJA-B cell lines used as positive control, whereas Oct-2A expression was missing in the HD-derived cell lines (Fig. 2). The Oct-2A signal does not reflect expression of a single protein but describes several human isoforms (24–26) that comigrate at 21 kDa and 20 kDa, respectively. Oct-2A mRNA is encoded by the 3' untranslated region of the two known human Oct-2 isoforms (Oct2.AS and Oct2.B). We detected transcripts for Oct-2A and Oct-2B in all of the HD-derived cell lines (Fig. 2). The Oct-2A signal does not reflect expression of a single protein but describes several human isoforms (24–26) that comigrate at 21 kDa and 20 kDa, respectively. Oct-2A mRNA is encoded by the 3' untranslated region of the two known human Oct-2 isoforms (Oct2.AS and Oct2.B). We detected transcripts for Oct-2A and Oct-2B in all of the HD-derived cell lines (Fig. 2).
Oct2.AS were used for amplification of Oct-2 cDNA. Lymphoblastoid B-cell lines IARC277 and BJA-B (Lanes 10–11, respectively). No template; L428, KM-H2, DEV, L591, L540, and HDLM-2 (Lanes 3–9, respectively); and in the lymphoblastoid B-cell lines IARC277 and BJA-B (Lanes 10–11, respectively). Lane 12, no template; M, molecular size marker (100-bp ladder). Oligonucleotides Oct2.5 and Oct2.1S were used for amplification of Oct-2 cDNA.

Fig. 1. RT-PCR analysis of the 3' end of Oct-2 shows transcription of different isoforms. Analysis of Oct2A and Oct2B transcription in naïve B cells (IgD+CD27+) and GC B cells (CD38+CD77+; Lanes 1 and 2, respectively); in HD-derived cell lines L1236, L428, KM-H2, DEV, L591, L540, and HDLM-2 (Lanes 3–9, respectively); and in the lymphoblastoid B-cell lines IARC277 and BJA-B (Lanes 10–11, respectively). Lane 12, no template; M, molecular size marker (100-bp ladder). Oligonucleotides Oct2.5 and Oct2.1S were used for amplification of Oct-2 cDNA.

Fig. 2. Western blot for Oct-2 expression using a polyclonal antibody mapping to the COOH terminus of Oct-2. Analysis of the lymphoblastoid B-cell line BJA-B (Lane 1), the fibroblast cell line NIH3T3 (Lane 2), and the HD-derived cell lines L1236, L428, and KM-H2 (Lanes 3–5, respectively). The fragment size of the molecular weight marker is given on the left side. The position of the Oct-2A complex is indicated on the right side.

Absence of Bob-1 transcription in HD-derived cell lines. Oct-2 and Bob-1 are both necessary for activation of immunoglobulin promoters. Therefore, we tested the HD-derived cell lines also for transcription of Bob-1. Bob-1 transcripts are completely absent in all of the HD-derived cell lines with the exception of DEV (Fig. 4). Notably, DEV is derived from a case of lymphocyte-predominant HD and expresses surface immunoglobulin. This is in line with the fact that we, in contrast to others (28), were unable to detect Oct-2 protein in B-cell HD-derived cell lines in Western blot experiments using two different Oct-2 specific antibodies.

Bob-1 recently has been identified as a B-cell-specific cofactor that is necessary for promoter-proximal activity together with either Oct-1 or Oct-2 (14). These data strongly support the idea that Bob-1 contributes to the transcriptional regulation in B cells. In fact, up-regulation of Bob-1 has been detected in GC B cells, whereas there was little expression of Bob-1 in naïve cells. In a study by Greiner et al. (29), GC-derived B-cell lymphomas including Burkitt lymphoma, follicular lymphoma, and diffuse large-cell B-cell lymphoma showed an up-regulation of Bob-1 similar to their physiological counterpart, the GC B cell.

H-RS cells are derived from GC B cells (16) and, thus, are expected to express Bob-1. We addressed the question whether Bob-1 is transcribed in HD-derived cell lines using RT-PCR. Our results show transcription of Bob-1 in GC cells and in naïve B cells, consistent with previous studies (29). Bob-1 mRNA was detectable in two lymphoblastoid cell lines but not in a T-cell line (Jurkat). Surprisingly, in four B-cell lines from patients with classical HD, a complete lack of Bob-1

DISCUSSION

Lack of immunoglobulin gene expression has been shown by in situ hybridization in primary cases of classical HD, despite the detection of potentially functional Ig VDJ gene rearrangements in most of these cases (3). Therefore, we investigated a potential mechanism of transcriptional deregulation of immunoglobulin genes in classical HD, namely expression of Oct-2 and Bob-1.

Results from RT-PCR indicate a low-level transcription of Oct-2 in the HD-derived cell lines. Because the number of transcripts is similar in HD-derived cell lines of both T- and B-cell origin, this may indicate a non-B-cell-specific baseline Oct-2 gene activity. That view is in line with the fact that in naïve cells and in contrast to others (28), were unable to detect Oct-2 protein in B-cell HD-derived cell lines in Western blot experiments using two different Oct-2 specific antibodies.

Exon 12 (8 amino acids) and the 5' part of exon 14 (12 amino acids). Therefore, Oct-2B cannot be detected using this antibody, because the antibody-binding site is disrupted, attributable to the splicing of exon 13. To elucidate whether Oct-2 protein expression is present in HD-derived cell lines, we performed a Western blot experiment using an antibody raised against the NH2 terminus of all of the Oct-2 isoforms. However, also using this NH2-terminal-binding antibody, Oct-2A and Oct-2B expression was absent in the three HD-derived cell lines (Fig. 3).

Lack of Oct-2 and Bob-1 protein expression in H-RS cells. Staining for Oct-2 and Bob-1 was performed in 20 cases of classical HD at primary diagnosis and in one reactive lymph node. For immunohistochemistry, staining of a nonmalignant reactive lymph node specimen was used as a positive control for Oct-2 and Bob-1 expression. Staining revealed nuclear expression of both Oct-2 and Bob-1 in GC lymphocytes (Fig. 5, A and B). In addition to these controls, epithelial cells and, if present, residual GCs were used as an internal negative and positive control, respectively. Analysis of 20 cases of classical HD showed absence of Oct-2 and Bob-1 expression in 18 and 20 cases, respectively (Table 1; Fig. 5, C and D). Two cases of

S. Poppema and N. L. Groningen, personal communication.

Fig. 4. RT-PCR analysis of Bob-1 shows the lack of transcription in six of seven HD-derived cell lines. Analysis of Bob-1 transcription in naïve B cells (IgD+CD27+) and GC B cells (CD38+CD77+; Lanes 1 and 2, respectively); in the B-lineage HD-derived cell lines L1236, L428, KM-H2, DEV, and L591 (Lanes 3–7, respectively); in the T-lineage HD-derived cell lines L540 and HDLM-2 (Lanes 8–9, respectively); in the lymphoblastoid B-cell lines IARC277 and BJA-B; and in Jurkat (Lanes 10–12, respectively). Lane 13, no template; M, molecular size marker (100-bp ladder).
transcription was observed. In contrast, transcription of Bob-1 was present in the cell line (DEV) derived from a patient with lymphocyte-predominant HD. Because the malignant clone in lymphocyte-predominant HD but not in classical HD expresses immunoglobulin genes, absence of Bob-1 expression in classical HD may reflect transcriptional deregulation of immunoglobulin genes specific for classical HD.

Previous studies (1–5, 30) demonstrated that the lack of immunoglobulin gene expression in a substantial proportion of classical HD cases is because of obviously destructive mutations of the rearranged immunoglobulin genes. Because transcription is important for somatic hypermutation (31) and H-RS cells harbor somatic mutations within their rearranged immunoglobulin genes, immunoglobulin gene transcription should have taken place in these cells. Thus, it is likely that in cases harboring nonfunctional immunoglobulin gene rearrangements the deregulation of transcription factors as presented here is a secondary event after the destructive immunoglobulin gene mutations.

Because three of the four analyzed HD-derived cell lines of B-cell origin [L1236 (5), L428 (32), and L5915] harbor destructive mutations within their immunoglobulin genes, in these cell lines the down-regulation of Oct-2 and Bob-1 seems to be a secondary event regarding absence of immunoglobulin gene expression. For the B-cell-derived cell line KM-H2, data are lacking with regard to the IgH and IgL genes and, therefore, the relevance of the down-regulation of both transcription factors as a primary event in the deregulation of immunoglobulin gene transcription is unclear.

To test the hypothesis that the lack of Oct-2 and Bob-1 is a common feature in H-RS cells of primary cases of classical HD, we performed immunohistochemistry for Oct-2 and Bob-1 in 20 cases of classical HD. In contrast to GC B cells, which showed strong nuclear staining for both Oct-2 and Bob-1, H-RS cells stained negative for both proteins in all of the informative cases. Results show that the lack of both transcription factors is a peculiar feature of H-RS cells. Because it is known that in a proportion of cases of classical HD the H-RS cells harbor potentially functional immunoglobulin gene rearrangements (3), one might conclude that in these cases, absence of Oct-2 and Bob-1 may represent the main cause for absence of immunoglobulin gene expression.

In summary, both Oct-2 and Bob-1 are absent in classical HD-derived cell lines and in all of the primary cases of classical HD tested thus far. Given that Oct-2 and Bob-1 expression is present in GC B cells, lack of Oct-2 and Bob-1 expression in classical HD-derived B-cell lines and in primary H-RS cells was an unexpected finding and may represent a novel mechanism involved in transcriptional deregulation of immunoglobulin genes in classical HD.

ACKNOWLEDGMENTS

We thank Julia Jesdinsky and Nadia Massoudi for excellent technical assistance.

REFERENCES


Oct-2 and Bob-1 Deficiency in Hodgkin and Reed Sternberg Cells

Daniel Re, Markus Müsschen, Tahamtan Ahmadi, et al.


Updated version
Access the most recent version of this article at:
http://cancerres.aacrjournals.org/content/61/5/2080

Cited articles
This article cites 31 articles, 16 of which you can access for free at:
http://cancerres.aacrjournals.org/content/61/5/2080.full.html#ref-list-1

Citing articles
This article has been cited by 22 HighWire-hosted articles. Access the articles at:
/content/61/5/2080.full.html#related-urls

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.