Induction of methyl-CpG-binding domain proteins in coronavirus infection.

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Coronavirus SARS-CoV-2 (“COVID-19”) has infected close to 20,000,000 people worldwide^{1,2}. We mined published and public microarray data³⁻⁸ to determine in an unbiased fashion genes most transcriptionally perturbed in the host following infection with a series of human coronaviruses, including SARS-CoV-1, MERS-CoV and HCoV-229E. We observed significant transcriptional induction of the methyl-CpG-binding proteins MBD5 and MeCP2 following infection with two genetically distinct MERS-CoV isolates in human cells *in vitro*. Analysis of independent microarray data revealed less significant differential expression of MBD5 and MeCP2 in the lungs of mice following infection with SARS-CoV-1 *in vivo*. Epigenetic mechanisms involving methyl-CpG-binding proteins may be important to establishment of coronavirus infection in the human host.

Keywords: coronavirus, COVID-19, MERS-CoV, SARS-CoV-1, HCoV-229E, MBD5, MeCP2, epigenetics of coronavirus infection.

Seven coronaviruses are capable of infecting humans^{1,2,9-14} including the COVID-19-associated virus, SARS-CoV-II, which in less than one year has resulted in the death of 776,000 people, 170,000 of which occurred in the United States^{1,2}. Our understanding of mobilization of epigenetic machinery during coronavirus infections is limited¹⁵. We performed differential gene expression analysis of six coronavirus infection models *in vivo* and *in vitro* by mining published and public³⁻⁸ microarray data and found significant induction of two separate methyl-CpG-binding domain-containing proteins following coronavirus infections. These data provide descriptions of host transcriptional response to coronavirus infection suggesting importance of epigenetic mechanisms involving reading of methylated CpG on host DNA.

Methods

We used datasets GSE56677³, GSE100509⁴, GSE59185⁵, GSE68820⁶, GSE22581⁷ and GSE89167⁸ for this analysis of gene expression changes following coronavirus infection. GSE56677 was generated using Agilent-039494 SurePrint G3 Human GE v2 8x60K Microarray 039381 technology with $n=3$ each for CALU3 2B4 cells infected with MERS-CoV London (Eng1): at 0 hours, 3 hours, 7 hours, 12 hours, 18 hours and 24 hours post-infection. GSE100509 was generated using Agilent-026652 Whole Human Genome Microarray 4x44K v2 technology with $n=5$ each for primary human microvascular endothelial cells infected with MERS-CoV at 0 hours, 12 hours, 24 hours, 36 hours and 48 hours. GSE59185 was generated using Agilent-028005 SurePrint G3 Mouse GE 8x60K Microarray technology with $n=3$ lung tissue from mock-infected BALB/c mice and $n=3$ lung tissue from SARS-CoV-1-infected BALB/c mice, both at 2 days post-infection. GSE68820 was generated using Agilent-014868 Whole

1 Mouse Genome Microarray 4x44K G4122F technology with $n=5$ for lung tissue from mock-
2 infected C57BL6/NJ mice and $n=5$ for lung tissue from SARS-CoV-1-infected C57BL6/NJ mice,
3
4 both at 2 days post-infection. GSE22581 was generated using Affymetrix Canine Genome 2.0
5 Array technology with $n=3$ each for both ferret lung and ferret blood on day 0, day 1 and day 2
6 post-infection through the intranasal route with SARS-CoV-1. GSE89167 was generated using
7
8 039494 SurePrint G3 Human GE v2 8x60K Microarray 039381 technology with $n=2$ HuH-7
9 cells and $n=2$ HCoV-229E infected HuH-7 cells.

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11 The Benjamini and Hochberg method of p -value adjustment was used for ranking of
12 differential expression but raw p -values were used for assessment of statistical significance of
13 global differential expression. Log-transformation of data was auto-detected, and the NCBI
14 generated category of platform annotation was used. A statistical test was performed to evaluate
15 the significance of difference in MDB5 and MECP2 mRNA expression levels in CALU3 2B4
16 cells with MERS-CoV infection at 3 hours, 7 hours, 12 hours, 18 hours and 24 hours post-
17 infection as compared to CALU3 2B4 cells at baseline (0 hours) using a one-way ANOVA with
18
19 Dunnett's multiple comparisons test. Only p -values less than 0.05 were considered statistically
20 significant. We used PRISM for all statistical analyses (Version 8.4.0)(455).
21
22

23 **Results**

24
25 We performed systems-level, unbiased differential expression gene analysis to discover
26 genes transcriptionally perturbed following infection with a series of human coronaviruses using
27 published and public microarray data³⁻⁸.
28

Infection of CALU3 cells with MERS-CoV London results in significant differential expression of MBD5 and MeCP2.

We observed significant differential expression of the methyl-CpG-binding domain-containing proteins MBD5 and MeCP2 following infection of CALU3 2B4 cells with MERS-CoV London (Eng1), a MERS-CoV isolate obtained from an infected patient³ (Table 1; Figure 1). When sorting each of the transcripts measured by microarray based on significance of change in expression between uninfected and MERS-CoV London infected cells, MBD5 ranked 237 out of 28653 transcripts, and MeCP2 ranked 214 out of 28653 transcripts. Differential expression of both MBD5 and MeCP2 following infection of CALU3 cells with MERS-CoV London was statistically significant (Table 1; $p=1.58E-11$ and $p=1.19E-11$, respectively).

Infection of primary human microvascular epithelial cells with MERS-CoV results in significant differential expression of MBD5 and MeCP2.

Analysis of a separate MERS-CoV infection dataset⁴ revealed significant differential expression of MBD5 and MeCP2 following infection of primary human microvascular epithelial cells with MERS-CoV (Table 2). When sorting each of the transcripts measured by microarray based on significance of change in expression between uninfected and MERS-CoV infected cells, MBD5 ranked 4556 out of 34127 transcripts, and MeCP2 ranked 4967 out of 34127 transcripts. Differential expression of both MBD5 and MeCP2 was statistically significant (Table 2; $p=1.59E-16$ and $p=3.87E-16$, respectively).

1 MeCP2 and MBD5 are differentially expressed in the lungs of C57BL6/NJ mice following
2 infection with SARS-CoV-1.

3 We mined microarray data from three separate *in vivo* models of SARS coronavirus
4 infection to determine if differential expression of MeCP2 and MBD5 could be observed by
5 other coronavirus members: in the lungs of C57BL6/NJ mice, in the lungs of BALB/c mice, and
6 in the lungs of ferrets infected intranasally with SARS-CoV-1.
7

8
9 In C57BL6/NJ mice⁵, we found statistically significant differential expression of MBD5
10 and MeCP2 at 2 days post-infection with SARS-CoV-1, but this expression was drastically less
11 differential than in MERS-CoV infection models. When sorting each of the transcripts measured
12 by microarray based on significance of change in expression between the lungs of mock-infected
13 and SARS-CoV-1 infected C57BL6/NJ mice, MBD5 ranked 15225 out of 29649 transcripts.
14
15 Differential expression of MBD5 in SARS-CoV-1 infected C57BL6/NJ mice was statistically
16 significant (Table 3; $p=4.4E-03$). When sorting each of the transcripts measured by microarray
17 based on significance of change in expression between the lungs of mock-infected and SARS-
18 CoV-1 infected C57BL6/NJ mice, MeCP2 ranked 13842 out of 29649 transcripts. Differential
19 expression of MeCP2 in SARS-CoV-1 infected C57BL6/NJ mice was statistically significant
20
21 (Table 3; $p=1.99E-03$).
22

23
24 In BALB/c mice⁶, we observed differential expression, albeit less significant than in
25 MERS-CoV infection models, of MBD5 in the lungs at 2 days post-infection with SARS-CoV-1.
26 When sorting each of the transcripts measured by microarray based on significance of change in
27 expression between the lungs of mock-infected and SARS-CoV-1 infected BALB/c mice, MBD5
28

1 ranked 7615 out of 62976 transcripts. Differential expression of MBD5 was statistically
2 significant (Table 4; $p=6.77E-03$).
3

4 MeCP2 and MBD5 are not significantly differentially expressed in multiple models of SARS-
5 CoV-1 infection *in vivo*.

6
7 Neither MBD5 nor MeCP2 were differentially expressed in the lungs of ferrets⁷
8 following infection with SARS-CoV-1 (Table 5), nor in the blood of ferrets⁷ following intranasal
9 infection with SARS-CoV-1 (Table 6).
10

11 MBD5 and MeCP2 are not significantly differentially expressed following infection of Huh-7
12 cells with human coronavirus 229E (HCoV-229E).

13 We also queried published microarray data from a human coronavirus 229E *in vitro*
14 infection model⁸ to answer two questions. First, was the significant differential expression of
15 MBD5 and MeCP2 a function of *in vitro* infection with a coronavirus? Secondly, is SARS-
16 CoV-1 infection of using the ferret model an exception or does infection with other
17 coronaviruses fail to result in significant differential expression of MeCP2 and MBD5? We
18 failed to observe any significant differential expression of MeCP2 to MBD5 in Huh-7 cells
19 following infection with HCoV-229E (Table 7). Thus, differential expression of MBD5 and
20 MeCP2 is not simply an artifact of *in vitro* coronavirus infection, and MBD5/MeCP2 differential
21 expression is a feature of coronavirus infection shared by some but not all coronaviruses.
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26 Within 12 hours of MERS-CoV infection, MBD5 and MeCP2 are transcriptionally induced.

27 We obtained exact mRNA expression levels for MBD5 and MeCP2 in CALU3 cells to
28 assess kinetics of transcriptional induction following infection with MERS-CoV London (Eng1).

For both MeCP2 and MBD5, transcriptional induction could be observed within 12 hours of infection with MERS-CoV London (Figure 2). Transcriptional induction of MeCP2 and MBD5 was statistically significant (Figure 2; $p=0.0003$ at 12 hours as compared to baseline for both MeCP2 and MBD5). We calculated a mean fold change in MeCP2 expression of 0.9898 ± 0.0051 at 3 hours, 0.9885 ± 0.0191 at 7 hours, 1.0572 ± 0.0116 at 12 hours, 1.1387 ± 0.0105 at 18 hours, and 1.1847 ± 0.0117 at 24 hours (Table 1). For MBD5, we calculated a mean fold change in expression of 0.9344 ± 0.0101 at 3 hours, 1.0007 ± 0.0205 at 7 hours, 1.1050 ± 0.0366 at 12 hours, 1.1867 ± 0.0113 at 18 hours, and 1.3181 ± 0.0130 at 24 hours as compared to baseline (Table 2).

Thus, we observed significant differential expression of MBD5 and MeCP2 in human cells *in vitro* following infection with two types of MERS-CoV. Infection of CALU3 cells with MERS-CoV London resulted in marked induction of MeCP2 and MBD5 within 12 hours of infection *in vitro*. Less significant differential expression of MeCP2 and MBD5 could be found in the lungs of C57BL6/NJ mice after SARS-CoV-1 infection. Transcriptional induction of MeCP2 and MBD5 appears to be conserved among MERS and SARS coronaviruses.

Discussion

We performed the first integrated systems-level analysis of host transcription following infection across a multitude of human coronaviruses infection models by using published and public microarray data³⁻⁸. Among our findings was the observation that methyl-CpG-binding domain-containing proteins MeCP2 and MBD5 are rapidly transcribed following infection with MERS-CoV.

1 There is little information describing host epigenetic responses to coronavirus infection
2 or coronavirus manipulation of host epigenetic machinery to propagate the viral life cycle¹⁵.
3
4 MeCP2 can occupy methylated promoters and repress transcription of associated genes but does
5 not repress promoters lacking CpG methylation; repression requires CpG methylation¹⁶.
6
7 Foundational studies in human cells and in *Xenopus* demonstrated that a histone deacetylase
8 (HDAC) and the co-repressor Sin3 co-fractionated with MeCP2, and that transcriptional
9 repression by the MeCP2 repression domain (MRD) of MeCP2 could be impaired by trichostatin
10 A, an HDAC inhibitor^{17,18}. Silencing of the H19 gene by MeCP2 involved accumulation of
11 methyl marks on lysine 9 of Histone H3, demonstrating a link between DNA methylation and
12 histone methylation in repression of gene expression by MeCP2¹⁹. MeCP2 is described at length
13 as a neuronal-specific transcriptional modulator^{20,21} but a descriptions of functions for MeCP2 in
14 viral infection is lacking.
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17 Binding of MBD5 to methylated CpG has not been clearly demonstrated²². Instead,
18 while MBD5 associates with heterochromatin, it appears that MBD5 may be recruited to
19 genomic sites through interactions with the mammalian Polycomb group PR-DUB complex
20 containing BAP1 and ASXL2²³.
21
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23 These data indicate that the host response to coronavirus infection may involve
24 recruitment of epigenetic machinery to host genes through the methyl-CpG-binding domains of
25 MBD5 and/or MeCP2. Future studies can determine if transcriptional induction of MBD5 and
26 MeCP2 is found in SARS-CoV-2 and what effect inhibition of MeCP2 and/or MBD5 is on host
27 coronaviral infection dynamics.
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Methyl-CpG binding proteins MERS-CoV London

Figure 1: Rapid transcriptional induction of MeCP2 and MBD5 following infection of human cells with MERS-CoV London (Eng1).

Expression of MECP2 (left) and MBD5 (right) is graphically represented with p -values relative to baseline (0 hours) denoting statistically significant changes in expression for each time point. (****): $p < 0.0001$; (***): $0.0001 > p > 0.0002$; (*): $0.05 > p > 0.0021$.

Rank	ID	p-value	F	FC	Gene	Gene name
214	A_33_P3339036	1.19E-11	122.307	<u>3hr</u> : 0.9898 ± 0.0051 <u>7hr</u> : 0.9885 ± 0.0191 <u>12hr</u> : 1.0572 ± 0.0116 <u>18hr</u> : 1.1387 ± 0.0105 <u>24hr</u> : 1.1847 ± 0.0117	MeCP2	methyl CpG binding protein 2 (Rett syndrome)
237	A_33_P3854030	1.58E-11	117.7319	<u>3hr</u> : 0.9344 ± 0.0101 <u>7hr</u> : 1.0007 ± 0.0205 <u>12hr</u> : 1.1050 ± 0.0366 <u>18hr</u> : 1.1867 ± 0.0113 <u>24hr</u> : 1.3181 ± 0.0130	MBD5	methyl-CpG binding domain protein 5

Table 1: MeCP2 and MBD5 are among the genes most significantly differentially expressed following infection of CALU3 2B4 cells with MERS-CoV London (Eng1).

The rank of differential expression, p-value with respect to global differential expression, the F statistic, fold change in MECP2 or MBD5 expression relative to 0 hours (baseline), gene and gene name are listed in this chart.

Rank	ID	p-value	F	Gene	Gene name
4556	A_33_P3854030	1.59E-16	155.7956	MBD5	methyl-CpG binding domain protein 5
4967	A_24_P237486	3.87E-16	143.9314	MeCP2	methyl CpG binding protein 2 (Rett syndrome)

Table 2: Differential expression of MeCP2 and MBD5 following infection of primary human microvascular epithelial cells with MERS-CoV.

The rank of differential expression, p-value with respect to global differential expression, the t statistic, B, the log-odds of differential expression when comparing infected and uninfected cells, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
13842	A_51_P424232	1.99E-03	-4.09928	-2.673925	MeCP2	methyl CpG binding protein 2
15225	A_51_P332185	4.4E-03	-3.62231	-3.500719	Mbd5	methyl-CpG binding domain protein 5

Table 3: Statistically significant differential expression of MeCP2 and MBD5 in the lungs of C57BL6/NJ mice following infection with SARS-CoV-1.

The rank of differential expression, p-value with respect to global differential expression, the t statistic, B, the log-odds of differential expression when comparing mock infected and infected mouse lung, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
7615	45685	6.77E-03	-3.71	-3.08016	Mbd5	methyl-CpG binding domain protein 5
16752	26062	7.47E-02	-2.07	-5.56291	Mecp2	methyl CpG binding protein 2

Table 4: MBD5 but not MeCP2 is differentially expressed in the lungs of BALB/c mice following infection with SARS-CoV-1.

The rank of differential expression, p-value with respect to global differential expression, the t statistic, B, the log-odds of differential expression when comparing mock infected and infected mouse lung, gene and gene name are listed in this chart.

Rank	ID	p-value	F	Gene	Gene name
23177	CfaAffx.9251.1.S1_at	9.19E-02	3.34	MBD5	methyl-CpG binding domain protein 5
39540	CfaAffx.29729.1.S1_at	6.62E-01	4.36E-01	MECP2	methyl CpG binding protein 2

Table 5: MeCP2 and MBD5 are not differentially expressed in the lungs of ferrets following intranasal infection with SARS-CoV-1.

The rank of differential expression, p-value with respect to global differential expression, the t statistic, B, the log-odds of differential expression when comparing mock infected and infected ferret lung, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
4323	CfaAffx.9251.1.S1_at	7.17E-02	-2.14385	-3.9706	MBD5	methyl-CpG binding domain protein 5
23035	CfaAffx.29729.1.S1_at	4.7E-01	-0.767246	-5.4095	MeCP2	methyl CpG binding protein 2

Table 6: MeCP2 and MBD5 are not differentially expressed in the blood of ferrets following intranasal infection with SARS-CoV-1.

The rank of differential expression, p-value with respect to global differential expression, the t statistic, B, the log-odds of differential expression when comparing mock infected and infected ferret blood, gene and gene name are listed in this chart.

Rank	ID	p-value	t	B	Gene	Gene name
16637	53123	0.20738	-1.4027764	-4.591	MBD5	methyl-CpG binding domain protein 5
28957	59399	0.393257	0.9153473	-4.985	MECP2	methyl CpG binding protein 2 (Rett syndrome)

Table 7: MeCP2 and MBD5 are not differentially expressed in Huh-7 cells following infection with HCoV-229E *in vitro*.

The rank of differential expression, p-value with respect to global differential expression, the t statistic, B, the log-odds of differential expression when comparing infected and uninfected cells, gene and gene name are listed in this chart.

Figure 2: Rapid transcriptional induction of MeCP2 and MBD5 following infection of human cells with MERS-CoV London (Eng1).

Expression of MBD5 (left) and MECP2 (right) is graphically represented with mean mRNA expression levels marked and exact *p*-values relative to baseline (0 hours) describing statistical significance of changes in expression for each time point.