Comparative Proteomics Analysis of Mice Lymphocytes in Early Stages of Infection by Different Strains of Rabies Virus

Behrouz Vaziri · Fatemeh Torkashvand ·
Naser Eslami · Ahmad Fayaz

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Abstract The CNS immune response to rabies virus has been shown to be influenced by virulence of the virus strains. There is no comprehensive report of the peripheral immune response against different strains of rabies virus. In this report we used a comparative proteome analysis to find the early events in the spleen lymphocytes of mice infected by a street strain and an attenuated strain of the rabies virus. Differentially expressed proteins were identified which play important biological roles such as T and B lymphocyte activation (coronin 1), antiviral activity (peroxiredoxin 1), and cytoskeletal reorganization (cofilin 1). These results could be strong hints of early divergence on peripheral immune response under influence of viral strain and their pathogenicity.

Keywords Comparative proteomics · Rabies · Spleen lymphocyte · Coronin 1

Introduction

Rabies is one of the oldest recognized fatal infectious diseases. The causative agent of the disease is Rabies virus (RV), a negative stranded RNA virus of the *rabdoviridae*

family [19]. The rate of universal annual death from Rabies is nearly 60,000 humans and millions of animals [24].

The host immune response mechanism to rabies is not fully known. The available data on host immune response to rabies are mostly focused on CNS immune system. In attenuated rabies infection, the destruction of a few neurons causes the paralysis in the majority of the surviving animals and the brain is preserved resulting in the survival of the infected animals [8]. IFN γ , MIP1- α and IP10 are produced in attenuated rabies infection, these molecules could trigger the destruction of infected neurons through the induction of apoptosis pathway mediated by active migratory T cells [8]. In contrary, the adaptive antiviral host response in nervous system is impaired by pathogenic strains of virus. Infection by street virus (SV) cause a restricted inflammation process in CNS which is related to the induction of neuroprotective IL-6 and destruction of the migratory T cells [1]. Inactivation or apoptosis of migratory T cells results in preserving the neural integrity in favor of more viral invasion which finally leads to complete neural dysfunction and host death [15].

While the potential role of IL-1 β and TNF- α in rabies-encephalopathy has been shown by immunohistochemical staining of autopsy material, the precise role of cytokines participating in the pathogenesis of human rabies encephalitis needs to be cleared [21].

It has been shown that both challenge virus standard (CVS) strain of RV and attenuated virus could induce peripheral antigen specific T cell and B cell response with the same intensity. Besides, intramuscular injection or nasal instillation of RV provoked local and systemic immune responses by appearance of activated lymphocytes (CD69+) [11]. A remarkable decrease in the number of mononuclear cells has been reported in the spleen of mice infected with street rabies virus (SV), while the number of

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B. Vaziri (✉) · F. Torkashvand
Protein Chemistry Unit, Biotechnology Research Center,
Pasteur Institute of Iran, 69, Pasteur St, 13164 Tehran, Iran
e-mail: behrouz-vaziri@pasteur.ac.ir

N. Eslami · A. Fayaz
WHO Collaborating Center for Reference and Research on
Rabies, Pasteur Institute of Iran, Tehran, Iran

these cells increased in the spleen of mice infected with an attenuated strain [23].

In search of molecular mechanisms induced in early stages of infection, we used a comparative proteomics analysis on mice spleen lymphocytes in response to SV and an attenuated strain, Pasteur strain of RV (PV), 4 days after infection. In this report we show that such approach could effectively determine the molecular basis of the different peripheral immune response to different strains of RV. This preliminary experiment determined the significant differentially expressed proteins in spleen lymphocytes which could be interpreted as a strong hint of early immunodiversion in periphery.

Materials and Methods

Animals, Viruses, and Other Reagents

Eight-week-old male NMRI mice were provided by Pasteur Institute of Iran. All experiments related to using of animals were performed under the control of the institutional ethic committee. SV isolated from a rabid dog and Pasteur strain of the rabies virus (PV) was kindly provided by Institut d'Pasteur (France). IPG strips and ultrapure electrophoretic reagents were obtained from BioRad (France), Merck (Germany) and Sigma Aldrich (UK). Rabbit polyclonal antibody to peroxiredoxin 1, mouse monoclonal antibody to enolase 1, rabbit polyclonal antibody to cofilin 1 and goat polyclonal antibody to coronin 1 were purchased from Abcam (UK). Nitrocellulose membrane (Hybond ECL) and ECL plus kit were purchased from GE Healthcare (UK). Gentamicine and HRP-conjugated anti goat and anti rabbit secondary antibodies were purchased from Raybiotech (Iran).

Sample Preparation

Two groups of six male mice were separately infected with two different rabies virus strains (totally 1×10^6 IM injection in both hind legs) and the healthy control group of the same size kept at the same situation. Virus stocks were prepared, as described by Ubol et al. [22]. Four days after inoculation, spleens were removed, their lymphocytes were collected as previously described [17], and washed three times with washing buffer (10 mM Tris pH 7 and 250 mM sucrose). The cells were resuspended in lysis buffer (7 M urea, 2 M thiourea, 4 % CHAPS, 40 mM Tris, 0.2 % Biolyte 3/10, and 50 mM DTT). Whole-cell extracts were prepared by sonication of cell suspension for four cycles of 30 kHz each last 40 s with 20 s intervals followed by centrifugation at $14,000 \times g$ for 15 min at

4 °C. Protein concentration was determined by Bradford assay using BSA standards. The lysate aliquoted and kept in -80 °C for further use.

2-DE

In order to have three separate 2-DE gels in each group, 100 µg of 3 different lysates from each group were separately dissolved in rehydration buffer (8 M urea, 4 % CHAPS, 0.2 % 100× Biolyte and 50 mM DTT) and loaded onto IPG strips (17 cm, nonlinear pH 3–10) and kept at room temperature for 16 h. IEF was carried out using the PROTEAN IEF cell (BioRad, USA) exerting three steps of increasing voltage from 250 V to 10 kV with total focusing of 60kVh. IPG strips were equilibrated for 20 min in the equilibration solution (50 mM Tris-HCl pH 8.8, 6 M urea, 20 % glycerol, 2 % SDS, 0.01 % bromophenol blue) containing 2 % DTT and then alkylated for 20 min in the equilibration solution containing 2.5 % iodoacetamide. For performance of second-dimension, the strips were transferred on top of vertical 12 % SDS-PAGE handmade slab gels and overlaid with 1 % agarose. The gels were run at 16 mA/gel for 30 min and 24 mA/gel for 5 h at 18 °C and stained with MS compatible silver nitrate method [12].

Image Acquisition and Analysis

The stained gels were scanned at a resolution of 400 dpi using GS-800 Calibrated Densitometer (BioRad). Nine resulting gel images (three of each experimental group) were analyzed by ImageMaster 2D Platinum 6.0 software (GE Healthcare). Statistical analysis of protein variations was carried out in 2D gels prepared from three replicates in each group. In each group, matched spots with coefficient variation less than 50 % on vol. % were included for further between group analyses. The student *t* test analysis on vol. % of matched spots between groups was done to find out significant expressional changes (*p* value <0.05). Proteins determined to be differentially expressed were selected for MS identification.

In Gel Digestion and MS Analysis and Protein Identification

Spots were manually cut from 2-D gels and dried completely. Silver was removed from gel pieces by Farmer's reagent (15 mM potassium ferricyanide/50 mM sodium thiosulphate). Gel plugs were covered by Farmer's reagent and leaved at room temperature for 10 min until the gels go clear, then the supernatant was removed. The Ettan Spot Handling Workstation (GE Healthcare, UK) used for automatic in gel digestion of samples. Each silver removed

gel plug was soaked in 100 mM ammonium bicarbonate for 1 h and washed twice in 50 % ACN/100 mM ammonium bicarbonate. The gel pieces then dehydrated by incubation with 0.1 mL ACN for 10 min. Samples then were re-hydrated by the addition of freshly prepared trypsin solution (0.5 µg modified porcine trypsin in 25 µL 20 mM NH_4HCO_3), and incubated for 240 min at 37 °C. Peptides were extracted from the gel plugs, by washing twice in 100 µL of 50 % ACN, 0.1 % TFA and transferred in solution to a fresh 96 well plate, where samples were dried.

Tryptic peptides were resuspended in 3 µL of 50 % ACN, 0.1 %TFA. 0.3 µL of resuspended tryptic peptides were spotted onto a steel Applied Biosystems 192 sample MALDI target plate, and mixed (while wet) with 0.3 µL of a 90 % saturated CHCA in 50 % ACN, 0.1 % TFA. The dried samples were analyzed using a MALDI-TOF/TOF MS (4700 Proteomics Analyzers, Applied Biosystems, and UK), performing MS analysis and subsequent MS/MS analysis on up to 10 precursor peptides. Each sample was internally calibrated by reference to specific autolytic fragments of trypsin. The PMF and MS/MS information were automatically searched against the NCBI mouse database using the Mascot search engine (Matrix Science, UK). Mass tolerance settings of 1.2 Da for parent ion and 0.5 Da for fragment ions were applied. Search settings allowed one missed cleavage with trypsin and two modifications (carboxamidomethylation of cysteine and oxidation of methionine). Statistical confidence limits of 95 % were applied for protein identification.

Immunoblot Analysis

Aliquots of the protein samples (35 µg) were loaded on 12 % SDS-PAGE. Subsequently, they were transferred to a nitrocellulose membrane using Towbin buffer (25 mM Tris, 192 mM glycine, and 20 % methanol) by a semidry Trans-blot cell (Bio-Rad) and transfer was verified by ponceau S staining. The membrane was incubated overnight in blocking buffer (2.5 % skim milk, 2.5 % glycerol, 0.05 % tween-20 in TBS) at 4 °C. The membrane was rinsed in TTBS (100 mM Tris-HCl, 0.9 % NaCl and 0.05 % Tween-20, pH 7.5) for 10 min. It was then incubated for 2 h with blocking solution containing primary antibodies: 1:1,000 rabbit polyclonal to peroxiredoxin 1, 1:300 rabbit polyclonal to cofilin 1, 1:300 goat polyclonal to coronin 1a, 1:150 mouse monoclonal to enolase 1 and 1:500 mouse monoclonal to β -actin. After three washes of 5 min with TTBS, the membrane was incubated again for 1 h in 1:500 HRP conjugated anti-goat IgG, anti-rabbit IgG and anti-goat IgG secondary antibodies (RayBiotech, Iran) and developed using ECL plus kit.

Results and Discussion

The spleens of control (C), SV, and PV infected mice were removed after 4 days and lymphocytes were separated by metal mesh sieving and density gradient medium. Whole lymphocyte protein extracts were prepared and undergone the 2-DE analysis (Fig. 1). Generally, the 2-DE protein profile of SV infected group showed minor changes compared to control group, while the 2-DE profile of PV infected group showed much more differences with both other groups. Image analysis of 3 experimental replicates of control (C), SV, and PV infected lymphocytes was performed and statistical analysis (*t* test, *p* value <0.05) on vol. % of matched spots between these three groups were done to determine the significant expressional changes. The spots in different groups were statistically analyzed in 3 different classes: C/PV, C/SV, and PV/SV (*t* student test, *p* value <0.05) (suppl. 1). Among the proteins with significant expressional changes, 10 proteins could be successfully identified by MALDI TOF/TOF mass spectrometry analysis (Table 1). All these 10 proteins were under expressed in PV group in comparison to control group, among which 8 proteins were also showed under expressed level in comparison to SV group. Two proteins were under expressed in SV and PV group in comparison to control group (Table 1). Expressional changes of four differentially expressed proteins (Fig. 2), including coronin 1, peroxiredoxin 1, cofilin 1, and enolase 1, were further confirmed by Immunoblotting analysis (Fig. 3). Coronin 1, enolase 1 and cofilin 1 were under expressed in PV group in comparison to SV and control group. These proteins showed no significant expressional change between control and SV group. Peroxiredoxin 1 was under expressed in PV and SV group in comparison to control group.

The nature of immune response to RV infection and the pathological consequences has been shown to be strongly related to the virus strain. Detectable level of antigen specific T and B lymphocyte response in lymph nodes and spleens of mice upon IM injection of attenuated and invasive strains of RV has been reported [11], and it has been proposed that rabies virus strategy to escape from immune response is not developed in periphery [15]. Nevertheless, there are reports on the suppression of the cell-mediated cytotoxic activity of the spleen cells of mice infected by SV strains which occurred on fourth day of infection [9, 13]. Moreover, it has been shown that after four days, mice infected by PV developed non-specific signs of disease while the CD4^+ to CD8^+ ratio of migrated T cells in CNS was close to that observed in the spleen or lymph nodes [8]. According to these reports and in order to investigate the early molecular events related to the possible differences of peripheral immune response to invasive and attenuated strains of RV, we made a comparative

Fig. 1 Representative examples of silver stained 2-D gels derived from control mice spleen lymphocytes (C), Pasteur virus infected mice spleen lymphocytes (PV) and Street virus infected mice spleen lymphocytes (SV). Proteins were extracted from 3 biological

replicates and separately analyzed by 2-DE. IPG strips (17 cm) with nonlinear pH range of 3–10 and 12 % SDS-PAGE were used in the first dimension and the second dimension, respectively

Table 1 Summary of protein identification using MALDI TOF/TOF analysis

Protein name	Accession no	Theoretical Mr/pI	Observed Mr/pI	Protein score	Pep. count	Sequence coverage (%)	Expressional fold change PV*/SV*	Expressional fold change SV/C*	Expressional fold change PV/C
Heterogeneous nuclear ribonucleoprotein L (hnRNP L)	gil46577278	60.71/6.65	60/6.7	99	14	34	−4.8	NC*	−4.5
Peroxiredoxin 1	gil6754976	22.39/8.26	22.5/7.2	79	9	52	NC	−1.9	−2.5
Predicted: similar to Glyceraldehyde-3-phosphate dehydrogenase isoform 3	gil149266431	31.29/7.62	34/7.6	95	9	47	−3.4	NC	−3.7
Isocitrate dehydrogenase 3 (NAD ⁺) alpha, isoform CRA	gil148693875	35.02/5.88	35.5/5.5	69	10	36	−1.4	NC	−2.4
Hspd1 protein	gil76779273	59.56/8.09	59/5.3	96	15	36.6	−2.6	NC	−1.6
Annexin A1	gil124517663	38.99/6.97	35/6.5	82	12	45.6	NC	−1.7	−1.9
Cofilin 1, non-muscle	gil6680924	18.77/8.22	18/7.3	68	8	60.8	−1.5	NC	−1.56
Mitochondrial malate dehydrogenase 2, NAD	gil89574115	32.11/7.7	35/7.7	106	12	53.5	−2.7	NC	−2
Coronin-1	gil4895037	51.63/6.05	52/6.0	106	15	34.5	−3.7	NC	−3.4
Enolase 1	gil34784434	40.09/5.86	40/6.2	264	14	56.3 %	−4.1	NC	−3.7

* PV Pasteur virus treated group, SV street virus treated group, C control group, NC not significantly changed

proteomics analysis on spleen lymphocytes of mice infected by PV and SV. Ten proteins were successfully identified with significant expressional level changes between groups (Table 1). All 10 proteins under-expressed in PV infected group compared to control group, among which

eight proteins also showed under-expressed pattern in comparison to SV infected group.

Among the proteins identified, coronin 1 is a leukocyte specific regulator of Ca²⁺-dependent signaling which interacts with phospholipase C- γ 1 and is critical for the

Fig. 2 Representative examples of four identified protein spots with significant expression differences between control (C), Pasteur virus (PV) infected, and Street virus (SV) infected groups. Between groups, statistical analysis (*t* test, *p* value < 0.05) on vol % of matched spots were done to determine the significant expression changes (information of these spots is included in Table 1)

Fig. 3 A representative immunoblot analysis of four identified spots by MS. β -actin (as a control), peroxiredoxin 1, coronin 1, cofilin 1 and enolase 1 in control (C), Pasteur virus infected (PV) and Street virus infected (SV) lymphocytes. Immunoblot analysis for coronin1 was performed in control, PV and SV groups, for cofilin 1 and peroxiredoxin 1 was performed only in control and PV groups, and for enolase 1 was done in PV and SV groups (see the Table 1)

generation of inositol-1,4,5-trisphosphate. Coronin 1 is essential for the function and survival of peripheral T lymphocytes through release of Ca^{2+} from intracellular stores. While exerting the same task in B lymphocytes, it is not essential for in vivo B cell signaling [2, 18]. Our results showed a significant decrease in expression level of coronin 1 in spleen lymphocytes of mice infected by

attenuated strain of RV while the lymphocytes of mice infected by SV strain of RV showed the same level of coronin 1 compared to control group. This observation suggests a probable change in the activation signaling pathway of T cell and B cell receptor in response to different strains of RV after 4 days of viral infection. Since it has already been shown that B cells have compensatory mechanisms for activation in lack of coronin 1 [2], it could be speculated that severe decrease in coronin 1 expression level in response to PV, could be critically diminished peripheral T cell activation level while B cell response is not seriously affected.

Peroxiredoxin 1 (prx1) is a member of peroxiredoxins which are antioxidant proteins comprising critical catalytic cysteine residues that use thioredoxin to reduce hydrogen peroxide, lipid hydroperoxides and peroxynitrite [14]. Prx1, as a ubiquitous protein, plays different roles in different cells and tissues. Helminthes prx1 could activate host macrophages to induce Th2 responses [5]. It has been assumed that endogenous Prx1 through suppression of IL2 production and its antioxidant activity could diminish the allergen induced Th2-type airway inflammation [10]. Prx1 could be considered as a plasma cell marker and act as a chaperone for correcting the folding of immunoglobulins [3, 4]. The increase of sensitivity to oxidative stress and decrease of cell proliferation in Prdx1-deficient cells has been reported [20]. Generally, prx1 seems to play an immunomodulating role in different immune responses. Consequently, the decrease of prx1 in our experiment could be considered as an early sign of change in level of immunomodulation. Nevertheless, the accurate interpretation of this change needs more studies.

Cofilin is an important actin-regulating protein extensively distributed in all eukaryotes [25]. In human immune system, cofilin has been implicated in T cell activation through its participation in immunological synapse creation. The association of CD2 or CD28 receptors to their ligands results in cofilin dephosphorylation, activation and its association with the actin cytoskeleton. These events cause actin cleavage and its depolymerization which are critical for actin cytoskeleton remodeling and T cell activation [7, 16]. The blocking of cofilin binding to actin results in severe deficiencies in T cell activation [7]. In this study, cofilin has a slight decrease in PV group compared to control group. It seems that cytoskeleton reorganization as an important event in T cell activation slightly has been changed in PV group compared to control group after 4 days of infection.

Other differentially expressed proteins play important roles in different pathways such as metabolic pathway (enolase 1, malate dehydrogenase, etc.) and RNA processing pathway (hnRNPL). hnRNPL is a constituent of the heterogeneous nuclear ribonucleoprotein (hnRNP)

complexes which provide the substrate for the processing events that pre-mRNAs undergo before becoming functional and translatable mRNAs in the cytoplasm [6]. According to obtained results, it appears that significant decrease in hnRNPL can lead to severe decrease in many proteins in this group compared to other groups.

In conclusion, our results showed that in early stage of infection, attenuated PV exerts more changes in protein profile of spleen lymphocytes in comparison to SV and these changes are happened in different set of proteins. Regarding the more immunogenic nature of PV, these results could be somehow predictable but it is the first report using proteomics analysis in order to mining the early biochemical events in peripheral lymphocytes in response to different strains of RV. Our results could be considered as a hint of deviation on peripheral immune response under influence of viral strains and their pathogenicity. The significant decrease in expression level of coronin 1, as a lymphocyte signaling regulator, in PV infected lymphocytes is a potentially significant evidence for this claim. Indeed the fate of the disease could be directly connected to these early events in peripheral immune response, and time course study on the lymphocytes proteome changes on targeted proteins will be very informative to determine the molecular nature of the response to different strains of RV and their related pathogenesis.

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