

Transcriptomic analyses suggest that mucopolysaccharidosis patients may be less susceptible to COVID-19

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We used transcriptomic (RNA-seq) analyses to determine whether patients suffering from all types and subtypes of mucopolysaccharidosis (MPS), a severe inherited metabolic disease, may be more susceptible to coronavirus disease 2019 (COVID-19). The expression levels of genes encoding proteins potentially involved in SARS-CoV-2 development were estimated in MPS cell lines. Four genes (*GTF2F2*, *RAB18*, *TMEM97*, *PDE4DIP*) coding for proteins potentially facilitating virus development were down-regulated, while two genes (*FBN1*, *MFGE8*), the products of which potentially interfere with virus propagation, were up-regulated in most MPS types. Although narrowing of respiratory tract and occurrence of thick mucus, characteristic of MPS, are risk factors for COVID-19, transcriptomic analyses suggest that MPS cells might be less, rather than more, susceptible to SARS-CoV-2 infection.

Keywords: COVID-19; mucopolysaccharidosis; transcriptomic analyses

Recently started and still ongoing outbreak of coronavirus disease 2019, or COVID-19 (as officially named by World Health Organization), is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Over 16 million patients have been diagnosed by the date of submission of this report, including over 650 000 fatal cases, and this pandemic spread of the disease caused serious disturbance not only in medical care but also in socioeconomic aspects of human life [2–4]. Apart from general understanding of the mechanisms of the disease, which should lead to the development of effective therapies and prevention strategies, including production of vaccines, identification of groups of people either especially susceptible or resistant to SARS-CoV-2 infection appears to be crucial for appropriate management of the epidemic. On the other hand, despite thousands of articles published on general or specific aspects of COVID-19, only a small fraction of publications concerns problems of

patients suffering from other diseases as risk groups. Recently published reports include papers analyzing problems linked to SARS-CoV-2-mediated infections of patients with as different disorders as dental problems [5], cardiovascular diseases [6,7], dermatologic diseases [8], or gastrointestinal dysfunctions [9], to list just a few. However, patients suffering from genetic diseases may be a special risk group, not only as potentially affected persons but also from the epidemiological point of view, due to severity of the primary conditions and requirement for constant care by others. On the other hand, primary genetic defects often cause multiple changes in expression of a battery of genes which may potentially affect, either positively or negatively, viral development.

Mucopolysaccharidoses (MPS) are a group of 11 genetic diseases caused by mutations in one of genes coding for lysosomal enzymes involved in degradation of glycosaminoglycans (GAGs), complex carbohydrates

Abbreviations

COVID-19, coronavirus disease 2019; FDR, false discovery rate; GAG, glycosaminoglycan; MPS, mucopolysaccharidosis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[10]. GAG storage leads to the development of severe symptoms which progressively appear in the course of the disease development, and the clinical patient's state worsens gradually, causing a death usually by the end of the second decade [11]. Most organs are affected in MPS patients, including heart, gastrointestinal tract, respiratory system, skin, bones, muscles, central nervous system (in some types), and others [11]. Thus, one might suspect that such patients might be a high risk group for COVID-19; however, no reports were published to date on COVID-19 in MPS. On the other hand, recent studies indicated that in cells of MPS patients, there are hundreds of genes which expression is significantly changed relative to healthy persons [12–14]. This might potentially modify susceptibility of these patients to infection by SARS-CoV-2. Therefore, in this report, we have analyzed transcriptomes of cells derived from patients suffering from all MPS types relative to control cells (derived from a healthy person) in the light of potential susceptibility to COVID-19.

Materials and methods

Cell lines and cultures

Cultures of fibroblast of all MPS types, as well as control fibroblasts (HDFa line), were employed. These cell lines were purchased from the NIGMS Human Genetic Cell Repository at the Coriell Institute for Medical Research; all documentation on bio-ethical issues is provided by the institute. The MPS fibroblasts bear specific mutations in genes corresponding to following types: MPS I (p.Trp402Ter/p.Trp402Ter in *IDUA*), MPS II (p.His70ProfsTer29 in *IDS*), MPS IIIA (p.Glu447Lys/p.Arg245His in *SGSH*), MPS IIIB (p.Arg626Ter/p.Arg626Ter in *NAGLU*), MPS IIIC (undetermined mutations in *HGSNAT*), MPS IIID (p.Arg355Ter/p.Arg355Ter in *GNS*), MPS IVA (undetermined mutations in *GALNS*), MPS IVB (p.Trp273Leu/p.Trp509Cys in *GLB1*), MPS VI (undetermined mutations in *ARSB*); MPS VII (p.Trp627Cys/p.Arg356Ter in *GUSB*), and MPS IX (undetermined mutations in *HYALI*). Diagnosis of patients with undetermined mutations was based on measurement of urinary GAG levels and determination of activities of lysosomal enzymes in plasma. Cells were cultured in the Dulbecco's Modified Eagle Medium supplemented with antibiotics and 10% FBS, at 37 °C, 95% humidity, and saturation with 5% CO₂.

RNA isolation

RNA isolation was conducted in four biological repeats for each cell line (i.e., four independent cultures from different passages). The procedure was performed exactly as described previously [12].

RNA-seq analyses

RNA-seq analyses were performed as described previously [12]. Raw data are deposited at NCBI Sequence Read Archive (SRA), under accession no. PRJNA562649.

Western blotting

Fibroblasts (6×10^5 cells) were passaged on 10 cm diameter plates and allowed to attach overnight, and the cultivation was continued for 48 h. A solution composed of 1% Triton X-100, 0.5 mM EDTA, 150 mM NaCl, 50 mM Tris, pH 7.5, and a mixture of protease and phosphatase inhibitors (Roche Applied Science, Penzberg, Germany) was used for cell lysis. The lysate was cleared by centrifugation. Proteins were separated using the WES system (WES—Automated Western Blots with Simple Western; ProteinSimple, San Jose, CA, USA). The 12–230 kDa Separation Module and Anti-Mouse Detection Module were employed as described in the manufacturer's manual. Specific antibodies against tested proteins were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA, USA).

Statistical analyses

One-way ANOVA on $\log_2(1 + x)$ values revealing normal continuous distribution was employed to determine statistical significance. The Benjamini–Hochberg method was used to estimate the false discovery rate (FDR). *Post hoc* Student's *t*-test with Bonferroni correction was used for comparisons between two groups. The R software v3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria) was used for all statistical analyses.

Results and Discussion

We have analyzed transcriptomes of fibroblasts derived from patients suffering from all known MPS types (I, II, IIIA, IIIB, IIIC, IIID, IVA, IVB, VI, VII, and IX), obtained in the RNA-seq analysis, relative to control fibroblasts (HDFa cell line) (SRA accession no. PRJNA562649). The quality of the RNA-seq data was confirmed previously and assessed to be reliable on the basis of RT-qPCR analyses of selected genes [12–14]. Because of the severity of the disease, fibroblasts are most often used type of cells in genetic and genomic studies on MPS; in fact, availability of other biological material is technically and ethically poor, due to conditions of patients.

We have considered human genes coding for proteins which have been reported recently as those interacting with polypeptides encoded by SARS-CoV-2 [15,16]. The newest database lists 332 physical interactions between proteins encoded by human and the

virus [16]. We found that among genes coding for human proteins involved in interactions with SARS-CoV-2's proteins, there were between 13 and 41 transcripts (depending on MPS type) which levels were significantly up- or down-regulated in MPS fibroblasts relative to control cells (Fig. 1). The full list of such transcripts, which expression was significantly changed in fibroblasts of particular MPS types, is included in Table S1. It is worth noting that vast majority of changes in expression of almost every single gene is the same for the direction of the change, irrespective of the MPS type, that is, every gene is either down- or up-regulated in all MPS types. These results may suggest that the response of MPS patients to SARS-CoV-2 infection may considerably differ from that of general population due to differences in intracellular virus development. Interestingly, in most MPS types, number of down-regulated genes was higher than up-regulated genes (Fig. 1, Table S1).

Unfortunately, expressions of two human genes crucial for the virus adsorption and intracellular penetration, *ACE2* and *TMPRSS2*, coding for the SARS-CoV-2 receptor and specific protease, respectively [1–4], were at very low levels in fibroblasts (FPKM values < 1), precluding a reliable analysis. Nevertheless, it might be worth mentioning that while low mRNA levels of *ACE2* could be detected in HDFa cells, the determined corresponding values for vast majority of MPS cell lines were zero, except MPS IVA and VI, where negligible amounts of the transcripts could be found. If down-regulation of *ACE2* occurs in MPS cells indeed, the patients might be less susceptible for COVID-19; however, it should be underlined that such an assumption is highly speculative. Despite these difficulties, we aimed to detect *ACE2* and *TMPRSS2*

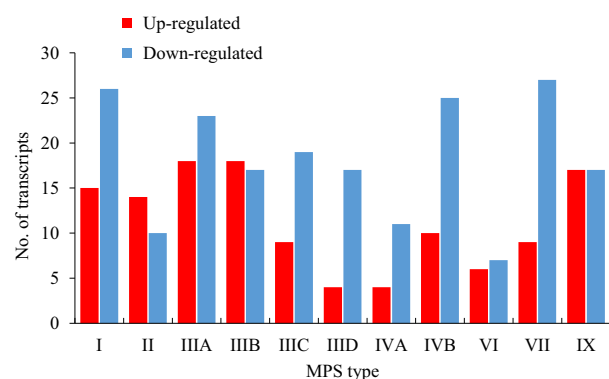


Fig. 1. Number of up-regulated (red columns) and down-regulated (blue columns) transcripts (at FDR < 0.1; $P < 0.1$) of genes (which products are potentially involved in interaction with SARS-CoV-2 proteins) in different types of MPS relative to control cells (HDFa).

proteins by high sensitive western blotting (using the WES system). Although we failed to visualize *ACE2* protein (data not shown), we were able to detect *TMPRSS2* (Fig. 2E). Quantitative analysis indicated that the level of this protein was decreased in MPS I, II, and IIIB fibroblasts while increased in other MPS types relative to control cells (Fig. 2F). This might suggest differential efficiency of adsorption of SARS-CoV-2 on the cells, depending on the MPS type.

When considering genes which were up- or down-regulated in most MPS types, we could find six genes which expression was changed in at least seven types relative to control cells. Expression analyses of these genes are presented as heat maps (Fig. 2A), and fold changes (FC) of levels of particular transcripts are demonstrated in Table 1. Four of these genes (*GTF2F2*, *RAB18*, *TMEM97*, and *PDE4DIP*) were down-regulated, and two (*FBN1* and *MFGES8*) were up-regulated in all MPS types. We asked if transcriptomic data could be confirmed at the level of abundance of corresponding gene products. Therefore, using western blotting, we tested levels of selected proteins, encoded by genes which revealed significantly changed expression at the mRNA level in at least seven MPS types. The results presented in Fig. 2B–D indicated that levels of the *PDE4DIP* protein were decreased in fibroblast of all MPS types but MPS IIIC, and levels of *FBN1* were increased in all MPS types but MPS IIIC and IIID, relative to control cells. Therefore, we concluded that the presented transcriptomic data are reliable and observed mRNA levels generally correspond to levels of gene products. Again, the western blotting results confirmed that expressions of tested genes are similarly regulated (up or down, depending on the gene) in most MPS types. Such uniform distribution of up- and down-regulated genes among MPS types indicates that the observed changes are not coincidental, but rather they represent a general tendency in MPS cells (this conclusion is corroborated by results for other genes, presented in Table S1).

The *GTF2F2* gene codes for the general transcription factor IIF subunit 2, known as TFIIF [17]; thus, it is likely involved in the viral gene expression positive control. *RAB18* is a Ras-related small GTPase involved in regulation of membrane trafficking and vesicular transport [18]. *TMEM97* is a transmembrane protein which regulates cholesterol levels [19]. The *PDE4DIP* gene codes for the phosphodiesterase 4D-interacting protein which is involved in Golgi apparatus functions [20]. One may predict that all these proteins are required for effective SARS-CoV-2 development; thus, down-regulation of their genes might cause lower susceptibility to COVID-19.

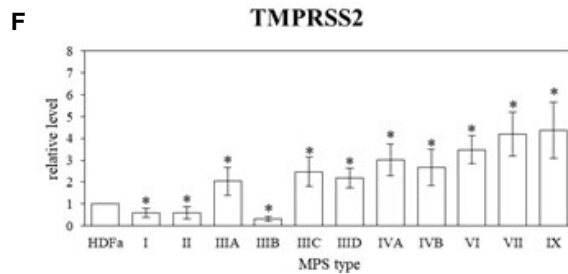
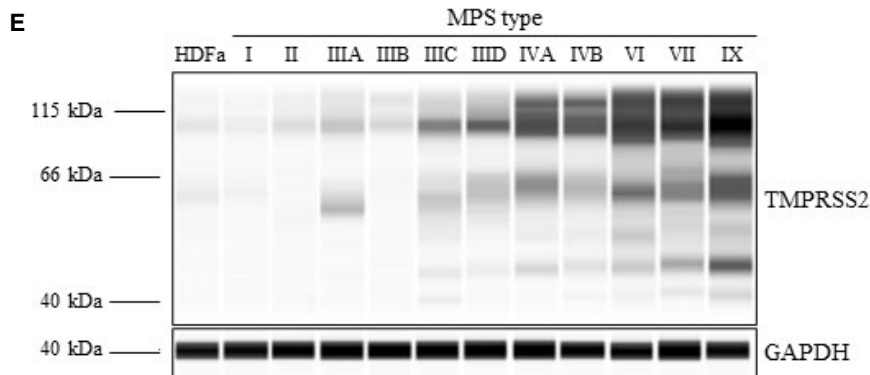
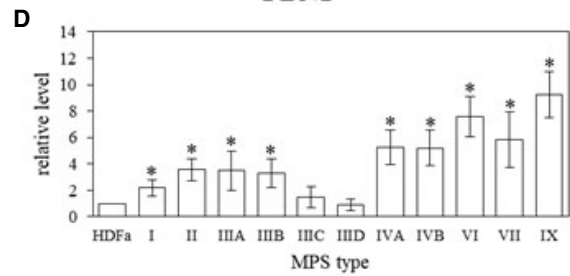
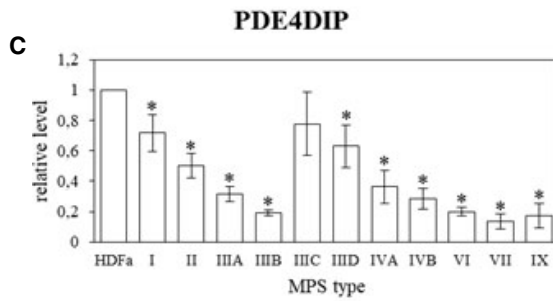
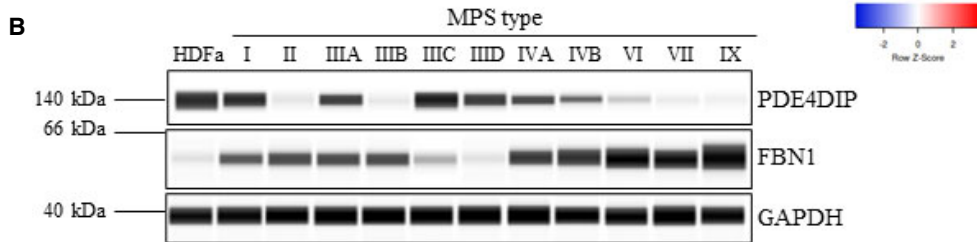
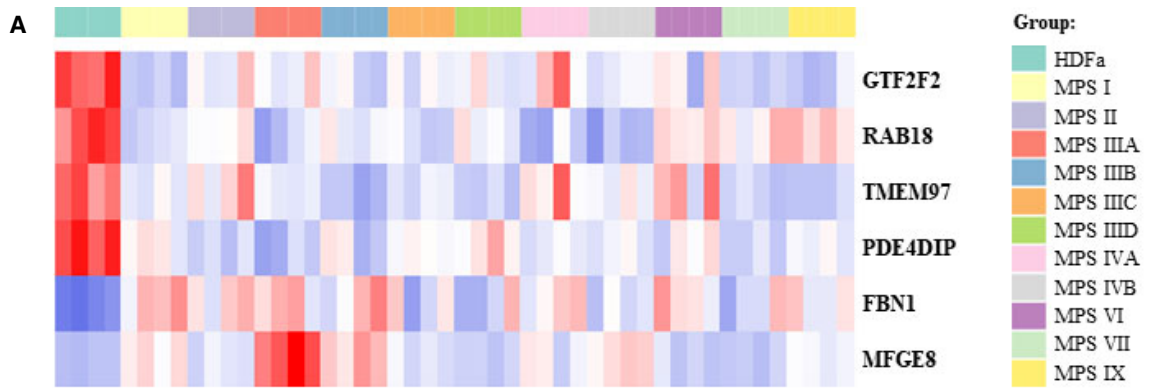


Table 1. Human genes (which products are potentially involved in interaction with SARS-CoV-2 proteins) with expression significantly changed (at FDR < 0.1; $P < 0.1$) in most (seven or more) MPS types relative to control cells (HDFa). Down-regulated genes are marked in italic numbers, and up-regulated genes are marked in bold numbers. Regular font values indicated results in which no statistically significant differences between MPS and HDFa were determined.

Transcript	\log_2 FC of selected transcripts' levels in particular MPS type vs. HDFa line										
	I	II	III A	III B	III C	III D	IVA	IVB	VI	VII	IX
<i>GTF2F2</i>	-1.34	-0.83	-0.84	-1.09	-0.95	-0.92	-0.57	-1.01	-0.87	-1.25	-1.30
<i>RAB18</i>	-0.88	-0.64	-0.98	-0.72	-0.87	-0.69	-1.01	-1.13	-0.51	-0.56	-0.44
<i>TMEM97</i>	-1.39	-0.64	-1.37	-2.50	-1.45	-1.96	-0.63	-1.20	-0.49	-1.88	-2.06
<i>PDE4DIP</i>	-0.94	-1.39	-1.65	-1.20	-1.00	-0.79	-1.18	-1.13	-1.00	-1.40	-1.08
<i>FBN1</i>	1.61	1.47	1.52	1.50	1.16	1.04	1.42	1.04	1.49	1.10	1.34
<i>MFGE8</i>	2.64	1.64	3.90	3.05	1.66	1.00	2.17	2.77	1.04	0.71	2.05

Table 2. Human genes (which products are potentially involved in interaction with SARS-CoV-2 proteins) with \log_2 FC > 2.0 in specific MPS type relative to control cells (HDFa). Up-arrowed and down-arrowed symbols indicate up- and down-regulation, respectively, while minus symbols indicate no significant changes. For some genes, more than one transcript were identified.

Transcript	High-level changes (\log_2 FC > 2) in expression of selected genes in MPS vs. HDFa										
	I	II	III A	III B	III C	III D	IVA	IVB	VI	VII	IX
<i>CAV1</i>	↓	–	–	–	–	–	–	↓	–	–	–
<i>UBE2I</i>	–	↓	–	–	–	–	–	–	↓	–	–
<i>HOXC6</i>	–	–	–	–	↓	–	–	–	–	–	–
<i>HOXC6</i>	–	–	–	–	↓	–	–	↓	–	–	–
<i>TMEM97</i>	–	–	–	–	–	–	–	–	–	–	↓
<i>NUP88</i>	–	–	–	–	–	↓	–	–	–	–	–
<i>ARL6IP6</i>	–	↓	–	↓	↓	–	–	–	–	–	–
<i>MFGE8</i>	↑	–	↑	↑	–	–	–	↑	–	–	–
<i>MFGE8</i>	↑	–	↑	↑	–	–	–	↑	–	–	–
<i>MFGE8</i>	↑	–	↑	↑	–	–	–	↑	–	–	–
<i>MFGE8</i>	↑	–	↑	↑	–	–	–	–	–	–	–
<i>ATF5</i>	–	–	–	–	–	–	–	–	–	–	↑
<i>ATF5</i>	–	–	–	–	–	–	–	–	–	–	↑

The *FBN1* gene codes for fibrillin-1, a protein which is proteolytically cleaved to generate an extracellular matrix glycoprotein and asprosin, involved in glucose homeostasis [21]. *MFGE8* also codes for a polypeptide which after cleavage is converted into several polypeptides, among which lactahedrin is the major one; lactahedrin is a membrane glycoprotein promoting phagocytosis of apoptotic cells [22]. Therefore, one might speculate that up-regulation of these two genes in MPS cells could promote

antiviral defense cellular mechanisms, again lowering susceptibility of the patients to COVID-19.

We have also analyzed transcripts which levels were particularly significantly changed (\log_2 FC > 2) in certain MPS types. The results are shown in Table 2. In individual MPS types, following genes were down-regulated: *CAV1*, *UBE2I*, *HOXC6*, *TMEM97*, *NUP88*, and *ARL6IP6*. On the other hand, *MFGE8* and *ATF5* were up-regulated.

Fig. 2. Human genes (which products are potentially involved in interaction with SARS-CoV-2 proteins) with expression significantly changed in most (seven or more) MPS types relative to control cells (HDFa). A heat map is presented in panel A. Panel B shows representative results of western blotting of two proteins, PDE4DIP and FBN1 (with GAPDH as a loading control), and quantitative analysis (from three independent experiments) is presented in panels C and D, respectively (with asterisks indicating statistically significant differences, at $P < 0.05$, relative to control). Panel E shows representative results of western blotting of the Tmprss2 protein (with GAPDH as a loading control), and quantitative analysis (from three independent experiments) is presented in panel F (with asterisks indicating statistically significant differences, at $P < 0.05$, relative to control).

CAVI codes for caveolin-1, a protein involved in promoting cell cycle progression [23]. *UBE2I* is a ubiquitin conjugating enzyme E2I, involved in protein degradation mechanism, while it can also stimulate transcription [24]. *HOXC6* encodes a transcription factor involved in morphogenesis [25]. The *NUP88* gene product is one of the nucleoporins, required for communication of the nucleus with cytoplasm, particularly for mRNA transport [26]. *ARL6IP6* codes for ADP ribosylation factor like GTPase 6 interacting protein 6, a polypeptide involved in the protein modification processes [27]. One may predict that, together with *TMEM97* (described above), these genes facilitate intracellular development of SARS-CoV-2. Thus, their down-regulation in MPS cells may strengthen the putative impairment of the virus development. On the other hand, apart from previously described *MFGE8*, up-regulated in MPS I, IIIA, IIIB, and IVB, another strongly up-regulated gene in MPS IX is *ATF5*, coding for a transcription factor which may act as either activator or repressor of transcription [28]. Thus, these up-regulated genes might result in putative antiviral reactions operating in MPS cells.

In summary, results of transcriptomic analyses, presented in this report, might suggest that cells of patients suffering from MPS can reveal lower susceptibility to infection by SARS-CoV-2 due to specific changes in expression of genes coding for proteins involved in interactions with viral proteins, despite increased levels of *TMPRSS2* in some MPS types. On the other hand, it is necessary to take into consideration the fact that MPS patients are generally more sensitive to various infectious agents due to secondary anatomical and physiological changes, appearing as a result of the primary GAG storage [10,11]. These changes include narrowing of respiratory tract and occurrence of thick mucus which can be significant risk factors when considering COVID-19. Thus, one should still recommend particular caution when protecting MPS patients against SARS-CoV-2 infection. Moreover, in MPS types in which enzyme replacement therapy is available, potential interruption of the treatment (due to strategies of some hospitals, reluctant to the whole day procedure of intravenous administration of the drug to severely affected patients in the clinic) may have fatal consequences, as published reports clearly indicated that cessation of this therapy results in dramatic worsening of conditions of patients [29–31] which, in turn, would make them especially endangered by COVID-19. In fact, frequent and severe respiratory tract infections were reported as being among characteristic symptoms of enzyme replacement therapy interruption in MPS patients [29–31].

Nevertheless, presented analyses may shed a new light on the MPS course, underlining the importance of modifications of cellular processes, arising from changes in gene expression regulations, in the pathomechanism (as proposed recently [32]), and suggesting that patients suffering from this disease might reveal certain features making them potentially less susceptible to some other diseases.

It is also necessary to indicate limitations of this study. Only one cell line from each MPS type was used, due to technical reasons. This allowed us to test all MPS types and subtypes; however, internal variability in each MPS type could not be assessed. Nevertheless, similar patterns of expression of most human genes which products can be involved in SARS-CoV-2 development in most MPS types (either up- or down-regulation relative to control cells) might suggest that presented results correspond to general features of MPS cells. The used fibroblast lines were derived from patients suffering from severe forms of MPS types. This might give results more pronounced relative to experiments with cells representing milder forms of diseases.

The question what is the specific cause of changes in expression of tested genes in MPS cells remains unanswered. As indicated in recently published reports [12–14], expression of hundreds of genes is changed in MPS cells relative to controls. Specific mechanisms of these regulations remain to be elucidated; however, it was proposed that they reflect secondary and tertiary changes in cellular processes, after primary GAG storage [32]. On the other hand, it has been indicated that severity of MPS symptoms in patients does not simply correlate with GAG levels in organisms of such patients [33]. Therefore, specific regulation of cellular processes, including control of gene expression, in MPS cells, is a complex process, involving a complicated network of factors and processes which are changed in these cells relative to healthy cells. As proposed, MPS, as formally a monogenic disease, reflects changed expression of a large battery of genes which significantly modifies cell physiology [12].

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Author contributions

KP performed analyses and visualized the results. LG performed western blotting experiments and participated in data analysis. GW supervised the project,

participated in analyzing results, and drafted the manuscript.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Human genes (which products are potentially involved in interaction with SARS-CoV-2 proteins) with changed expression (at FDR < 0.1; $P < 0.1$) in specific MPS type relative to control cells (HDFa).