GEM/Kir is differentially expressed in multiple models of coronavirus infection.

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The coronavirus COVID19 pandemic is an emerging biosafety threat to the nation and the world (1). There are no treatments approved for coronavirus infection in humans (2) and there is a lack of information available regarding the basic transcriptional behavior of human cells and mammalian tissues following coronavirus infection. We mined multiple independent public (3) or published datasets (4-7) containing transcriptome data from infection models of human coronavirus 229E, the severe acute respiratory syndrome (SARS) coronavirus and Middle East respiratory syndrome (MERS) coronavirus to discover genes whose differential expression was conserved across the coronavirus family. We identified the GTP binding protein overexpressed in skeletal muscle, GEM (8), also known as Kir, as a differentially expressed gene following infection of human cells with two types of MERS coronavirus, after infection of human cells with human coronavirus 229E, and in the lungs of mice and ferrets infected with SARS coronavirus. GEM induction after viral infection appears to be conserved across the coronavirus family and may be found in patients infected with the novel coronavirus SARS-CoV-2.

Keywords: GEM, coronavirus, MERS coronavirus, SARS coronavirus, human coronavirus 229E, SARS-CoV-2, COVID19, systems biology of viral infection.

Viruses are classified according to a system known as the “Baltimore” classification of viruses (9) wherein the characteristics of the viral genome - whether it is positive-sense or negative-sense, whether it is single-stranded or double-stranded, whether it is composed of RNA or DNA - are used to group viruses into families. Coronaviruses are single-stranded, positive-sense RNA viruses that contain an envelope surrounding their viral particle (10). Their genome is largest of all RNA viruses, ranging from 27 to 33 kb in size (11). They obtain their name from the crown-like appearance of the viral particle imparted by the structure of the large-surface glycoprotein (11). The coronaviridae family includes seven viruses capable of infecting humans, including the severe acute respiratory distress syndrome, or SARS coronavirus (12), the Middle East respiratory syndrome coronavirus, or MERS coronavirus (13), the human coronaviruses (HCoV) 229E, OC43, HKU and NL63 (14-16), and the novel human coronavirus causing COVID19 infections now known as SARS-CoV-2 (17). As of March 19, 2020, the World Health Organization reported 209,839 cases of COVID19 and 8778 deaths from SARS-CoV-2 infection world-wide (18). There are no FDA-approved treatments for human coronavirus infection.

We used a systems-level approach to identify the genes whose expression changes most significantly following infection of human cells with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) using two independent datasets (3, 4) and compared these data to similar analyses of datasets generated using a human coronavirus 229E *in vitro* infection model (5) as well as two *in vivo* models of SARS coronavirus infection of the mouse lung and the ferret lung (6, 7). Across both of the MERS-CoV datasets, we identified the GTP binding protein overexpressed in skeletal muscle, or GEM as among the genes most differentially expressed following MERS coronavirus infection. Albeit less pronounced, GEM was also differentially expressed in HCoV 229E and SARS coronavirus infection models. GEM represents a transcriptional target of the host cell gene expression program following infection with coronaviruses in human cells as well as in the lungs of mice and ferrets.

Methods

We used datasets GSE100509 (3) and GSE56677 (4), GSE89167 (5), GSE59185 (6) and GSE22581(7) for this systems-level differential gene expression analysis of coronavirus infections in conjunction with GEO2R.

The Benjamin and Hochberg method of p-value adjustment was used for ranking of differential expression but raw p-values were used for assessment of statistical significance of global differential expression. Log-transformation of data was auto-detected, and the NCBI generated category of platform annotation was used.

A statistical test was performed to evaluate the significance of difference in GEM mRNA expression levels in CALU3 2B4 cells with MERS-CoV infection as compared to CALU3 2B4 cells at baseline (0 hours) using a one-way ANOVA with Tukey's multiple comparisons test. A statistical test was performed to evaluate the significance of difference in GEM mRNA expression levels in human primary microvascular endothelial cells with MERS-CoV as compared to baseline infection at 0 hours using a one-way ANOVA with Tukey's multiple comparisons test. Only p-values less than 0.05 were considered statistically significant. We used PRISM for all statistical analyses (Version 8.4.0)(455).

Results

We mined two independent microarray datasets, public (3) and published (4) containing transcriptome data from models of MERS coronavirus infection in primary human cells and cell culture. We integrated this data with similar analyses of an *in vitro* infection models of human coronavirus 229E (5) and two *in vivo* models of SARS coronavirus infection, in the lungs of mice and in the lungs of ferrets (6, 7). Across experimental models, we found that GEM was among the genes whose expression changed most significantly following infection with a coronavirus.

GEM is differentially expressed in primary human microvascular endothelial cells when comparing cells infected with wild-type Middle East respiratory syndrome coronavirus (MERS-CoV), icMERS-CoV EMC2012 and uninfected cells.

We identified GEM as differentially expressed following infection of primary human microvascular endothelial cells with wild-type Middle East respiratory syndrome coronavirus (MERS-CoV), icMERS-CoV EMC2012 when compared to non-infected cells (Table 1) (3). When sorting all of the transcripts expressed in human microvascular endothelial cells measured by microarray based on change in expression with and without infection, GEM ranked 11 out of 34127 transcripts. Differential expression of GEM in primary human microvascular endothelial cells following infection with MERS-CoV was statistically significant (Table 1; $p=1.55E-30$).

GEM is differentially expressed in the human cell line CALU3 2B4 when comparing cells infected with MERS-CoV London and uninfected cells.

We also identified GEM as differentially expressed in the human cell line CALU3 2B4 when comparing cells infected with MERS-CoV London from at 3 hours, 7 hours, 12 hours, 18 hours and 24 hours to cells infected at baseline (0 hours) (Table 2) (4). When sorting all of the transcripts expressed in CALU3 2B4 cells measured by microarray based on change in expression with and without MERS-CoV London infection, GEM ranked 13 out of 28653 transcripts. Differential expression of GEM in CALU3 2B4 cells following infection with MERS-CoV London was statistically significant (Table 2; $p=2.63E-15$).

GEM is differentially expressed in the human cell line Huh-7 when comparing cells infected with human coronavirus 229E (HCoV 229E) and uninfected cells.

In a cell line infection model of human coronavirus 229E infection, we identified GEM as differentially expressed when compared to uninfected cells. When sorting all of the transcripts expressed in Huh-7 cells based on change in expression between infected and uninfected cells, GEM ranked 1732 out of 62976 transcripts. Thus, the expression of GEM changed to a greater degree than 97.25% of the transcriptome following infection with HCoV 229E.

Differential expression of GEM was statistically significant (Table 3; $p=0.00894537$).

GEM is differentially expressed in the lungs of BALB/c mice infected with SARS-CoV when compared to the lungs of mock infected mice.

In an *in vivo* model of SARS coronavirus infection of the mouse, we identified GEM as differentially expressed in the lungs when compared to the lungs of mock infected mice. When sorting all of the transcripts expressed in the mouse lung based on change in expression between infected and mock infected mice, GEM ranked 341 out of 62976 transcripts. Thus, the expression of GEM changed to a greater degree than 99.46% of the mouse lung transcriptome following infection with SARS coronavirus. Differential expression of GEM in the SARS-infected mouse lung was statistically significant (Table 4; $p=4.65E-07$).

GEM is differentially expressed in the lungs of ferrets infected with SARS-CoV when compared to the lungs of uninfected ferrets.

In another *in vivo* model of SARS coronavirus infection of the ferret, we identified GEM as differentially expressed in the lungs when compared to the lungs of uninfected ferrets. When sorting all of the transcripts expressed in the mouse lung based on change in expression between infected and uninfected ferrets, GEM ranked 4537 out of 43035 transcripts. Thus, the expression of GEM changed to a greater degree than 89.46% of the ferret lung transcriptome following infection with SARS coronavirus. Differential expression of GEM in the SARS-infected ferret lung was statistically significant (Table 5; $p=7.04E-04$).

GEM is transcriptionally repressed following infection of primary human microvascular endothelial cells with wild-type Middle East respiratory syndrome coronavirus (MERS-CoV), icMERS-CoV EMC2012.

We extracted exact mRNA expression values for GEM from primary human microvascular endothelial cells infection with wild-type Middle East respiratory syndrome coronavirus (MERS-CoV), icMERS-CoV, and from uninfected primary human microvascular endothelial cells in order to compare expression levels of GEM between these two groups rather than relative to the rest of the transcriptome as assessed in differential gene expression analysis. This dataset contained transcriptome information from infection of primary human microvascular endothelial cells at 12 hours, 24 hours, 36 hours and 48 hours post-infection at

1 compared to baseline (0 hours). We also performed a statistical test to evaluate whether the
2 difference in expression of GEM in primary human microvascular endothelial cells infection with
3 and without MERS-CoV infection was statistically significant. Despite an initial modest but
4 statistically significant decrease in GEM expression at 12 hours post-infection (Figure 1;
5 $p=0.0022$), GEM was expressed at significantly higher levels at 24 hour, 36 hours, and 48 hours
6 post-infection with MERS-CoV as compared to cells infected at baseline (0 hours) (Figure 1;
7 $p<0.0001$ for all comparisons). We calculated a fold change in GEM expression, relative to
8 baseline (0 hours), of 0.9570 ± 0.0141 at 12 hours, of 1.4848 ± 0.0294 at 24 hours, of $1.7196 \pm$
9 0.0089 at 36 hours, and of 1.7057 ± 0.0134 at 48 hours post-infection (Table 1).

11 GEM is transcriptionally induced in the human cell line CALU3 2B4 following infection with 12 MERS-CoV London.

13 We also extracted exact mRNA expression values for GEM from CALU3 2B4 cells
14 following infection with MERS-CoV London and from CALU3 2B4 cells infected with MERS-
15 CoV London at baseline in order to compare expression levels of GEM between these two
16 groups. We also performed a statistical test to evaluate whether the difference in expression of
17 GEM in CALU3 2B4 cells following infection with MERS-CoV London as compared to cells
18 infected with MERS-CoV London at baseline was statistically significant. Consistent with the
19 induction of GEM after infection of primary human microvascular endothelial cells with wild-
20 type MERS-CoV, GEM was expressed at significantly higher levels post-infection MERS-CoV
21 London at 12, 18 and 24 hours (Figure 2; $p<0.0001$ for all comparisons). We calculated a fold
22 change in GEM expression, relative to baseline (0 hours), of 1.0049 ± 0.0210 at 3 hours, of
23 1.0160 ± 0.0339 at 7 hours, of 1.514 ± 0.0163 at 12 hours, of 1.3565 ± 0.0380 at 18 hours, and
24 1.7064 ± 0.0083 at 24 hours post-infection (Table 2).

26 Thus, we found that GEM was among the genes whose expression changed most
27 significantly after infection of human cells with MERS-CoV wild-type and MERS-CoV London,
28 and that GEM was transcriptionally induced in primary human microvascular endothelial cells
and in a human lung adenocarcinoma cell line following infection with wild-type MERS-Cov

1 and MERS-CoV London, respectively. GEM was also significantly differentially expressed in a
2 human cell line (Huh-7) following infection with human coronavirus 229E, in the lungs of mice
3 infected SARS coronavirus, and in the lungs of ferrets infected with SARS coronavirus.
4 Differential expression of GEM after coronavirus infection appeared to be conserved across the
5 coronavirus family, with the most striking differential expression found after MERS coronavirus
6 infection.

7 8 **Discussion**

10 COVID19 is a newly discovered coronavirus that infects humans and whose spread has
11 lead to a global pandemic (15) with zero available therapeutic strategies. To facilitate target
12 discovery and to further understanding of the basic transcriptional program of cells and tissues
13 following coronavirus infection, we mined two independent microarray datasets containing
14 transcriptome data of human cells infected with wild-type MERS-CoV and MERS-CoV London,
15 in primary cells and in cell culture (3, 4). Across experimental models, we identified GEM as
16 one of the genes whose expression changed most significantly following infection with a
17 MERS coronavirus. GEM was also significantly differentially expressed in the lungs of mice
18 infected SARS coronavirus, in the lungs of ferrets infected with SARS coronavirus, and in a
19 human cell line (Huh-7) infected with human coronavirus 229E. In both MERS experimental
20 models analyzed, GEM expression significantly increased after infection with coronavirus, with
21 a modest but statistically significant initial decrease in GEM expression at 12 hours in primary
22 human microvascular endothelial cells.

25 GEM, also known as Kir, is a GTP-binding protein and GTPase and belongs to the RGK
26 group of the Ras superfamily of GTPases which includes Rem, Rem2 and Ges (8). Over-
27 expression of Gem induces endothelial sprouting (8). High intracellular levels of Gem induce
28 profound reorganization of the actin cytoskeleton leading to changes in cell morphology such
as cell elongation (8). Gem interacts with both microfilaments and microtubules (8). In this

1 role, Gem associates with the kinesin-like protein KIF9 (8). Gem has been demonstrated to
2 negatively regulate the Rho kinase pathway, and in this role Gem interacts with the Rho kinase
3 beta (ROK beta) (19). The molecular chaperone calmodulin binds to GEM and inhibits the
4 GTPase function of GEM (20). Calmodulin, as well as 14-3-3, regulate the sub-cellular
5 localization of GEM (21). In cancer, GEM is the most highly expressed gene in neuroblastoma
6 samples that have developed ganglionic morphology (22). The only information we could
7 identify regarding a role for GEM in viral infection was in the human T-lymphotrophic virus
8 HTLV-I, where Gem was part of a group of genes up-regulated in T-lymphocytes by HTLV-I
9 infection, specifically by the Tax oncoprotein (23). A 28-fold induction of Gem was found in
10 Tax-expressing cells, and Tax recruited CREB and CBP to the Gem promoter to transactivate
11 gene expression of Gem (23). Mechanistically, Gem was found to promote cell migration and
12 chemotaxis, as well as to enhance formation of cell-cell conjugates, thereby promoting viral
13 transmission between cells and subsequent viral infectivity (23).

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15 We found that GEM was differentially expressed in a human cell line, CALU3 2B4
16 following infection with the human coronavirus MERS-CoV London as well as in primary human
17 endothelial cells after infection with wild-type MERS-CoV. GEM was also significantly
18 differentially expressed in the lungs of mice infected SARS coronavirus, in the lungs of ferrets
19 infected with SARS coronavirus, and in a human cell line (Huh-7) infected with human
20 coronavirus 229E. GEM expression should be evaluated in the cells and tissues of patients
21 infected with the novel coronavirus SARS-CoV-2 to assess whether COVID19 infection similarly
22 leads to induction of GEM. We suggest that transcriptional induction of GEM is conserved
23 among the coronaviruses based on differential expression in mice, ferrets and human cells
24 after infection with multiple coronavirus types: SARS-CoV, MERS-CoV, and HCoV 229E. If
25 GEM expression in coronavirus infections functions similarly to that of HTLV-I infection,
26 promoting viral infectivity (23), modulation of GEM expression may represent a therapeutic
27 strategy in coronavirus infection. The role of GEM in SARS-CoV-2 infection remains to be
28 determined.

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Rank	ID	p-value	F	Fold change	Gene	Gene name
11	A_23_P257043/ NM_005261	1.55E-30	2533.0324	12 hr: 0.9570 ± 0.0141 24 hr: 1.4848 ± 0.0294 36 hr: 1.7196 ± 0.0089 48 hr: 1.7057 ± 0.0134	GEM	GTP binding protein overexpressed in skeletal muscle

Table 1: GEM is among the most differentially expressed gene in primary human microvascular endothelial cells when comparing cells infected with wild-type Middle East respiratory syndrome coronavirus (MERS-CoV), icMERS-CoV EMC2012 and non-infected cells.

The rank of differential expression globally, the probe/transcript ID, the p-value of differential expression globally, F, a statistic used when more than two groups are compared in differential gene expression analysis (rather than the moderated t-statistic “t”), the gene and gene name are listed in this chart.

Rank	ID	p-value	F	Fold change	Gene	Gene name
13	A_23_P257043 NM_005261	2.63E-15	380.9614	3 hr: 1.0049 ± 0.0210 7 hr: 1.0160 ± 0.0339 12 hr: 1.1514 ± 0.0163 18 hr: 1.3565 ± 0.0380 24 hr: 1.7064 ± 0.0083	GEM	GTP binding protein overexpressed in skeletal muscle

Table 2: GEM is among the most differentially expressed genes in human lung adenocarcinoma cells (CALU3 2B4) when comparing cells infected with MERS-CoV London from 3 to 24 hours and cells infected at baseline.

The rank of differential expression globally, the probe/transcript ID, the p-value of differential expression globally, F, a statistic used when more than two groups are compared in differential gene expression analysis (rather than the moderated t-statistic “t”), the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
1732	43810/ NM_005261	0.00894537	3.86	-2.208752	GEM	GTP binding protein overexpressed in skeletal muscle

Table 3: GEM is among the most differentially expressed genes in a human liver cell line when comparing Huh-7 cells infected with HCoV 229E and uninfected cells.

The rank of differential expression globally, the probe/transcript ID, the p-value of differential expression globally, t, a moderated t statistic, B, the log-odds of differential expression between the groups compared, the gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
341	58705/ NM_010276	4.65E-07	1.62E+01	7.2065	Gem	GTP binding protein (gene overexpressed in skeletal muscle)

Table 4: GEM is among the most differentially expressed in the lungs of mice infected with SARS coronavirus when compared to the lungs of mock-infected mice.

The rank of differential expression globally, the probe/transcript ID, the p-value of differential expression globally, t, a moderated t statistic, B, the log-odds of differential expression between the groups compared, the gene and gene name are listed in this chart.

Rank	ID	p-value	F	Gene	Gene name
4537	Cfa.7147.1.A1_at	7.04E-04	2.24E+01	GEM	GTP binding protein overexpressed in skeletal muscle

Table 5: GEM is among the most differentially expressed in the lungs of ferrets infected with SARS coronavirus when compared to the lungs of ferrets on Day 0.

The rank of differential expression globally, the probe/transcript ID, the p-value of differential expression globally, t, a moderated t statistic, B, the log-odds of differential expression between the groups compared, the gene and gene name are listed in this chart.

Figure 1: GEM is transcriptionally induced in primary human microvascular endothelial cells following infection with wild-type Middle East respiratory syndrome coronavirus (MERS-CoV), icMERS-CoV.

Expression of GEM at the mRNA level is graphically represented with the mean value marked and the p-value listed for each comparison relative to baseline infection at 0 hours.

Figure 2: GEM is transcriptionally induced in the human lung adenocarcinoma cell line CALU3 2B4 after infection with MERS-CoV London.

Expression of GEM at the mRNA level is graphically represented with the mean value marked and the p-value listed for each comparison relative to baseline infection at 0 hours.