Molecules, 2017, vol.22, N5

The transcriptome of type i murine astrocytes under interferon-gamma exposure and remyelination stimulus

Kudriaeva A., Galatenko V., Maltseva D., Khaustova N., Kuzina E., Tonevitsky A., Gabibov A., Belogurov A.
Kazan Federal University, 420008, Kremlevskaya 18, Kazan, Russia

Abstract

© 2017 by the authors. Astrocytes are considered to be an important contributor to central nervous system (CNS) disorders, particularly multiple sclerosis. The transcriptome of these cells is greatly affected by cytokines released by lymphocytes, penetrating the blood-brain barrier - in particular, the classical pro-inflammatory cytokine interferon-gamma (IFNγ). We report here the transcriptomal profiling of astrocytes treated using IFNγ and benztropine, a putative remyelinization agent. Our findings indicate that the expression of genes involved in antigen processing and presentation in astrocytes are significantly upregulated upon IFNγ exposure, emphasizing the critical role of this cytokine in the redirection of immune response towards self-antigens. Data reported herein support previous observations that the IFNγ-induced JAK-STAT signaling pathway may be regarded as a valuable target for pharmaceutical interventions.

http://dx.doi.org/10.3390/molecules22050808

Keywords

Affymetrix, Antigen presentation, Astrocytes, Benztropine, Immunoproteasome, Interferon-gamma, Major histocompatibility complex, MicroRNA, PA28/11S/REG, Transcriptome

References

[1] Noseworthy, J.H.; Lucchinetti, C.; Rodriguez, M.; Weinshenker, B.G. Multiple sclerosis. N. Engl. J. Med. 2000, 343, 938-952. [CrossRef] [PubMed]

[2] Correale, J.; Farez, M.F. The role of astrocytes in multiple sclerosis progression. Front. Neurol. 2015, 6, 180. [CrossRef] [PubMed]

[3] Arellano, G.; Ottum, P.A.; Reyes, L.I.; Burgos, P.I.; Naves, R. Stage-specific role of interferon-gamma in experimental autoimmune encephalomyelitis and multiple sclerosis. Front. Immunol. 2015, 6, 492. [CrossRef] [PubMed]

[4] Deshmukh, V.A.; Tardif, V.; Lyssiotis, C.A.; Green, C.C.; Kerman, B.; Kim, H.J.; Padmanabhan, K.; Swoboda, J.G.; Ahmad, I.; Kondo, T.; et al. A regenerative approach to the treatment of multiple sclerosis. Nature 2013, 502, 327-332. [CrossRef] [PubMed]

[5] Dong, X.; You, Y.; Wu, J.Q. Building an RNA sequencing transcriptome of the central nervous system. Neuroscientist 2016, 22, 579-592. [CrossRef] [PubMed]

[6] Sharma, K.; Schmitt, S.; Bergner, C.G.; Tyanova, S.; Kannaiyan, N.; Manrique-Hoyos, N.; Kongi, K.; Cantuti, L.; Hanisch, U.K.; Philips, M.A.; et al. Cell type- and brain region-resolved mouse brain proteome. Nat. Neurosci. 2015, 18, 1819-1831. [CrossRef] [PubMed]

[7] Patzig, J.; Jahn, O.; Tenzer, S.; Wichert, S.P.; de Monasterio-Schrader, P.; Rosfa, S.; Kuharev, J.; Yan, K.; Bormuth, I.; Bremer, J.; et al. Quantitative and integrative proteome analysis of peripheral nerve myelin identifies novel myelin proteins and candidate neuropathy loci. J. Neurosci. 2011, 31, 16369-16386. [CrossRef] [PubMed]

[8] Zeisel, A.; Munoz-Manchado, A.B.; Codeluppi, S.; Lonnerberg, P.; La Manno, G.; Jureus, A.; Marques, S.; Munguba, H.; He, L.; Betsholtz, C.; et al. Brain structure. Cell types in the mouse cortex and hippocampus revealed by single-cell RNA-seq. Science 2015, 347, 1138-1142. [CrossRef] [PubMed]

[9] Gokce, O.; Stanley, G.M.; Treutlein, B.; Neff, N.F.; Camp, J.G.; Malenka, R.C.; Rothwell, P.E.; Fuccillo, M.V.; Sudhof, T.C.; Quake, S.R. Cellular taxonomy of the mouse striatum as revealed by single-cell RNA-seq. Cell Rep. 2016, 16, 1126-1137. [CrossRef] [PubMed]

[10] Holtman, I.R.; Noback, M.; Bijlsma, M.; Duong, K.N.; van der Geest, M.A.; Ketelaars, P.T.; Brouwer, N.; Vainchtein, I.D.; Eggen, B.J.; Boddeke, H.W. Glia open access database (goad): A comprehensive gene expression encyclopedia of glia cells in health and disease. Glia 2015, 63, 1495-1506. [CrossRef] [PubMed]

[11] Thakurela, S.; Garding, A.; Jung, R.B.; Muller, C.; Goebbels, S.; White, R.; Werner, H.B.; Tiwari, V.K. The transcriptome of mouse central nervous system myelin. Sci. Rep. 2016, 6, 25828. [CrossRef] [PubMed]

[12] Zhang, Y.; Chen, K.; Sloan, S.A.; Bennett, M.L.; Scholze, A.R.; O'Keeffe, S.; Phatnani, H.P.; Guarnieri, P.; Caneda, C.; Ruderisch, N.; et al. An RNA-sequencing transcriptome and splicing database of glia, neurons, and vascular cells of the cerebral cortex. J. Neurosci. 2014, 34, 11929-11947. [CrossRef] [PubMed]

[13] Aaker, J.D.; Elbaz, B.; Wu, Y.; Looney, T.J.; Zhang, L.; Lahn, B.T.; Popko, B. Transcriptional fingerprint of hypomyelination in zfp191null and shiverer (mbpshi) mice. ASN Neuro 2016, 8, 1-17. [CrossRef] [PubMed]

[14] Ettle, B.; Kerman, B.E.; Valera, E.; Gillmann, C.; Schlachetzki, J.C.; Reiprich, S.; Buttner, C.; Ekici, A.B.; Reis, A.; Wegner, M.; et al. Alpha-synuclein-induced myelination deficit defines a novel interventional target for multiple system atrophy. Acta Neuropathol. 2016, 132, 59-75. [CrossRef] [PubMed]

[15] Kudriaeva, A.A.; Khaustova, N.A.; Maltseva, D.V.; Kuzina, E.S.; Glagoleva, I.S.; Surina, E.A.; Knorre, V.D.; Belogurov, A.A., Jr.; Tonevitsky, A.G.; Gabibov, A.G. Mrna expression profile of mouse oligodendrocytes in inflammatory conditions. Dokl. Biochem. Biophys. 2016, 469, 264-268. [CrossRef] [PubMed]

[16] Evangelidou, M.; Karamita, M.; Vamvakas, S.S.; Szymkowski, D.E.; Probert, L. Altered expression of oligodendrocyte and neuronal marker genes predicts the clinical onset of autoimmune encephalomyelitis and indicates the effectiveness of multiple sclerosis-directed therapeutics. J. Immunol. 2014, 192, 4122-4133. [CrossRef] [PubMed]

[17] Solga, A.C.; Pong, W.W.; Walker, J.; Wylie, T.; Magrini, V.; Apicelli, A.J.; Griffith, M.; Griffith, O.L.; Kohsaka, S.; Wu, G.F.; et al. Rna-sequencing reveals oligodendrocyte and neuronal transcripts in microglia relevant to central nervous system disease. Glia 2015, 63, 531-548. [CrossRef] [PubMed]

[18] Zhang, D.; Yang, G.; Chen, X.; Li, C.; Wang, L.; Liu, Y.; Han, D.; Liu, H.; Hou, X.; Zhang, W.; et al. Mir-300 promotes self-renewal and inhibits the differentiation of glioma stem-like cells. J. Mol. Neurosci. 2014, 53, 637-644. [CrossRef] [PubMed]

[19] Bai, J.; Zhang, Z.; Li, X.; Liu, H. Microrna-365 inhibits growth, invasion and metastasis of malignant melanoma by targeting nrp1 expression. Int. J. Clin. Exp. Pathol. 2015, 8, 4913-4922. [CrossRef] [PubMed]

[20] Qian, J.; Li, R.; Wang, Y.Y.; Shi, Y.; Luan, W.K.; Tao, T.; Zhang, J.X.; Xu, Y.C.; You, Y.P. Mir-1224-5p acts as a tumor suppressor by targeting creb1 in malignant gliomas. Mol. Cell. Biochem. 2015, 403, 33-41. [CrossRef] [PubMed]

[21] Belogurov, A., Jr.; Kuzina, E.; Kudriaeva, A.; Kononikhin, A.; Kovalchuk, S.; Surina, Y.; Smirnov, I.; Lomakin, Y.; Bacheva, A.; Stepanov, A.; et al. Ubiquitin-independent proteosomal degradation of myelin basic protein contributes to development of neurodegenerative autoimmunity. FASEB J. 2015, 29, 1901-1913. [CrossRef] [PubMed]

[22] Belogurov, A., Jr.; Kudriaeva, A.; Kuzina, E.; Smirnov, I.; Bobik, T.; Ponomarenko, N.; Kravtsova-Ivantsiv, Y.; Ciechanover, A.; Gabibov, A. Multiple sclerosis autoantigen myelin basic protein escapes control by ubiquitination during proteasomal degradation. J. Biol. Chem. 2014, 289, 17758-17766. [CrossRef] [PubMed]

[23] Kuzina, E.; Kudriaeva, A.; Smirnov, I.; Dubina, M.V.; Gabibov, A.; Belogurov, A., Jr. Glatiramer acetate and nanny proteins restrict access of the multiple sclerosis autoantigen myelin basic protein to the 26s proteasome. Biomed. Res. Int. 2014, 2014, 926394. [CrossRef] [PubMed]

[24] Kuzina, E.S.; Chernolovskaya, E.L.; Kudriaeva, A.A.; Zenkova, M.A.; Knorre, V.D.; Surina, E.A.; Ponomarenko, N.A.; Bobik, T.V.; Smirnov, I.V.; Bacheva, A.V.; et al. Immunoproteasome enhances intracellular proteolysis of myelin basic protein. Dokl. Biochem. Biophys. 2013, 453, 300-303. [CrossRef] [PubMed]

[25] Tewari, M.K.; Sinnathamby, G.; Rajagopal, D.; Eisenlohr, L.C. A cytosolic pathway for mhc class ii-restricted antigen processing that is proteasome and tap dependent. Nat. Immunol. 2005, 6, 287-294. [CrossRef] [PubMed]

[26] Fabre, B.; Lambour, T.; Garrigues, L.; Amalric, F.; Vigneron, N.; Menneteau, T.; Stella, A.; Monsarrat, B.; Van den Eynde, B.; Burlet-Schiltz, O.; et al. Deciphering preferential interactions within supramolecular protein complexes: The proteasome case. Mol. Syst. Biol. 2015, 11, 771. [CrossRef] [PubMed]

[27] Groettrup, M.; Soza, A.; Eggers, M.; Kuehn, L.; Dick, T.P.; Schild, H.; Rammensee, H.G.; Koszinowski, U.H.; Kloetzel, P.M. A role for the proteasome regulator pa28alpha in antigen presentation. Nature 1996, 381, 166-168. [CrossRef] [PubMed]

[28] Belogurov, A., Jr. (Shemyakin-Ovchinnikov Institute of bioorganic chemistry, Moscow, Russia). Personal communication, 2016.

[29] McCarthy, K.D.; de Vellis, J. Preparation of separate astroglial and oligodendroglial cell cultures from rat cerebral tissue. J. Cell Biol. 1980, 85, 890-902. [CrossRef] [PubMed]

[30] Nathan, J.A.; Spinnenhirn, V.; Schmidtke, G.; Basler, M.; Groettrup, M.; Goldberg, A.L. Immuno- and constitutive proteasomes do not differ in their abilities to degrade ubiquitinated proteins. Cell 2013, 152, 1184-1194. [CrossRef] [PubMed]

[31] Maltseva, D.V.; Khaustova, N.A.; Fedotov, N.N.; Matveeva, E.O.; Lebedev, A.E.; Shkurnikov, M.U.; Galatenko, V.V.; Schumacher, U.; Tonevitsky, A.G. High-throughput identification of reference genes for research and clinical rt-qpcr analysis of breast cancer samples. J. Clin. Bioinform. 2013, 3, 13. [CrossRef] [PubMed]

[32] Krainova, N.A.; Khaustova, N.A.; Makeeva, D.S.; Fedotov, N.N.; Gudim, E.A.; Ryabenko, E.A.; Shkurnikov, M.U.; Galatenko, V.V.; Sakharov, D.A.; Maltseva, D.V. Evaluation of potential reference genes for qRT-PCR data normalization in hela cells. Appl. Biochem. Microbiol. 2013, 49, 743-749. [CrossRef]

[33] Oliveira-Ferrer, L.; Rossler, K.; Haustein, V.; Schroder, C.; Wicklein, D.; Maltseva, D.; Khaustova, N.; Samatov, T.; Tonevitsky, A.; Mahner, S.; et al. C-fos suppresses ovarian cancer progression by changing adhesion. Br. J. Cancer 2014, 110, 753-763. [CrossRef] [PubMed]

[34] Sakharov, D.A.; Maltseva, D.V.; Riabenko, E.A.; Shkurnikov, M.U.; Northoff, H.; Tonevitsky, A.G.; Grigoriev, A.I. Passing the anaerobic threshold is associated with substantial changes in the gene expression profile in white blood cells. Eur. J. Appl. Physiol. 2012, 112, 963-972. [CrossRef] [PubMed]

[35] Barrett, T.; Wilhite, S.E.; Ledoux, P.; Evangelista, C.; Kim, I.F.; Tomashevsky, M.; Marshall, K.A.; Phillippy, K.H.; Sherman, P.M.; Holko, M.; et al. NCBI GEO: Archive for functional genomics data sets-Update. Nucleic Acids Res. 2013, 41, 991-995. [CrossRef] [PubMed]

[36] Ding, X.; Yan, Y.; Li, X.; Li, K.; Ciric, B.; Yang, J.; Zhang, Y.; Wu, S.; Xu, H.; Chen, W.; et al. Silencing ifn-gamma binding/signaling in astrocytes versus microglia leads to opposite effects on central nervous system autoimmunity. J. Immunol. 2015, 194, 4251-4264. [CrossRef] [PubMed]

[37] Hidano, S.; Randall, L.M.; Dawson, L.; Dietrich, H.K.; Konradt, C.; Klover, P.J.; John, B.; Harris, T.H.; Fang, Q.; Turek, B.; et al. Stat1 signaling in astrocytes is essential for control of infection in the central nervous system. mBio 2016, 7, 1-15. [CrossRef] [PubMed]

[38] Aki, M.; Shimbara, N.; Takashina, M.; Akiyama, K.; Kagawa, S.; Tamura, T.; Tanahashi, N.; Yoshimura, T.; Tanaka, K.; Ichihara, A. Interferon-gamma induces different subunit organizations and functional diversity of proteasomes. J. Biochem. 1994, 115, 257-269. [CrossRef] [PubMed]

[39] Namiki, S.; Nakamura, T.; Oshima, S.; Yamazaki, M.; Sekine, Y.; Tsuchiya, K.; Okamoto, R.; Kanai, T.; Watanabe, M. Irf-1mediates upregulation of lmp7 by ifn-gamma and concerted expression of immunosubunits of the proteasome. FEBS Lett. 2005, 579, 2781-2787. [CrossRef] [PubMed]

[40] Brucet, M.; Marques, L.; Sebastian, C.; Lloberas, J.; Celada, A. Regulation of murine tap1 and lmp2 genes in macrophages by interferon gamma is mediated by stat1 and irf-1. Genes Immun. 2004, 5, 26-35. [CrossRef] [PubMed]

[41] Meissner, T.B.; Li, A.; Biswas, A.; Lee, K.H.; Liu, Y.J.; Bayir, E.; Iliopoulos, D.; van den Elsen, P.J.; Kobayashi, K.S. Nlr family member nlrc5 is a transcriptional regulator of mhc class i genes. Proc. Natl. Acad. Sci. USA 2010, 107, 13794-13799. [CrossRef] [PubMed]

[42] Steimle, V.; Siegrist, C.A.; Mottet, A.; Lisowska-Grospierre, B.; Mach, B. Regulation of mhc class ii expression by interferon-gamma mediated by the transactivator gene ciita. Science 1994, 265, 106-109. [CrossRef] [PubMed]

[43] Kobayashi, K.S.; van den Elsen, P.J. Nlrc5: A key regulator of mhc class i-dependent immune responses. Nat. Rev. Immunol. 2012, 12, 813-820. [CrossRef] [PubMed]

[44] Reith, W.; LeibundGut-Landmann, S.; Waldburger, J.M. Regulation of mhc class II gene expression by the class ii transactivator. Nat. Rev. Immunol. 2005, 5, 793-806. [CrossRef] [PubMed]

[45] Constantinescu, C.S.; Tani, M.; Ransohoff, R.M.; Wysocka, M.; Hilliard, B.; Fujioka, T.; Murphy, S.; Tighe, P.J.; Das Sarma, J.; Trinchieri, G.; et al. Astrocytes as antigen-presenting cells: Expression of il-12/il-23. J. Neurochem. 2005, 95, 331-340. [CrossRef] [PubMed]

[46] Schwab, N.; Bien, C.G.; Waschbisch, A.; Becker, A.; Vince, G.H.; Dornmair, K.; Wiendl, H. Cd8+ T-cell clones dominate brain infiltrates in rasmussen encephalitis and persist in the periphery. Brain 2009, 132, 1236-1246. [CrossRef] [PubMed]