Expression and Specificity of FcIgG Receptor Sites on Neoplastic Lymphocytes

By Christoph Huber, Hans Dieter Flad, Kenneth Nilsson, Hans Wigzell, Gert Michlmayr, Heinrich Frischauf, and Herbert Braunsteiner

We investigated the ability of an FcIgG receptor marker to discriminate between subtypes of malignant lymphoproliferative diseases that differed in their clinical presentations. A quantitative radioimmunoassay was established that enabled us to evaluate average receptor densities on a population basis. Surface receptors were first saturated with IgG complexes. The number of membrane associated IgG molecules was subsequently determined with 125I-staphylococcal protein A. Results obtained with this assay on a battery of malignant lymphocytes suggested that the range of receptor densities of malignant B and T cells might overlap each other but would correlate with the degree of tumor cell differentiation and the clinical stage of the underlying disease. This behavior limits the use of this marker in the characterization of the derivation of malignant lymphocytes; these findings, however, may be useful in the prognostic classification of lymphomas of known origin.

During the last few years surface marker analyses have gained increasing importance in clinical hematology. One reason for this is that these analyses permit a reasonable classification of malignant lymphoproliferative diseases based upon the origin of the pathologic cells. In the present study we investigated surface receptors for the Fc portion of IgG (FcIgG-R), a structure frequently expressed on malignant lymphocytes. The primary goal of this study was to evaluate the ability of this marker to discriminate (1) between lymphomas of different origins and (2) between poorly and well differentiated malignancies of identical derivation.

Materials and Methods

Cells. Blood mononuclear cells and biopsy suspensions were studied from 22 patients with lymphoproliferative diseases, from 12 lymphoid cell lines, and from healthy controls. Twenty patients had non-Hodgkin lymphomas, which were morphologically classified according to the scheme of Lennert. Chronic lymphocytic leukemia (CLL) patients were staged according to the method of Rai into early (stage 0--II) and advanced (stage III--IV) disease. Two patients had T cell acute lymphocytic leukemia (T-ALL). The diagnoses were substantiated by immunologic and cytochemical standard techniques. Cell lines U-715, U-698, and U-937 were derived from non-Hodgkin lymphoma biopsies. All lines expressed surface immunoglobulins; two of them in addition exhibited complement receptors (U-715 and U-937). Two lines, Raji, Daudi, and U-47703 were obtained from Burkitt lymphoma biopsies. All three had surface immunoglobulins and complement receptors. The lines JIM, CCRF-CEM, CCRF-HSB 2, and MOLT-4 were estab-

From the Department of Internal Medicine, University of Innsbruck, Austria; Departments of Pathology and Immunology, University of Uppsala, Sweden; and the Department of Clinical Physiology, University of Ulm, Federal Republic of Germany.

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Address for reprint requests: Ch. Huber, M.D., Dept. of Internal Medicine, University of Innsbruck, Haematol. Immunol. Lab. II, A-6020 Innsbruck, Austria.

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lished from T-ALL patients. All four lines were to some extent capable of forming spontaneous rosettes and binding heterologous rabbit and human T cell sera. Cell line K-562 was established from a patient with chronic myelogeneous leukemia. This line lacks surface immunoglobulins and does not bind rabbit anti-human T cell sera. Besides these truly malignant cells, two lymphoblastoid lines of presumably nonmalignant origin (U-255 Bm, U-919 P1) were studied. The criteria for distinction of malignant cell lines from lymphoblastoid cells have been previously described.

**Isolation and storage of cells.** Mononuclear blood cells were isolated by means of gradient centrifugation on Lymphoprep (Nyegaard, Oslo, Norway). Phagocytic cells were removed by repeated iron treatment. Single-cell suspensions from grossly involved lymph nodes or spleens were obtained as previously described. Cells were tested on the same day or were frozen using a programmed freezing apparatus (Cryocon, Miden Beemster, The Netherlands). Frozen cells were kept in liquid nitrogen at a concentration of 4 x 10^6/ml in RPMI-1640 (Gibco, Grand Island, N.Y.) supplemented with 10% heat-inactivated fetal calf serum (Flow Laboratories) and 10% DMSO (Merck, Darmstadt, West Germany). Cryopreservation usually did not alter cell viability, nor did it change Fcγ-R density.

**Labeling of proteins with 125I.** Proteins were labeled with a modification of the chloramine-T method. Free ^125^I was removed on Sephadex G-25 (Pharmacia Fine Chemicals, Uppsala, Sweden). In most experiments specific activities of approximately 2 μCi/μg protein were used.

**Aggregation of IgG and isolation of the aggregates.** Human IgG (Behringwerke, Marburg, West Germany), 10 mg/ml in PBS, pH 7.4 was heat aggregated at 63°C for 20 min. Large aggregates were isolated by salt precipitation followed by ultracentrifugation, as reported earlier. Monomeric IgG and aggregates of defined sizes were obtained from linear sucrose density gradients after ultracentrifugation. Details will be published elsewhere. All aggregate preparations were centrifuged immediately before use at 2000 g for 20 min in order to remove insoluble complexes.

**Measurement of the average Fcγ-R density on a population basis.** Certain technical prerequisites were necessary in order to allow useful comparison of receptor densities among different types of lymphoid cells because some receptor assays show a striking specificity for Fcγ-R on L cells whereas others lack such restriction. The differences among the various methods were explained on the basis of a comparatively higher receptor affinity for L cells that permitted their detection at lower concentrations of IgG complexes.

To evaluate both high- and low-affinity receptors the following radioimmunoassay was established: Surface receptors were first saturated with IgG complexes. After appropriate washes the receptor number was then defined by the amount of surface-associated IgG molecules using ^125^I-labeled staphylococcal protein A (SpA). Under these conditions the amount of surface-bound IgG should be proportional to the number of Fcγ-R binding sites. We established the following microradioimmunoassay: 5 x 10^5 cells were first incubated with saturating amounts of HA IgG in a total volume of 150 μl phosphate-buffered saline with 0.02% sodium azide (PBS-A) for 30 min at 4°C in round-bottomed microtiter plates (System Cook; Greiner, Nürringen, West Germany). In prior experiments saturation curves were constructed by adding increasing amounts of IgG aggregates (from 5 to 1000 μg/ml) to a constant number of cells. Aggregate concentrations of 150 μg/ml were found to be saturating. This amount and a twofold higher concentration were routinely used in further experiments. Free aggregates were removed by washing four times with 200 μl PBS-A. The plates were centrifuged in a Hettich centrifuge (Hettich, West Germany) equipped with a plate holder. The cells were then resuspended in 100 μl PBS-A, and 50 μl ^125^I-SpA containing 1 x 10^5 cpm was added. After 30 min incubation at 4°C the plates were washed thrice and the cells were resuspended in 100 μl PBS-A and transferred to disposable plastic tubes. The tubes were counted for 1 min in a well-type gamma counter (Beckman, Biogamma II). All samples were tested in duplicate. The results are expressed in cpm of the aggregate samples minus SpA background. The latter was obtained from samples incubated in the absence of HA IgG. Controls performed included the use of erythrocytes instead of lymphocytes and the testing of the cell association of the label by means of autoradiography.

Fcγ-R were also demonstrated by autoradiography after incubation of viable cells with ^125^I-heated aggregated human IgG (HA IgG). Their distribution pattern on single cells was studied by means of quantitative autoradiography. Grain count distribution curves were performed from autoradiograms of normal and neoplastic lymphocytes.
**FC1gG RECEPTOR SITES ON LYMPHOCYTES**

**Binding of ¹²⁵I-IgG.** Direct binding studies were performed with labeled monoclonal or polyclonal IgG as well as with heat aggregates of defined sizes. Lymphocytes (2 x 10⁵) in 100 µl PBS-A were incubated with 0.5 µg ¹²⁵I-labeled protein. Incubations were performed in microtiter plates for 30 min at 4°C. After being washed four times the cells were transferred into counting vials as described above.

**Characterization of B and T lymphocytes.** B lymphocytes were characterized autoradiographically by the demonstration of surface-bound immunoglobulins.³,⁶ Routinely, ¹²⁵I-labeled monospecific antisera against human heavy and light chains were used.

T cells were characterized by spontaneous rosette formation with neuraminidase-treated sheep red blood cells¹⁷ and by specific binding of a rabbit anti-human T cell serum (generously supplied by Dr. H. Rodt, Institute für Hämatologie, München).

In some experiments FC1gG-R were demonstrated using rosette formation with rabbit 7S antibody coated sheep red blood cells.¹²

**Antibody-dependent cell-mediated cytotoxicity (ADCC).** A micromethod was established using the mouse lymphoma line L 1210 (Associated Biomedic Systems, Buffalo, N.Y.) as target cells and rabbit anti-L 1210 IgG antibody. The system was shown to measure human K cell activity of nonadherent, nonphagocytic cells.¹⁸ L 1210 cells were labeled with 250 µCi ⁵¹Cr (specific activity 100-200 Ci/mg Cr). Two thousand labeled L 1210 cells in 50 µl RPMI-1640 were incubated in microtiter plates with 50 µl of anti-L 1210 antibody diluted 1:1000 for 30 min at 4°C. Thereafter, various numbers of mononuclear cells were added in a volume of 100 µl. The mixture was incubated for 4 hr at 37°C and centrifuged at 500 g for 10 min at 4°C; then 100 µl of the supernatant was added to liquid scintillation fluid (Instagel, Packard). Counts per minute were measured in a liquid scintillation counter (Packard Model 3380). The percentage of specific ⁵¹Cr release was determined according to the formula

\[
\text{Percentage} = \frac{\text{CPM with antiserum} - \text{CPM with normal rabbit serum}}{\text{CPM total lysis in Zaponin} - \text{CPM with normal rabbit serum}} \times 100.
\]

Lytic units were determined graphically and expressed as that number of effector cells x 10⁻⁵ necessary to give a specific ⁵¹Cr release of 30%. Thus the number of killer cells in a given suspension is indirectly correlated with the number of lytic units.

**RESULTS**

**Density of FC1gG-R on a single cell level.** Relative receptor densities were evaluated from individual cell suspensions by means of quantitative autoradiography. As shown in Fig. 1, a multimodal distribution profile was found on normal blood lymphocytes. With respect to the receptor density, at least two major subsets of normal lymphocytes were characterized, one with a high and one with a very low FC1gG-R concentration. Fractionation procedures and double-staining techniques showed that the low-density peak was composed almost exclusively of T lymphocytes; cells with a high FC1gG-R density (>40 grains after 7 days of exposure) were mainly B and non-B and non-T cells contaminated with a small percentage of strongly FC1gG-R+ T cells.

The following experiments were performed: Combination of spontaneous rosette formation with autoradiographic demonstration of aggregate binding showed that approximately 2% of T lymphocytes had high receptor density (12 experiments; see also ref. 3). Almost no FC-R⁺ cells were detected in suspensions after passage through Ig/anti-Ig-coated Degelan columns¹⁸,¹⁹ (three experiments). In contrast, suspensions depleted of spontaneous rosette-forming cells by density gradient centrifugation contained 84% cells with high receptor expression; 51% showed surface-bound IgM, and only 5% formed spontaneous rosettes (three experiments; see also ref. 3).

In contrast to the result with normal cells, a unimodal, Gaussian-like dis-
Fig. 1. Grain count distribution curves of human peripheral blood lymphocytes and established lymphoid cell lines after incubation with \(^{125}\)I-HA\(\text{lgG}\). HPBL, human peripheral blood lymphocytes; K 562, myeloid cell line; Raji, Burkitt lymphoma line; Molt-4, T cell line.

Distribution was observed in cases of neoplastic lymphocyte proliferation, indicating the homogeneity of these cells.

**Density of Fc_{\text{IgG}}-R on a population basis.** Average Fc_{\text{IgG}}-R density on a population basis was measured on a variety of different lymphoid cell suspensions using the SpA assay. In prior experiments we compared the \(^{125}\)I-SpA data with those obtained in direct binding experiments. The latter contained rosette formation with 7S rabbit antibody-coated sheep red blood cells, with \(^{125}\)I-labeled myeloma proteins, and with \(^{125}\)I-labeled HA\(\text{lgG}\). A representative experiment using four cell types of different origins is shown in Table 1. From these data we concluded that the sandwich assay described here represented a useful tool for the evaluation of Fc_{\text{IgG}}-R. Tables 2 and 3 indicate the cell-associated IgG quantitated after saturation of surface Fc_{\text{IgG}}-R with HA\(\text{lgG}\).

Well-differentiated malignant B cells had a higher average receptor number than poorly differentiated ones from lymphoma biopsies and lines (Table 2). The average values of the latter were comparable with those of poorly differentiated malignant T cells (Table 3). In contrast, almost no Fc_{\text{IgG}}-R were detected on leukemic blood cells from one case of T-CLL (Table 3). Thus it would appear that Fc_{\text{IgG}}-R expression among malignant lymphocytes depends on both their derivation and their degree of morphologic differentiation.

Other experiments compared receptor densities of nonmalignant and malignant lymphocytes. On the average, normal lymphocytes with high receptor expression, as well as lymphoblastoid cell lines of nonmalignant derivation, had higher receptor numbers than malignant B or T cells (Table 2 and 3). Among well-differentiated lymphomas of B cell origin, however, some cases disclosed values in the range of the above-mentioned nonmalignant cell types (Table 2).
The measurement of the average receptor density on a population basis therefore does not clearly distinguish between nonmalignant and malignant lymphocytes.

The effect of activation of normal lymphocytes on receptor expression was also studied. 

<table>
<thead>
<tr>
<th>B Cell Type</th>
<th>No. of Cases</th>
<th>SpA Assay (cpm ± SEM) (SpA-Background)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>Poorly differentiated, lymphoblastic lymphomas, EBV negative lymphoma lines (U-715, U-698, U-937)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Burkitt lymphoma lines (Daudi, Raji, U-47 703)</td>
<td>3</td>
</tr>
<tr>
<td>Malignant</td>
<td>Well-differentiated, lymphocytic lymphomas</td>
<td>17</td>
</tr>
<tr>
<td>Nonmalignant</td>
<td>Poorly differentiated, lymphoblastoid cell lines u-255 Bm, U-919 Pl</td>
<td>2</td>
</tr>
<tr>
<td>Nonmalignant</td>
<td>Well-differentiated, normal peripheral blood lymphocytes with high density of FcγR*</td>
<td>6</td>
</tr>
</tbody>
</table>

* The values for normal peripheral blood lymphocytes with high density of FcγR* were calculated using the formula:

\[
\text{Percentage cells with high FcγR expression} = \frac{\text{cpm 125I-SpA assay}}{100}. 
\]

Well-differentiated lymphocytes: small cells, very thin layer of cytoplasm, and nuclei containing large coarse chromatin masses. Poorly differentiated lymphocytes: large size, easily visible cytoplasm, and chromatin less pachychromatic than in small lymphocytes.
Fig. 2. FcigG-R density on blood lymphocytes of CLL patients in early (stage 0–II) and advanced (stage III–IV) disease ($t = 3.5430$, $df = 17$, $p < 0.005$).

Average blood lymphocyte receptor densities were compared between patients with early (stage 0–II) and advanced (stage III–IV) disease. Both groups had comparable average leucocyte counts. The data shown in Fig. 2 suggest that during progression of CLL FcigG-R density diminishes.

Specificity of FcigG-R on neoplastic lymphocytes. The subclass and the aggregate specificity of FcigG-R were analyzed on several neoplastic lymphocyte populations. To test the subclass specificity of FcigG-R, human $^{125}$I-labeled myeloma proteins of the four subclasses of IgG were subsequently tested in a
direct binding assay against a panel of tumor cells and normal blood lymphocytes. Figure 3 shows a representative experiment from this series. Although marked quantitative differences were observed among the different cell types tested, the labeling patterns of the four myeloma proteins remained constant. Thus IgG3 bound better than IgG1, IgG1 better than IgG2, and IgG2 better than IgG4. In particular, no differences were observed between malignant and normal cells.

To test the aggregate specificity of the receptor, 125I-labeled heat aggregates of defined sizes, isolated by means of density gradient ultracentrifugation as well as monomeric IgG, were tested for their capacity to bind to normal and neoplastic lymphocytes. As shown in Table 4, all suspensions tested bound more large aggregates than small ones. Very low and unstable binding was found with monomeric IgG. Again no difference between the malignant populations tested and the normal blood lymphocytes was detectable.

**Table 4. Binding of 125I-labeled Aggregated and Monomeric IgG to Various Lymphoid Cells**

<table>
<thead>
<tr>
<th>Complex Size</th>
<th>HPBL</th>
<th>Burkitt Lymphoma (Raji)</th>
<th>ALL (Molt-4)</th>
<th>CLL (LW)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;80S</td>
<td>5.4</td>
<td>2.5</td>
<td>1.7</td>
<td>4.7</td>
</tr>
<tr>
<td>80-50S</td>
<td>5.9</td>
<td>1.7</td>
<td>1.5</td>
<td>6.1</td>
</tr>
<tr>
<td>50-20S</td>
<td>3.2</td>
<td>1.2</td>
<td>0.9</td>
<td>3.3</td>
</tr>
<tr>
<td>7S</td>
<td>0.5</td>
<td>0.1</td>
<td>0.1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Amount of surface-bound 125I-labeled IgG (pg protein/3 × 10^6 cells).
Fig. 4. Fc\textsubscript{\textit{mg}}-R density and lytic capacity of blood lymphocytes of normal controls and CLL patients. Average density values of strongly Fc\textsubscript{\textit{mg}}-R\textsuperscript{+} cells were calculated as described in Table 2. Serial dilutions of effector cells were performed to define the number of lytic units required to gain a 30% target cell lysis. Hatched area represents range of normal blood lymphocytes (\(n = 6\)); dots, individual CLL cases tested.

Analyses of surface markers on cells holds promise for the understanding of membrane-controlled functions. A molecule that has attracted major interest in this regard is a structure expressed on certain cells of the immune system called the Fc\textsubscript{\textit{mg}}-R. Macrophages,\textsuperscript{21} and neutrophils,\textsuperscript{22} as well as certain types of lymphocytes, express such receptors. High receptor numbers were found on at least three different subpopulations of normal lymphocytes: on B cells,\textsuperscript{23} 24 on undefined cells with lymphoid morphology lacking B or T cell–specific surface markers (O, U, L cells),\textsuperscript{26} 28 and on a small subset of T cells,\textsuperscript{25} 29,30 capable of mediating ADCC. Average receptor densities of strongly Fc\textsubscript{\textit{mg}}-R\textsuperscript{+} cells were calculated as described above. Their numbers were plotted against the numbers of lytic units required to gain a 30% target cell lysis (Fig. 4). Normal lymphocyte suspensions contained less than 25% of strongly Fc\textsubscript{\textit{mg}}-R\textsuperscript{+} cells. The average receptor density of these cells was high, and only very few lytic units were required to gain a 30% target cell lysis. In contrast, CLL blood on average contained 70% strongly Fc\textsubscript{\textit{mg}}-R\textsuperscript{+} cells. These cells expressed a lower average receptor density, and many more lytic units were required than in normal controls. This highly reduced capacity to mediate ADCC, however, was observed in one CLL case where a nearly normal Fc\textsubscript{\textit{mg}}-R density was expressed. We therefore concluded that a simple reduction of the receptor numbers does not exclusively account for the deficient ADCC response of CLL lymphocytes.

DISCUSSION

Analyses of surface markers on cells holds promise for the understanding of membrane-controlled functions. A molecule that has attracted major interest in this regard is a structure expressed on certain cells of the immune system called the Fc\textsubscript{\textit{mg}}-R. Macrophages,\textsuperscript{21} and neutrophils,\textsuperscript{22} as well as certain types of lymphocytes, express such receptors. High receptor numbers were found on at least three different subpopulations of normal lymphocytes: on B cells,\textsuperscript{23} 24 on undefined cells with lymphoid morphology lacking B or T cell–specific surface markers (O, U, L cells),\textsuperscript{26} 28 and on a small subset of T cells,\textsuperscript{25} 29,30 capable of mediating ADCC. Average receptor densities of strongly Fc\textsubscript{\textit{mg}}-R\textsuperscript{+} cells were calculated as described above. Their numbers were plotted against the numbers of lytic units required to gain a 30% target cell lysis (Fig. 4). Normal lymphocyte suspensions contained less than 25% of strongly Fc\textsubscript{\textit{mg}}-R\textsuperscript{+} cells. The average receptor density of these cells was high, and only very few lytic units were required to gain a 30% target cell lysis. In contrast, CLL blood on average contained 70% strongly Fc\textsubscript{\textit{mg}}-R\textsuperscript{+} cells. These cells expressed a lower average receptor density, and many more lytic units were required than in normal controls. This highly reduced capacity to mediate ADCC, however, was observed in one CLL case where a nearly normal Fc\textsubscript{\textit{mg}}-R density was expressed. We therefore concluded that a simple reduction of the receptor numbers does not exclusively account for the deficient ADCC response of CLL lymphocytes.
suppressing B lymphocyte differentiation. In studies of malignant lymphocytes, we and others have observed that FcIgG-R represent primarily a feature of malignant B cells and undefined lymphocytes. In this paper we further investigated the ability of this marker to discriminate between subtypes of malignant lymphoproliferations differing in their clinical presentations.

**Receptor expression on malignant lymphocytes.** Receptor density was studied on a battery of neoplastic B and T cells obtained from poorly or well-differentiated malignant lymphomas at various stages of disease. These experiments were aimed at answering three main questions: Do B and T cell malignancies basically differ in their FcIgG-R numbers? Do poorly and well-differentiated malignant lymphomas of identical derivation differ in their receptor densities? Do malignant cells from early stages of certain malignant lymphomas differ in their receptor numbers from those obtained from advanced stages?

The results obtained from a still limited number of malignant proliferations suggested that the average receptor density of malignant B and T cells overlap each other but correlate with the degree of tumor cell differentiation and the clinical stage of the underlying disease. This conclusion is based upon the following main findings: The average receptor density of poorly differentiated B malignancies equaled that of poorly differentiated T malignancies. Poorly differentiated B cell malignancies had a lower receptor expression than well-differentiated B cell malignancies. B-CLL cells from early stages had higher receptor numbers than those from advanced stages. These findings limit the value of the FcIgG-R marker in typing malignant lymphocytes by population. However, they suggest the utility of such studies in the further prognostic classification of malignant lymphoproliferative disease of known origin.

**Comparison of FcIgG-R features between normal and malignant lymphocytes.** Further experiments compared some features of FcIgG-R in normal and malignant lymphocytes including quantitative receptor expression, ADCC mediation, IgG subclass, and aggregate size specificity. Also investigated was the receptor density of resting, well-differentiated versus activated, poorly differentiated cells. Receptor analyses on a single-cell level by means of quantitative autoradiography showed marked differences in the receptor patterns of normal and malignant lymphocytes. Whereas malignant lymphocyte suspensions were predominantly composed of cells with rather homogeneous receptor density, normal lymphocytes had a polyclonal pattern. Fractionation experiments of the latter confirmed earlier reports indicating that high receptor expression is primarily associated with B cells, L cells, and a small subset of T lymphocytes. Very low receptor density was a feature of the major population of peripheral T cells. In contrast to the single-cell data, evaluation of the average receptor expression on a population basis rarely enabled us to discriminate between normal and neoplastic cells, largely because of the marked variations of receptor densities observed among different types of lymphoproliferative diseases. Our study failed to disclose any relationship between FcIgG-R density of malignant lymphocytes and their capacity to mediate ADCC. Both low and high receptor-positive malignant B cells failed to lyse IgG-coated targets. Normal B cells have also been shown to lack this capacity. It therefore seemed unlikely that a simple reduction of the receptor molecules accounts exclusively for this defi-
ciency. Whether the lack of ADCC responsiveness is due to the B cell nature of CLL or is consequent to the malignant state remains to be determined.

Our search failed to demonstrate clearcut differences in the IgG subclass and aggregate size specificity of Fc\_lgG-R on normal and malignant lymphocytes. Since normal lymphocytes not further fractionated into subsets were used, the existence of distinct receptor properties on certain normal subsets was not excluded.

Further experiments concerned changes in the receptor expression during activation of normal lymphocytes. Cell suspensions, which after passage through Ig/anti-Ig columns were almost exclusively composed of Fc\_lgG-negative T cells, were activated in MLC. The average receptor density of sensitized lymphocytes at the peak of the response was greater than that of unsensitized cells. These findings are in agreement with those obtained in experimental animal models and support the view that the expression of Fc\_lgG-R may change during cellular differentiation.

In conclusion, we thus would state that Fc\_lgG-R expression among human lymphocytes depends not only on their lineage but also on their stage of differentiation. This behavior limits the use of such structures in the characterization of the derivation of malignant cells but is promising for the prognostic classification of lymphomas of known origin.

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