Nuclear Protein Patterns in Normal T-Lymphocytes and Lymphoblastoid Cells

Josep M. Estañol, Neus Agell, and Oriol Bachs

ABSTRACT

We compared the two-dimensional patterns of nuclear proteins obtained from normal quiescent T lymphocytes with those from normal proliferating T lymphocytes and three lymphoblastoid cell lines (CEM, Namalwa, and Molt-4). We identified sets of nuclear proteins which are specific for normal quiescent or normal proliferating T lymphocytes, or shared by the three lymphoblastoid cell lines and absent from the normal T cells. The protein patterns from two nuclear subfractions, i.e., S1 fraction, obtained after nuclease extraction, and the nuclear matrix, were also analyzed. In S1 nuclear fraction, 6 proteins of 75 kDa (isoelectric point (pI) 4.4), 55 kDa (pI 6.7), 41 kDa (pI 4.1), 39 kDa (pI 5.0), 32 kDa (pI 5.5), and 29 kDa (pI 6.6) were found to be specifically present in normal quiescent cells but not in normal proliferating or lymphoblastoid cell lines. Five proteins of 23 kDa (pI 4.2), 23 kDa (pI 4.3), 22 kDa (pI 4.4), 21 kDa (pI 4.5), and 21 kDa (pI 4.6) were observed only in the S1 fraction of normal proliferating lymphocytes, whereas they were absent in normal quiescent cells and in the transformed cell lines. Eight proteins of 56 kDa (pI 4.7), 50 kDa (pI 4.6), 45 kDa (pI 4.4), 43 kDa (pI 4.3), 42 kDa (pI 4.3), 41 kDa (pI 4.3), 43 kDa (pI 4.2), and 42 kDa (pI 4.1) were found only in the nuclear matrix of normal quiescent cells. Moreover, two doublets of proteins of 31–33 kDa (pI 4.3) and 31–33 kDa (pI 4.2) were found only in the nuclear matrix of the normal proliferating cells and three proteins of 37 kDa (pI 3.8), 37 kDa (pI 3.7), and 35 kDa (pI 4.5) were specifically present in the nuclear matrix of the lymphoblastoid cell lines, but not in normal quiescent or activated lymphocytes.

INTRODUCTION

The genesis and progression of a tumor are suspected to be consequence of a multistep process involving a number of mutations in specific genes. These mutations generate aberrations in the expression of cell growth and tissue-specific genes and in consequence the mechanisms that control normal cell proliferation become deregulated. Thus, the identification of the genes whose expression is specifically modified during the onset and progression of neoplasia and the mechanisms responsible are fundamental to understand how a cell transforms from normal to neoplastic.

During the last few years some of the key genes involved in the control of the cell cycle have been identified. Examples are retinoblastoma, p53, cyclins, cyclin-dependent kinases and cyclin-dependent kinase inhibitors (1–5). The deregulation of these genes is very important in the genesis of different types of tumors (6–12), although the expression of other genes involved in cell proliferation is also altered in cancer cells and supposed to participate in oncogenesis (13). In spite of the abundant information about genes altered in cancer cells, a clear picture of how a cell becomes cancerous is still not established. To complete this picture, the precise function of these genes has to be elucidated. It also seems evident that other genes involved in oncogenesis still remain to be identified. Thus, the finding of new genes that participate in the control of cell proliferation is still an important aim to be achieved to elucidate the steps leading to cell transformation.

One of the approaches recently developed to identify gene products whose expression is modified in tumor cells is the comparative analysis of protein patterns obtained by high-resolution two-dimensional electrophoresis from normal and tumor cells. Attention has been preferentially paid in the analysis of the protein patterns from nuclear matrix fractions (14–18). Nuclear matrix is a nonchromatin nuclear substructure organized as a proteinaceous network of fibers which may contribute to the organization of the chromatin, transcriptional regulation of gene expression, and DNA replication (19, 20). Since nuclear matrix plays an essential role in supporting most of the important nuclear functions, it has been postulated that during oncogenesis, the pattern of proteins associated with this nuclear structure would be altered.

Differences in nuclear matrix proteins between normal tissues and tumors have been recently reported (14–18). Thus, nuclear matrix proteins present in tumor cells but not in their normal counterparts have been identified in a variety of organs such as colon, prostate, bone, and breast. These proteins present only in tumor cells are tissue specific and appear to be demonstrative of cell protein alterations occurring during the establishment of the neoplastic phenotype; however, the significance of these changes has not been established. Thus, the functional characterization of these proteins is an interesting aim to be achieved to clarify the oncogenetic process. Likewise, these proteins can be useful as a markers of at least several types of tumors.

Despite that recent studies have been specifically dedicated to the nuclear matrix, proteins from other subnuclear fractions can also be important in the genesis of a tumor cell. To identify nuclear proteins specifically expressed in lymphoblastoid cell lines, but not present in normal lymphocytes, we have analyzed the two-dimensional protein patterns of whole nuclei and two nuclear subfractions (a fraction extracted with nucleases and the nuclear matrix) from three different lymphoblastoid cell lines and compared them to normal quiescent and proliferating human T lymphocytes. To perform these studies, we selected three lymphoblastoid cell lines (CEM, Namalwa, and Molt-4) that are very different in origin and behavior, with the aim of finding proteins shared by all of these different cell lines but not present in normal quiescent and proliferating cells. These nuclear proteins common to all of the lymphoblastoid cell lines would represent protein associated with the malignant status.

We report here the identification of several proteins specifically expressed in the nucleus of the lymphoblastoid cells and also the identification of proteins which are specifically present in normal quiescent or normal proliferating cells but not in the three lymphoblastoid cell lines.

MATERIALS AND METHODS

Cells and Culture Conditions. PBLs3 were used as a source of normal T lymphocytes. They were obtained from buffy coats of healthy donors by density gradient centrifugation on Ficoll-Hypaque (Pharmacia). To determine the amount of T lymphocytes in the PBL preparations, immunocytochemical detection of CD19 (specific for B lymphocytes), CD14 (specific for monocytes), and CD3 (specific for T lymphocytes) were performed.

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The abbreviations used are: PBL, peripheral blood lymphocyte; PHA, phytohemagglutinin.
cytes), and CD3 (specific for T lymphocytes) was performed. Only PBL preparations with a proportion of T lymphocytes higher than 85% were used for the experiments. Cells were cultured at 1 x 10^6 cells/ml in RPMI 1640 (Flow Laboratories) supplemented with 10% FCS (Life Technologies, Inc.) and 50 μg/ml of gentamicin and maintained at 37°C in a humidified atmosphere containing 5% CO₂. Cells were activated by adding PHA (Wellcome Diagnostics, Dartford, United Kingdom) at a final concentration of 100 μg/ml. The activated cells were collected at 72 h when DNA synthesis was maximal (21). Cell Lines CEM and Molt-4 as T-cell lines and Namalwa as a cell line derived from B lymphocytes were obtained from American Type Culture Collection and cultured as the normal T lymphocytes were but without PHA. To synchronize CEM cells, they were grown until confluence in RPMI 1640 plus 10% FCS. Cells were then changed to RPMI 1640 plus 0.5% FCS and incubated for 2 days. After that, hydroxyurea was added to a final concentration of 1.5 mM and the cells were incubated for 14 h. Finally, the cells were changed to RPMI 1640 plus 10% FCS. The cells were collected when DNA synthesis was maximum as determined by fluorescence-activated cell sorting analysis or [³H]thymidine incorporation into DNA.

Preparation of Nuclei and Nuclear Subfractions. Nuclei and nuclear subfractions were obtained as described previously (22, 23). Briefly, the nuclei were obtained by resuspending the cells in RSB [10 mM Tris-HCl (pH 7.5), 30 mM NaCl and 3 mM MgCl₂] containing 1 mM phenylmethylsulfonyl fluoride and 0.5 μg/ml aprotinin at a concentration of 5 x 10⁷ cells/ml. Then, NP40 to a final concentration of 0.5% was added and the samples were vortexed for 10 s. After centrifugation, nuclei were washed twice more in RSB without NP40. The nuclei were sedimented and used for electrophoresis or for the isolation of nuclear subfractions (S1 and nuclear matrix). To obtain the S1 nuclear subfraction, the purified nuclei were resuspended in STM buffer [250 mM sucrose, 5 mM MgSO₄, 50 mM Tris-HCl (pH 7.4), 1 mM phenylmethylsulfonyl fluoride, and 0.5 μg/ml aprotinin] containing 250 μg (500 Kunitz units/ml) DNase I (Sigma D-5025) and 250 μg (25 Kunitz units/ml) RNase A (Sigma R-5503). After a 1-h incubation at 4°C, the nuclei were sedimented at 800 x g for 15 min. The supernatant was collected and named S1. The pellet obtained after extraction of the sediment with 1.6 M NaCl corresponded to the nuclear matrix.

Gel Electrophoresis. Before running the electrophoresis, 70 μg from the samples were precipitated with acetone 80% (v/v), and the pellet was resuspended with loading buffer (7.9 mM urea, 0.06% SDS, 1.76% ampholines, 120 mM DTT, 3.2% NP40, and 40 mM Tris-HCl, pH 7.5).

Two-dimensional electrophoresis (isoelectric focusing) was performed according to the method of O’Farrell et al. (24) using a Millipore Investigator system. The isoelectric focusing was carried out in glass tubes of 1 mm in diameter using pH 3–10 ampholines (Millipore) for 17,500 V-h. An isoelectric focusing internal standard (Bio-Rad) consisting of conalbumin (76 kDa; pI 6.6–6.0), BSA (66 kDa; pI 5.4), bovine muscle actin (43 kDa; pI 5.0), and anhydrase (31 kDa; pI 6.0) was used to predict molecular weight and pI. After equilibration for 2 min in one-dimensional equilibration buffer [0.375 M Tris-HCl (pH 6.8), 3% SDS, 50 mM DTT, and 0.01% bromphenol blue], the tube gels were layered on the top of a 10% acrylamide slab gel (1-mm thick) and run for 8 h at 10,000 mW/gel. The gels were further fixed in 50% ethanol-12% acetic acid solution overnight and then silver stained according to the method of Blum et al. (25).

Image Analysis. Image analysis of the silver-stained two-dimensional gels was performed with a Bio-Image system. After acquisition of quantitative high-resolution images of the gels, digital filtering algorithms were used to remove both uniform and nonuniform background without removing critical image data. A two-dimensional gel analyzer and database software, version 6.02, were used to compute spot patterns. Triangulation from internal standards was used to determine the molecular weight and pI of each protein of interest.

Determination of Protein Content. The protein content of the samples was measured according to the method of Bradford (26) using BSA as standard.

RESULTS

Protein patterns of total nuclear extracts from normal quiescent T lymphocytes were compared with those from normal proliferating T lymphocytes which were activated by PHA (at 72 h after activation, which corresponds to the moment of maximal DNA synthesis) and also with those from three different lymphoblastoid cell lines, i.e., CEM, Namalwa, and Molt-4. Nuclei from the different cells were isolated as described in “Materials and Methods” and analyzed with high-resolution two-dimensional gel electrophoresis. The patterns obtained were then compared by using the Bio-Image system to select the polypeptides specifically expressed in normal quiescent or normal proliferating T lymphocytes, or were common to all three lymphoblastoid cell lines (but not present in normal quiescent or proliferating lymphocytes).

The general protein pattern of the nuclei of all of the samples is very similar (Fig. 1). The amount of several proteins varied from one sample to the other, although most of the proteins were found in all of the samples. However, some proteins were consistently found only in

Fig. 1. Two-dimensional protein patterns of total nuclear extracts from normal human T lymphocytes quiescent, activated with PHA, and three lymphoblastoid cell lines (CEM, Namalwa, and Molt-4). MW, molecular mass expressed in kDa. Arrow, position of actin.
NUCLEAR PROTEINS IN LYMPHOBLASTOID CELLS

3.8 5.0

Fig. 2. Amplified regions of two-dimensional protein patterns of total nuclear extracts from normal quiescent, normal activated, and three lymphoblastoid cell lines (CEM, Namalwa, and Molt-4).
The protein pattern of nuclear extracts from synchronized CEM cells (SYN-CEM) are also shown.
Interesting proteins are marked and correspond to the proteins with the same designation in Table 1.
Left, molecular mass markers are expressed in kDa.
Top, pl markers. Arrow, position of actin.

normal quiescent cells, in normal proliferating cells, or in the three lymphoblastoid cell lines. Most of these group-specific proteins were found in the acidic part of the gels and had relatively low molecular masses. Fig. 2 shows a magnification of the acidic part of typical gels from the different samples. It can be seen that a group of five proteins in the region called N1 (N1-1–N1-5; Figs. 2 and 3 and Table 1) with apparent molecular masses of 45 kDa (pl 4.4), 43 kDa (pl 4.3), 42 kDa (pl 4.3), 41 kDa (pl 4.3), and 43 kDa (pl 4.2), respectively, and two more proteins (N2 and N3) of 35 kDa (pl 4.3) and 34 kDa (pl 4.3), respectively, were present only in normal quiescent T lymphocytes.

Another set of proteins was found only in the nuclei of normal proliferating lymphocytes. It comprises two proteins (NA1 and NA2; Fig. 2 and Table 1) with apparent molecular masses of 33–31 kDa (pl 4.3) and 33–31 kDa (pl 4.2), respectively. A group of five proteins in the region named NA3 (NA3-1–NA3-5) of 23 kDa (pl 4.2), 23 kDa (pl 4.3), 22 kDa (pl 4.4), 21 kDa (pl 4.5), 21 kDa (pl 4.6; Figs. 2 and 4 and Table 1) was also specifically found in normal proliferating lymphocytes.

Three proteins (proteins 1–3; Fig. 2 and Table 1) of 55 kDa (pl 4.4), 37 kDa (pl 3.8), and 37 kDa (pl 3.7) were common to all three lymphoblastoid cell lines but were not found in normal quiescent or proliferating lymphocytes. These three proteins were also found in synchronized CEM cells (in the S-phase; Fig. 2). Finally, one protein (NNA1; Fig. 2 and Table 1) of 56 kDa (pl 4.7) was identified in both quiescent and proliferating T lymphocytes but not in any of the lymphoblastoid cell lines.

To analyze the intranuclear localization of these proteins, two nuclear subfractions were prepared from purified nuclei. One was a soluble fraction obtained after extraction of nuclei with DNase plus RNase (S1 fraction) and the other was the nuclear matrix obtained as the insoluble residual fraction after sequential extraction of nuclei with nucleases and a high salt-containing buffer. The two-dimensional protein patterns were also analyzed in these two nuclear subfractions.

The protein pattern of the S1 fraction from normal proliferating cells was quite similar to the patterns from Namalwa and CEM cells, whereas the pattern from normal quiescent cells was different (Fig. 5).
At least six proteins (S1N1–S1N6; Fig. 5 and Table 2) of 75 kDa (pI 4.4), 55 kDa (pI 6.7), 41 kDa (pI 4.1), 39 kDa (pI 5.0), 32 kDa (pI 5.5), and 29 kDa (pI 6.6) were present only in the S1 fraction of normal quiescent cells.

Five proteins in the region named S1NA3 (S1NA3-1–S1NA3-5) of 23 kDa (pI 4.2), 23 kDa (pI 4.3), 22 kDa (pI 4.4), 21 kDa (pI 4.5), and 21 kDa (pI 4.6; Figs. 2 and 4 and Table 1) were observed only in normal proliferating lymphocytes. This group of proteins is the same as NA3 observed in the whole-nucleus pattern from normal proliferating cells. Thus, these proteins were enriched in the S1 fraction, indicating that they could be associated with DNA or RNA. As mentioned above, the S1 protein patterns of CEM and Namalwa cells are very similar to that of normal activated cells, except that the proteins of the NA3 group were not found in this fraction of the transformed cell lines.

On comparing the protein patterns of the nuclear matrix from these cells, differences were also observed (Fig. 6). A group of five proteins in the region named MN1 (proteins 1–5) with apparent molecular masses of 45 kDa (pI 4.4), 43 kDa (pI 4.3), 42 kDa (pI 4.3), 41 kDa (pI 4.3), and 43 kDa (pI 4.2) and three proteins, MN2 of 56 kDa (pI 4.7), MN3 of 50 kDa (pI 4.6), and MN4 of 42 kDa (pI 4.1), were found only in normal quiescent cells (Figs. 3 and 6 and Table 3). Interestingly, the five proteins of the group MN1 are the same as those of the N1 group observed in whole-nucleus extract from quiescent cells (Fig. 3).

Two doublets of proteins MNA1 and MNA2 of 31–33 kDa (pI 4.3) and 31–33 kDa (pI 4.2) were found only in the nuclear matrix of the normal activated cells (Fig. 6 and Table 3). These proteins are the same as NA1 and NA2 found in the whole-nucleus extracts from normal activated cells (Figs. 2 and 6 and Table 3). Finally, three proteins (M1-M3) of 37 kDa (pI 3.8), 37 kDa (pI 3.7), and 35 kDa (pI 4.5), respectively, were found only in the nuclear matrix of the lymphoblastoid cell lines.

To our knowledge none of these proteins has been identified. The identification and functional characterization of these proteins is currently underway in our laboratory.

**DISCUSSION**

Recently, several studies have investigated the presence of specific proteins in the nuclear matrix of transformed or cancer cells with respect to their normal counterparts. Thus, specific nuclear matrix proteins in hepatoma cells (27), breast cancer cells (14), colon cancer cells (15), prostate cancer cells (16, 17), and osteosarcoma cells (18) have been identified. Interestingly, proteins that are present in nuclear matrix from normal cells but not in cancer cells have also been identified in all of these cell types. All of these results suggest that the disappearance of some nuclear matrix proteins and the appearance of new ones is a feature of oncogenesis.

Unfortunately, no study has been reported comparing the nuclear matrix protein patterns of normal and cancer cells from these different cellular types in the same laboratory to establish whether the proteins that are specifically expressed or absent in cancer cells of one cellular type are also expressed or absent in the other cellular types. Nevertheless, the analysis of the data presented in these different reports
suggessthatatleastmostofthe proteinswhicharespecifically
expressedorabsentincancercellsseemtobe cell-type specific. Thus,
until now tumor-specific proteins shared by all or most of the tumors
derivedfromdifferentcellulartypeshavenotbeen detected. Since the
methods used to perform the two-dimensional gels are not the same,
this suggestion should be taken carefully and comparative analysis of
the protein patterns of the nuclear matrix from different types of
tumors using the same protocol should be performed.

In these previous reports, the nuclear matrix was selected for this
type of study since it is a nuclear dynamic scaffold that participates in
the organization of chromatin and also in most of the important
nuclear functions such as DNA replication and gene expression.
Moreover, tissue-specific nuclear matrix proteins have been identified and changes in the presence or absence of specific nuclear matrix proteins have been associated with cellular transformation and differentiation (27–30), making nuclear matrix proteins good candidates for the analysis of changes during carcinogenesis.

We report here that different lymphoblastoid cell lines share specific nuclear matrix proteins. Moreover, nuclear matrix proteins present in normal quiescent but not in normal proliferating or in transformed cells were also identified. Likewise, nuclear matrix proteins specific for normal proliferating lymphocytes were also detected. Thus, these results are in agreement with those previously mentioned, supporting the hypothesis that specific nuclear matrix proteins are expressed during transformation of human lymphocytes, whereas other proteins disappear during this process.

Interestingly, we also report here that when whole total nuclear samples were analyzed by high-resolution two-dimensional gel electrophoresis, proteins located not in the nuclear matrix but in other nuclear subfractions, which are specific for normal quiescent, normal proliferating, or transformed lymphocytes, were identified. Moreover, one protein present in both normal quiescent and proliferating lymphocytes but not in any of the lymphoblastoid cell lines was identified. Thus, these results indicate that in addition to nuclear matrix proteins, other nuclear proteins can also participate in the expression of the malignant phenotype. Interestingly, some of the proteins present only in normal proliferating lymphocytes (the group named NA3) were found to be enriched in a nuclear fraction extracted with nucleases (S1 fraction), suggesting that these proteins could be associated with DNA or RNA and thus be involved in the regulation of DNA or RNA metabolism. It is also worth mentioning that in the S1 fraction from normal quiescent T cells, at least six proteins were identified as specific for these cells. All of these results indicate that the expression of proteins associated with DNA or RNA is modified during oncogenesis.

Although the molecular identification and functional characterization of these proteins remain to be established, these proteins appear to be of great interest for different purposes. The functional characterization of these proteins may contribute to our understanding of how a cell becomes transformed. Moreover, some of them can be

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Table 3 Nuclear matrix proteins specifically present in each cellular type

![Fig. 6. Protein patterns obtained with high-resolution two-dimensional gel electrophoresis of nuclear matrix fractions (see "Materials and Methods") from normal quiescent, normal activated, and two lymphoblastoid cell lines (CEM and Namalwa). Proteins of interest are marked and correspond to the proteins with the same name in Table 3. Left, molecular mass markers are expressed in kDa. Top, pI markers. Arrow, position of actin.](https://cancerres.aacrjournals.org/article-pdf/57/1/5/17507597/17507597.pdf)
potential tumor markers for lymphoblastoid cells and may thus assist in the diagnosis and management of cancer therapy.

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