Proteome-wide identification of proteoforms induced by adenosine-to-inosine mRNA editing in fruit fly, mouse and human brains

P-02.1-06

S. Moshkovskii[I,II], A. Kliuchnikova[I,II], L. Levitsky[III], A. Goncharov[I], K. Kuznetsova[I], M. Pyatnitskiy[I,IV], I. Ilina[I], S. Novikova[IV], M. Ivanov[III], M. Gorshkov[III]

[I]Federal Research and Clinical Center of Physical-Chemical Medicine, Moscow, Russia, [II]Pirogov Russian National Research Medical University, Moscow, Russia, [III]V.L. Talrose Institute for Energy Problems of Chemical Physics, N.N. Semenov Federal Research Center for Chemical Physics, Russian Academy of Sciences, Moscow, Russia, [IV]Institute of Biomedical Chemistry, Moscow, Russia

Effects of A-to-I RNA editing by ADAR enzymes which leads to non-synonymous mRNA substitutions were identified proteome-wide using publicly available and in-house shotgun mass spectrometry proteomic data for fruit fly, murine and human brains. This type of RNA editing plays its primary role in immunity regulation, and adaptive significance of protein recoding due to this type of editing is still being discussed. Using a modified database for containing edited protein sites predicted from RNA-seq data, we have shown that edited forms are generally depleted in proteomes in comparison to genomically encoded sequences. Thus, of thousands non-synonymous edited sites in fruit fly, mouse and human transcriptomes, we identified 1-2% sites at the proteome level in each brain proteome. In the fruit fly brain, edited sites were shown to be enriched in proteins of SNARE presynaptic complex and other vesicle trafficking components (Kuznetsova et al. (2018) J Proteome Res 17, 3889-3903). Selected findings were confirmed by targeted mass-spectrometry which also showed a dynamics in editing of some protein sites during insect ontogeny. Re-analysis of deep proteomes of murine and human brains could identify as few as 20 and 37 editing sites in mouse and human, respectively, of them eight sites in six proteins were conservative between species (Levitsky et al. (2019) Proteomics 19, e1900195). These findings were in accordance with a previous art, where GRIA2-3 glutamate receptor subunits, COPA coatomer protein and FLNA filamin alpha were recognized as RNA editing targets. Of these extensively edited sites, a functional significance was only known for the GRIA2 glutamate receptor subunit in brain and, preliminary, for the filamin alpha in vascular tissues. Thus, we have identified RNA editing sites at the level of shotgun proteomes. Adaptive significance of these sites, as well as their possible role in animal and human pathology, should be further elucidated by functional studies.