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SOLUBLE FORMS OF p55-IL-2Rα, CD8, AND CD30 MOLECULES AS MARKERS OF LYMPHOID CELL ACTIVATION IN INFECTIOUS MONONUCLEOSIS

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ABSTRACT

Background. **Epstein-Barr virus (EBV) infection in infectious mononucleosis (IM) is associated with lymphocyte activation leading to the expansion of cells expressing activation-associated antigens. Most of these antigens are released as soluble molecules *in vitro* and *in vivo*.**

Methods. **We investigated the serum levels of the soluble forms of the CD8 (sCD8), p55-IL-2Rα (sIL-2Rα), and CD30 (sCD30) molecules in 55 patients following primary EBV infection. These data were compared with the phenotypic pattern of circulating lymphoid subsets.**

Results. **In all cases at presentation, lymphocytosis, mainly characterized by the expansion of a $CD8^+$, $HLA\text{-}DR^+$, $p75\text{-}IL\text{-}2R\beta^+$, $p55\text{-}IL\text{-}2R\alpha^-$ population, was associated with high levels of the investigated soluble molecules. Their mean values (±SD) were: 17,172±12,885 U/mL for sCD8 (vs 334±95 in controls), 2,922±2,813 U/mL for sIL-2Rα (vs 331±115 in controls), and 477±451 U/mL for sCD30 (vs 4.9±6.4 in controls). Follow-up study (15 cases, up to 60 days) showed a progressive decline of all soluble molecules, associated with a reduction of activated $CD8^+/HLA\text{-}DR^+/p75\text{-}IL\text{-}2R\beta^+$ T-cells. By the 30th day, values of sIL-2Rα and sCD30 (729±333 U/mL and 20±21 U/mL, respectively) were only slightly higher than in normal controls, whereas sCD8 levels remained consistently higher (1,777±1,385 U/mL, p<.001).**

Conclusions. **sCD8, sIL-2Ra and sCD30 serum levels in IM reflect the total bulk and/or the activation-related events of infected and reactive cells. The variations in these soluble molecules during the follow-up provide useful information on the *in vivo* biological modifications occurring after EBV infection.**

Key words: infectious mononucleosis, cell activation, sCD8, sIL-2Rα, sCD30

Infectious mononucleosis (IM) results from Epstein-Barr virus (EBV) infection of B lymphocytes.[1] Following EBV infection, B-cells are activated and triggered to proliferate in response to a number of cytokines and EBV-encoded products.[2-5] The uncontrolled proliferation of infected B-cells is prevented by a transient reactive expansion of cytotoxic/suppressor polyclonal $CD8^+$ lymphocytes. These cells, which account for the lymphocytosis that characterizes the acute phase of IM,[1,6,7] display features of activated and cytotoxic T-cells, including the expression of HLA-DR antigens and p75 interleukin-2 receptor (IL-2Rβ) molecules.[6,7] Only a minority of them are EBV-specific HLA-restricted CTL.[8]

A number of activation-associated antigens are released as soluble molecules by lymphoid

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cells *in vitro* and *in vivo*. Among them, the soluble forms of the CD8 (sCD8), p55-IL-2Rα (sIL-2Rα), and CD30 (sCD30) molecules have been found at increased levels in the serum in a variety of neoplastic and reactive conditions, including IM.[9-19] In this latter condition the very high serum levels of sCD8 have been interpreted as the by-product of the expanded bulk of $CD8^+$ cells.[12,17,20]

On the contrary, the mechanisms leading to increased levels of sIL-2Rα and sCD30 in IM have not yet been elucidated. In fact, membrane expression of IL-2Rα is not detectable in a significant proportion of circulating cells in this condition,[7,17,21-23] and CD30 cell expression has not been investigated.

Interest in investigating the pattern of CD30 cell expression in IM derives from the knowledge that this activation-associated antigen, which is normally restricted to a few activated T and B blasts within normal lymphoid tissues, is inducible *in vitro* following EBV infection.[24-26]

In the present study we investigated the serum levels of sCD8, sIL-2Rα, and sCD30 in a large series of patients with IM at diagnosis, in relation to the phenotypic pattern of the circulating lymphoid subpopulations.

In addition, in order to investigate possible role of soluble molecule detection in monitoring the immunological events following antigen-driven lymphocyte expansion, and the reconstitution of lymphocyte homeostasis after immune response, we performed a time-course analysis of sCD8, sIL-2Rα, and sCD30 serum levels with relation to variations in the composite pattern of membrane antigen expression.

Materials and Methods

Patients

Fifty-five patients, aged 14 to 31 years, with acute-phase IM at diagnosis were studied. The diagnosis was based on typical clinical symptoms and hematological findings, and supported in all cases by specific serological parameters and morphological features of peripheral blood (PB) smears.[7] Fifteen patients were monitored for the investigated parameters (see below) at 1, 2, 3, and 4 weeks, and between 30 and 60 days from diagnosis when all clinical and hematological parameters had returned to normal. Normal controls were 30 age-matched healthy blood donors.

Suspensions of mononuclear cells (PBMC) were obtained after Ficoll-Hypaque gradient separation from freshly drawn heparinized PB. PBMC were incubated with fluorochrome-conjugated monoclonal antibodies (mAb) recognizing CD3, CD4, CD8, HLA-DR, CD19, CD25 (IL-2Rα) (from Becton-Dickinson, Sunnyvale, CA), and CD30 (Ki-1 and Ber-H2, Dako A/S, Glostrup, Denmark) molecules. Indirect immunofluorescence with unconjugated anti-p75-IL-2Rβ mAb (Tu27, kindly provided by Dr. M. Tsudo, Tokyo, Japan) was performed using a phycoerythrin (PE)-conjugated goat anti-mouse immunoglobulin mAb (from Becton-Dickinson) as revealing reagent. Double staining with CD4/CD8 and CD8/HLA-DR mAbs was also performed in all cases by combining fluorescein (FITC)- and (PE)-conjugated reagents. Checks were performed using isotype-matched mAbs. The analysis was carried out by flow cytometry (FACScan, Becton-Dickinson, Sunnyvale, CA).

In order to detect possible cytoplasmic expression of CD30 and CD25, these two antigens were also investigated on cytospin preparations of PBMC kept frozen at –70°C, using the alkaline phosphatase anti-alkaline phosphatase (APAAP) immunocytochemical technique.

Detection of serum levels of sIL-2Rα, sCD8 and sCD30 molecules

Frozen sera, collected at diagnosis and thereafter at the time of complete blood count and immunophenotypic analysis, were investigated by enzyme-linked immunosorbent assays for the levels of sCD8 (T8 test kit, T Cell Sciences, Cambridge, MA), sIL-2Rα (CELLFREE interleukin-2 Receptor Test Kit, T Cell Sciences, Cambridge, MA), and sCD30 (DAKO CD30 [Ki-1 antigen] ELISA, DAKO A/S, Glostrup, Denmark). The mean (±SD) serum levels of investigated soluble molecules in arbitrary units per mL (U/mL) in controls were 334±95 for sCD8, 331±115 for sIL-2Rα, and 4.9±6.4 for sCD30.

Statistical analysis

Student's t-test was used to compare the mean values of the parameters analyzed. Linear correlation analysis was utilized to correlate the serum levels of sCD8, sIL-2Rα, and sCD30 with other hematological data.

Results

The results of the immunophenotypic analysis performed at diagnosis are given in Table 1. A pronounced lymphocytosis was present in all cases (mean 9,700±7,112×10^6/L), mainly related to an expansion of T cells ($CD3^+$ lymphocytes: 80.4±9.1%) with a $CD8^+$ phenotype ($CD8^+$ cells: 58.2±14.25% vs 20±4.91% in controls). As a consequence, the CD4/CD8 ratio was 0.24±0.16 vs 2.2±0.6 in controls. The proportion of $CD8^+$ cells co-expressing HLA-DR was 40.48±21.32%, as compared to 5±2.9% in controls. Most PBMC expressed the p75-IL-2Rβ molecule (CD122: 61.4±21.74% vs 9.7±3.9% in controls), whereas only a small proportion of them were $CD25^+$ (p55-IL-2Rα), either at flow cytometry or at immunocytochemical analysis. B cells, as defined by CD19 immunoreactivity, were fewer than in controls when evaluated as a percentage (2.91±3.87 vs 9.03±3.1%), but quite similar or slightly increased in terms of absolute number (282.17±375.39 vs 195.95±67.27). $CD30^+$ cells were less than 1% in all cases at flow cytometry analysis. Similar figures were obtained at immunocytochemical analysis, with the $CD30^+$ cells accounting for less than 1% in each cytospin preparation in the various cases.

Each individual measurement of soluble molecules detected at diagnosis exceeded the range observed in normal controls (Figure 1).

Mean values were as follows: sCD8 17,172±12,885 U/mL, sIL-2Rα 2,922±2,813 U/mL, and sCD30 477±451 U/mL. The search for a possible correlation between individual values of the various soluble molecules and the absolute number of circulating lymphocytes, T-cells ($CD3^+$ cells), $CD8^+$ and $CD8^+$/HLA-DR^+ lymphocytes showed a significant relationship only between sCD8 values and $CD8^+$ cells ($r=0.37$; $p<0.01$).

Figure 2 summarizes the data for the investigated soluble molecules and circulating lymphoid populations, as obtained in 15 cases evaluated during follow-up (from diagnosis up to 60 days). From the 7th day on there was a progressive decline in all soluble molecules that paralleled the decrease in lymphocytes, $CD3^+$, $CD122^+$ and $CD8^+$/HLA-DR^+ cells. By the 30th day, the values of sIL-2Rα (729±333 U/mL) and sCD30 (20±21 U/mL) were still slightly higher than in controls ($p=.001$ and $p=.018$, respectively), whereas sCD8 levels remained consistently increased (1,777±1,385 U/mL vs 334±95; $p<.001$).

Discussion

In this study we demonstrated that in the

Table 1. Immunophenotypic analysis of peripheral blood lymphocytes in infectious mononucleosis at diagnosis (mean values±SD).

	Lymph. x10^6/L (n=55)	CD3 % (n=55)	CD19 % (n=49)	CD4 % (n=55)	CD8 % (n=55)	CD4/CD8 ratio (n=55)	CD8/ HLA-DR* (n=55)	CD25 % (n=42)	CD122 % (n=34)	CD30 % (n=32)
IM	9,700 ±7,112	80.4 ±9.1	2.91 ±3.87	13.73 ±7.11	58.2 ±14.25	0.24 ±0.16	40.48 ±21.32	2.11° ±1.69	61.4 ±21.74	<1
Controls (n=30)	2,170 ±189	73.1 ±8.3	9.03 ±3.1	45.60 ±8.12	20.0 ±4.91	2.2 ±0.6	5.0 ±2.9	<2°	9.7 ±3.9	none

*percentage among $CD8^+$ cells

°absolute number (x10^6/L): $CD25^+$ = 198±165 vs <80 in controls

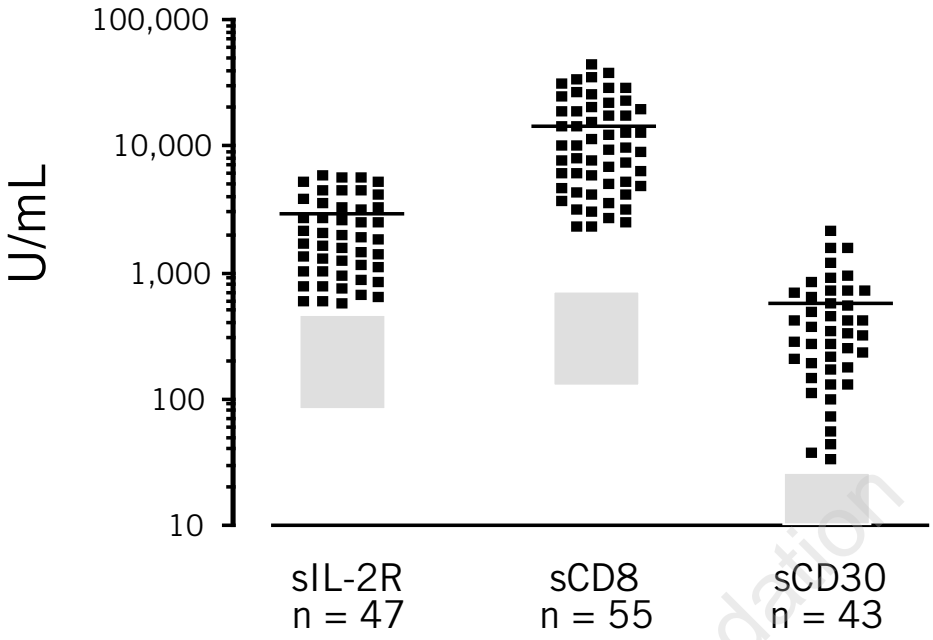

Figure 1. Individual serum values of sIL-2Rα, sCD8, and sCD30 in infectious mononucleosis at diagnosis. Shaded areas represent the range of values observed in controls.

acute phase of IM the expansion of the $CD3^+$ T-cell population with the $CD8^+$, $HLA\text{-}DR^+$, p75-IL-2Rβ^+ phenotype is associated with increased serum levels of sCD8, sIL-2Rα and sCD30 molecules. The increase was particularly striking for sCD8 and sCD30. The levels of these soluble molecules progressively declined, along with the reduction in the phenotypically recognizable activated T-cell population, which was strictly related to the cytotoxic potential generated after EBV activation to control the expansion of infected B-cells.[6-8] Therefore, serum levels of sCD8, sIL-2Rα, and sCD30 in IM appear to be markers of ongoing phenomena, closely related to the extent of immune activation. Our findings prompt a number of questions regarding the origin and the clinical and biological significance of sCD8, sIL-2Rα, and sCD30 in IM.

The source of the very high sCD8 serum levels observed during the active phase of IM is obviously the expanded $CD8^+$ cell population which, it has been suggested, becomes prone to release the circulating soluble form of the membrane-bound CD8 molecule as a consequence of activation.[12] This interpretation, however, has never been supported by formal proof. Indeed, most $CD8^+$ cells in active IM express activation-related antigens, such as HLA-DR and p75-IL-2Rβ molecules,[7-9] and the values of sCD8 levels parallel those of circulating activated $CD8^+$ cells in all clinical phases of the infection[12] (Figure 2). However, it has been demonstrated recently, both *in vitro* and *in vivo*, that T-cell activation is associated with a transition from a *naive* ($CD45RA^+$) to a *primed* ($CD45RO^+$) phenotype and with a decrease of bcl-2 expression.[27-30] These features were significantly correlated with the apoptotic death of activated T-cells.[29-31] On the basis of these observations, it is thought likely that the high sCD8 levels observed in IM are related not to the expansion of activated T-cells *per se*, but to their apoptotic death following activation. According to this interpretation, detection of sCD8 should be regarded as a marker of activation-related cell death.

Our data do not offer an obvious explanation for the finding of elevated serum levels of sIL-2Rα in IM at presentation, and or their progressive decrease in the following weeks. In fact, the

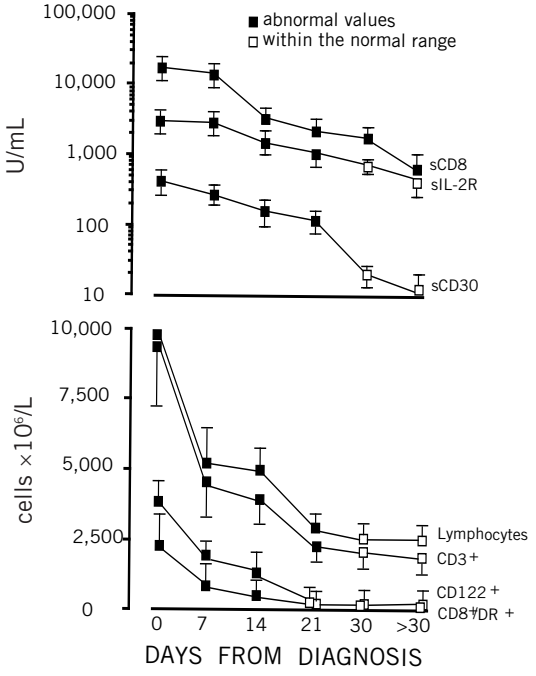

Figure 2. Variations of the mean serum levels (±SD) of sCD8, sIL-2Rα and sCD30 in relation to those of the main circulating lymphoid sub-populations observed in the time-course analysis in 15 patients with infectious mononucleosis.

increase in sIL-2Rα is not associated with the presence of a substantial number of circulating IL-2Rα⁺ cells, and this is in agreement with previous observations.[6-8,22,23] One possible explanation is that sIL-2Rα-releasing cells are not circulating in the blood, but are compartmentalized within the lymph nodes. Should this be the case, the possible candidates could be activated tissue-seeking T-cells, macrophages, or EBV-infected B-cells. Although extensive immunohistological studies are necessary to verify these possibilities, preliminary data obtained from immunostaining with the CD25 mAb of lymph node sections in two cases of IM failed to demonstrate substantial CD25 immunoreactivity (Chilosi, personal observation). The alternative, more plausible, possibility is that the increased sIL-2Rα levels derive from the expanded CD8⁺ cytotoxic/suppressor population, in which IL-2Rα membrane expression, induced in the early phase of the infection as a consequence of activation to confer on the IL-2R complex a high affinity for IL-2 (not ensured by the sole expression of p75-IL-2Rβ),[32] has been quickly down-regulated to decrease the proliferative potential. The rapid drop in sIL-2Rα levels observed during the time-course analysis of our cases seems to support this possibility, which is in line with the notion that T-cell activation *in vitro* induces transient expression of IL-2Rα followed by its down-regulation and disappearance within 72-96 hours.[21,22]

Previous studies demonstrated that CD30 antigen expression is inducible *in vitro* on lectin-stimulated blood T and B blasts and virally (HTLV-1 and 2, EBV) transformed T and B cells.[24,26] These observations suggest at least two possible sources for the release of sCD30 detected at high concentration in IM, i.e. activated T-cells, and EBV-infected B-cells. Our data do not support the former hypothesis, since CD30 expression was not observed in the large majority of circulating lymphocytes, mainly represented by activated T-cells. On the contrary, the low frequency of CD30⁺ cells suggests that CD30 may be expressed upon activation by EBV-infected B-cells. This possibility is supported by evidence that in IM EBV-encoded small nuclear RNA (EBER) is detectable in the peripheral blood, by *in situ* hybridization techniques, in percentages similar to those of CD30⁺ cells (Rigo, personal observation). CD30 expression by EBV-infected B-cells[15,24,26] could represent a key step for the regulation of their proliferation. In fact, CD30 is a receptor for a new membrane-bound cytokine, the CD30 ligand, that shares a number of structural and functional similarities with another cytokine like TNF,[33,34] which is involved in B cell proliferation.[33,35] In addition, CD30 expression is up-regulated by EBV-related viral molecules such as EBNA2 and, in particular, LMP1,[5,36] which is involved in controlling the proliferation of infected B-cells.[2-5,26] According to this view, CD30 molecule expression as a consequence of EBV-driven B-cell proliferation could be of importance in the development of certain malignant lymphomas, especially those arising in immunocompromized individuals.[37,38]

Taken together, our findings indicate that

sCD8, sIL-2Rα and sCD30 serum levels in IM reflect the total bulk and/or the activation-related events of infected and reactive cells. This issue must be viewed in the context of the complex network of cytokines released by EBV-infected cells and the neighboring EBV-negative ones in IM.[39] The variations in these soluble molecules during follow-up provide useful information on the *in vivo* biological modifications occurring after EBV infection.

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