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# Molecular mimicry of ACTH in SARS – implications for corticosteroid treatment and prophylaxis

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**Summary** For a virus to survive and replicate in an organism, it must employ strategies to evade and misdirect the host's immune response. There is compelling evidence that the primary immunoevasive strategy utilized by the SARS virus, like influenza, is to inhibit its host's corticosteroid stress response. This is accomplished by viral expression of amino acid sequences that are molecular mimics of the host's adrenocorticotropin hormone (ACTH). When the host produces antibodies against these viral antigens, the antibodies also bind to the host's own ACTH, which limits the host's stress response by interfering with ACTH's ability to stimulate the secretion of corticosteroids. This inadequate corticosteroid response provokes symptoms as a result of a relative adrenocortical insufficiency. Treatment with corticosteroids can relieve the patient's symptoms of adrenocortical insufficiency and give them the corticosteroid levels needed to fight their infection. Similarly, by taking moderate daily doses of corticosteroids as a prophylactic, it may be possible to avoid clinical infection with SARS. If SARS's ACTH mimic strategy never has an opportunity to get started, SARS's ability to evade its host's immune system while its viral load is low will be significantly impaired. In this article, amino acid sequences from the SARS and influenza viruses representing likely homology to human ACTH are identified. Evidence demonstrating that ACTH autoantibodies are produced during influenza infection is also presented. Early treatment with corticosteroids should lower the dose necessary to counteract SARS's ACTH autoantibody mechanism. If corticosteroid treatment is delayed until inflammatory cytokine levels are causing serious injury, only high doses of corticosteroids are likely to be effective.

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For a virus to survive and replicate in an organism, it must employ strategies to evade and misdirect the host's immune response. There is compelling evidence that the primary immunoevasive strategy utilized by the SARS virus, like influenza, is to inhibit its host's corticosteroid stress response. This is accomplished by viral expression of amino acid

sequences that are molecular mimics of the host's adrenocorticotropin hormone (ACTH). When the host produces antibodies against these viral antigens, the antibodies also bind to the host's own ACTH, which limits the host's stress response by interfering with ACTH's ability to stimulate the secretion of corticosteroids.

Autoantibodies are antibodies that have an affinity for an organism's own proteins, hormones, cytokines, RNA or DNA. Although autoantibodies

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may be naturally produced at very low levels, pathological levels are induced by infectious agents or immunization. When autoantibodies rise to pathological levels, they can damage or inflame organs and tissues, disrupt protein and hormone synthesis, or interfere with hormonal signals and cellular processes (for more information about autoantibodies, see Davidson and Diamond [1]).

Utilizing molecular mimicry, an infectious agent directs its host's immune system against the host by stimulating the creation of antibodies that crossreact with the host's own molecules. For example, *CHLAMYDIA* infection has been shown to cause myocarditis by expressing a molecular mimic to a segment of the cardiac-specific  $\alpha$  myosin heavy chain molecule [2]. Not only is an infectious agent able to survive better amidst a misdirected immune response, but if the autoantibodies are directed against significant molecules, the infection can thrive in a host with a critical system that is weakened.

## ACTH sequence homology to influenza and the SARS coronavirus

If molecular mimicry of ACTH increases the virulence of some infectious agents, a competitive advantage would be conferred to any animal that had a mutation that made their ACTH antigenically dissimilar while maintaining ACTH's function, an adaptation for avoiding parasitism. ACTH consists of 39 amino acids. The first 24 amino acids by themselves retain steroidogenic activity. The last 18 amino acids of the molecule are more immunologically active than the whole molecule and much more active than ACTH<sub>1-24</sub> [3].

ACTH<sub>25-39</sub> is a less conserved region between species than ACTH<sub>1-24</sub>. If the species differences are the result of successful antigenic separation, due to selective pressure, then the amino acid positions of these differences within classes of animals should point to the antigenically important amino acid positions (probable key residues). From

**Table 1** Known ACTH amino acid sequences of mammals (positions 25–39) (residues that differ from human ACTH are in bold)

2	3	
5	6	7 8 9 0 1 2 3 4 5 6 7 8 9
		Species (GenBank Accession Number)
N	G	A E D E S A E A F P L E F Human (NP_000930)
		Chimpanzee (AAM76608)
		Gorilla (AAM76609)
		Orangutan (AAM76610)
		Pig-tailed Macaque (P01201)
		American Mink (P11280)
		Finback Whale (P01195)
		Sei Whale (PN0127)
N	G	A E D E S A E A F P <b>V</b> E F Dog (AAK08973)
N	G	A E D E S A <b>Q</b> A F P L E F Cow (CTBOP)
		Sheep (CTSHP)
N	G	A E D E <b>L</b> A E A F P L E F Pig (P01192)
N	G	A E <b>G</b> E S A E A F P L E F African Savanna Elephant (P21252)
N	G	A E <b>E</b> E S A E A F P L E F Guinea Pig (AAB20814)
N	V	A E <b>N</b> E S A E A F P L E F Mouse (P01193)
		Rat (P01194)
N	S	A E <b>N</b> E S A E A F P L E F Cottontop Tamarin (AAM76612)
N	G	A E <b>N</b> E S A E A F P <b>V</b> E <b>V</b> Rabbit (P06297)

**Table 2** ACTH amino acid homologous regions. Sequences from example influenza proteins and the SARS coronavirus with 3 exact matches of the 6 probable key residues of human ACTH<sub>25-39</sub> (residues that are identical to human ACTH are in bold)*Influenza hemagglutinin*

	2		3						
	5	6	7	8	9	0	1	2	3
	NG	AE	DE	SA	EA	FP	LP	LE	F
Position									
	75	<b>A</b>	<b>G</b>	<b>W</b>	<b>I</b>	<b>L</b>	<b>G</b>	<b>N</b>	<b>P</b>
	430	<b>D</b>	<b>G</b>	<b>F</b>	<b>L</b>	<b>D</b>	<b>I</b>	<b>W</b>	<b>T</b>
	65	<b>L</b>	<b>E</b>	<b>L</b>	<b>G</b>	<b>D</b>	<b>C</b>	<b>S</b>	<b>I</b>
	73	<b>A</b>	<b>G</b>	<b>W</b>	<b>L</b>	<b>L</b>	<b>G</b>	<b>N</b>	<b>P</b>
	107	<b>P</b>	<b>G</b>	<b>S</b>	<b>F</b>	<b>N</b>	<b>D</b>	<b>Y</b>	<b>E</b>
	426	<b>D</b>	<b>G</b>	<b>F</b>	<b>L</b>	<b>D</b>	<b>V</b>	<b>W</b>	<b>T</b>
	463	<b>M</b>	<b>Q</b>	<b>L</b>	<b>R</b>	<b>D</b>	<b>N</b>	<b>V</b>	<b>K</b>
	19	<b>L</b>	<b>P</b>	<b>G</b>	<b>N</b>	<b>D</b>	<b>N</b>	<b>S</b>	<b>T</b>
	394	<b>N</b>	<b>G</b>	<b>K</b>	<b>L</b>	<b>N</b>	<b>R</b>	<b>L</b>	<b>I</b>
	66	<b>L</b>	<b>I</b>	<b>L</b>	<b>R</b>	<b>D</b>	<b>C</b>	<b>S</b>	<b>V</b>
	108	<b>P</b>	<b>G</b>	<b>N</b>	<b>F</b>	<b>N</b>	<b>D</b>	<b>Y</b>	<b>E</b>
	432	<b>D</b>	<b>G</b>	<b>F</b>	<b>L</b>	<b>D</b>	<b>V</b>	<b>W</b>	<b>T</b>
	470	<b>L</b>	<b>Q</b>	<b>L</b>	<b>R</b>	<b>D</b>	<b>N</b>	<b>A</b>	<b>K</b>
	242	<b>I</b>	<b>G</b>	<b>G</b>	<b>F</b>	<b>P</b>	<b>D</b>	<b>Q</b>	<b>T</b>
	298	<b>K</b>	<b>G</b>	<b>S</b>	<b>L</b>	<b>P</b>	<b>L</b>	<b>I</b>	<b>G</b>
	304	<b>I</b>	<b>G</b>	<b>E</b>	<b>A</b>	<b>D</b>	<b>C</b>	<b>L</b>	<b>H</b>
	228	<b>I</b>	<b>G</b>	<b>G</b>	<b>F</b>	<b>P</b>	<b>N</b>	<b>Q</b>	<b>T</b>
	284	<b>K</b>	<b>G</b>	<b>S</b>	<b>L</b>	<b>P</b>	<b>L</b>	<b>I</b>	<b>G</b>
	290	<b>I</b>	<b>G</b>	<b>E</b>	<b>A</b>	<b>D</b>	<b>C</b>	<b>L</b>	<b>H</b>

*Influenza nucleoprotein*

	2		3						
	5	6	7	8	9	0	1	2	3
	NG	AE	DE	SA	EA	FP	LP	LE	F
Position									
	244	<b>E</b>	<b>S</b>	<b>R</b>	<b>N</b>	<b>P</b>	<b>G</b>	<b>N</b>	<b>A</b>
	286	<b>A</b>	<b>S</b>	<b>G</b>	<b>H</b>	<b>D</b>	<b>F</b>	<b>E</b>	<b>R</b>
	361	<b>R</b>	<b>G</b>	<b>V</b>	<b>Q</b>	<b>I</b>	<b>A</b>	<b>S</b>	<b>N</b>
	444	<b>V</b>	<b>I</b>	<b>R</b>	<b>M</b>	<b>M</b>	<b>E</b>	<b>S</b>	<b>A</b>
	461	<b>R</b>	<b>G</b>	<b>V</b>	<b>F</b>	<b>E</b>	<b>L</b>	<b>S</b>	<b>D</b>
	476	<b>V</b>	<b>P</b>	<b>S</b>	<b>F</b>	<b>D</b>	<b>M</b>	<b>S</b>	<b>N</b>
	244	<b>E</b>	<b>S</b>	<b>R</b>	<b>N</b>	<b>P</b>	<b>G</b>	<b>N</b>	<b>A</b>
	361	<b>R</b>	<b>G</b>	<b>V</b>	<b>Q</b>	<b>I</b>	<b>A</b>	<b>S</b>	<b>N</b>
	244	<b>E</b>	<b>S</b>	<b>R</b>	<b>N</b>	<b>P</b>	<b>G</b>	<b>N</b>	<b>A</b>
	286	<b>A</b>	<b>S</b>	<b>G</b>	<b>Y</b>	<b>D</b>	<b>F</b>	<b>E</b>	<b>R</b>
	361	<b>R</b>	<b>G</b>	<b>V</b>	<b>Q</b>	<b>I</b>	<b>A</b>	<b>S</b>	<b>N</b>
	461	<b>R</b>	<b>G</b>	<b>V</b>	<b>F</b>	<b>E</b>	<b>L</b>	<b>S</b>	<b>D</b>
	476	<b>V</b>	<b>P</b>	<b>S</b>	<b>F</b>	<b>D</b>	<b>M</b>	<b>S</b>	<b>N</b>
	11	<b>A</b>	<b>G</b>	<b>T</b>	<b>I</b>	<b>D</b>	<b>K</b>	<b>T</b>	<b>P</b>
	372	<b>L</b>	<b>R</b>	<b>M</b>	<b>G</b>	<b>D</b>	<b>D</b>	<b>A</b>	<b>K</b>
	376	<b>D</b>	<b>A</b>	<b>K</b>	<b>D</b>	<b>K</b>	<b>S</b>	<b>Q</b>	<b>L</b>
	11	<b>T</b>	<b>G</b>	<b>T</b>	<b>I</b>	<b>D</b>	<b>K</b>	<b>T</b>	<b>P</b>
	372	<b>L</b>	<b>R</b>	<b>M</b>	<b>G</b>	<b>D</b>	<b>D</b>	<b>A</b>	<b>K</b>
	376	<b>D</b>	<b>A</b>	<b>K</b>	<b>D</b>	<b>K</b>	<b>S</b>	<b>Q</b>	<b>L</b>

Table 2 (continued)

## Influenza neuraminidase

	2	3		
	5	6	7	8
	9	0	1	2
	3	4	5	6
	7	8	9	
	NGAEDES	AEAFPLEF	Human	ACTH <sub>25-39</sub>
Position				
260	K <b>G</b> KI <b>I</b> K <b>S</b> V <b>E</b> KDAPNY	A/Wisconsin/10/98 (H1N1)		GenBank AAO88264
309	DYS <b>I</b> D <b>S</b> SYVCSGLVG	A/RI/5-/57 (H2N2)		P03484
326	PRKN <b>D</b> S <b>S</b> SSSHC <b>L</b> D <b>P</b>	A/Finland/620/99 (H3N2)		CAD29993
241	K <b>G</b> RVVK <b>S</b> V <b>E</b> LNAPNY	A/Hong Kong/516/97 (H5N1)		AAM76911
384	S <b>G</b> SFIQHP <b>E</b> LT <b>G</b> L <b>N</b> C			
15	S <b>G</b> GVLL <b>S</b> LYVS <b>A</b> LL <b>S</b>	B/Victoria/2/87		BAB32609
397	S <b>G</b> V <b>M</b> VSM <b>K</b> E <b>P</b> GW <b>S</b> <b>F</b>			
242	D <b>G</b> SASG <b>I</b> S <b>E</b> CR <b>F</b> L <b>K</b> I	B/Sichuan/379/99		AAN39801
397	S <b>G</b> V <b>M</b> VSM <b>E</b> E <b>P</b> GW <b>S</b> <b>F</b>			

## SARS coronavirus (Urbani and Tor2 strains)

	2	3		
	5	6	7	8
	9	0	1	2
	3	4	5	6
	7	8	9	
	NGAEDES	AEAFPLEF	Human	ACTH <sub>25-39</sub>
Position				
29	R <b>G</b> F <b>G</b> D <b>S</b> V <b>E</b> <b>E</b> A <b>L</b> S <b>E</b> A <b>R</b>	Replicase 1AB (AAP13442, AAP41036)		
242	T <b>E</b> R <b>S</b> D <b>K</b> S <b>Y</b> E <b>H</b> Q <b>T</b> P <b>F</b> E			
637	A <b>G</b> V <b>E</b> F <b>L</b> K <b>D</b> A <b>W</b> E <b>I</b> L <b>K</b> <b>F</b>			
1,096	V <b>G</b> P <b>N</b> L <b>N</b> A <b>G</b> E <b>D</b> I <b>O</b> L <b>L</b> K			
1,463	N <b>G</b> Y <b>L</b> T <b>S</b> S <b>S</b> K <b>T</b> S <b>E</b> E <b>H</b> <b>F</b>			
1,923	G <b>F</b> T <b>K</b> P <b>A</b> S <b>R</b> E <b>L</b> S <b>V</b> T <b>F</b> <b>F</b>			
1,993	T <b>K</b> P <b>V</b> D <b>T</b> S <b>N</b> S <b>F</b> E <b>V</b> L <b>A</b> V			
2,260	E <b>G</b> S <b>F</b> P <b>C</b> S <b>I</b> C <b>L</b> S <b>G</b> L <b>D</b> S			
2,437	T <b>G</b> S <b>T</b> F <b>I</b> S <b>D</b> E <b>V</b> A <b>R</b> D <b>L</b> S			
2,440	T <b>F</b> I <b>S</b> D <b>E</b> V <b>A</b> R <b>D</b> L <b>S</b> L <b>O</b> <b>F</b>			
2,554	V <b>S</b> D <b>V</b> G <b>D</b> S <b>T</b> E <b>V</b> S <b>V</b> K <b>M</b> <b>F</b>			
2,847	P <b>G</b> T <b>V</b> L <b>R</b> A <b>I</b> N <b>G</b> D <b>F</b> L <b>H</b> <b>F</b>			
2,963	H <b>G</b> T <b>C</b> E <b>R</b> S <b>E</b> V <b>G</b> I <b>C</b> L <b>S</b> T			
3,015	V <b>G</b> A <b>L</b> D <b>V</b> S <b>A</b> S <b>V</b> V <b>A</b> G <b>G</b> I			
3,048	F <b>G</b> E <b>Y</b> N <b>H</b> V <b>V</b> A <b>A</b> N <b>A</b> L <b>L</b> <b>F</b>			
3,077	F <b>L</b> P <b>G</b> V <b>Y</b> S <b>V</b> F <b>Y</b> L <b>Y</b> L <b>T</b> <b>F</b>			
3,092	Y <b>F</b> T <b>N</b> D <b>V</b> S <b>F</b> L <b>A</b> H <b>L</b> Q <b>W</b> <b>F</b>			
3,145	N <b>G</b> V <b>T</b> F <b>S</b> T <b>F</b> E <b>E</b> A <b>A</b> L <b>C</b> T			
3,577	W <b>S</b> L <b>F</b> F <b>F</b> V <b>Y</b> E <b>N</b> A <b>F</b> L <b>P</b> <b>F</b>			
3,644	L <b>E</b> L <b>A</b> D <b>T</b> S <b>L</b> S <b>G</b> Y <b>R</b> L <b>K</b> D			
3,733	R <b>A</b> I <b>V</b> E <b>V</b> C <b>V</b> E <b>Y</b> P <b>L</b> L <b>F</b>			
4,505	E <b>G</b> N <b>C</b> D <b>T</b> L <b>K</b> E <b>I</b> L <b>V</b> T <b>Y</b> N			
4,639	L <b>L</b> K <b>Y</b> D <b>F</b> T <b>E</b> E <b>R</b> L <b>C</b> L <b>F</b> D			
4,723	V <b>H</b> N <b>Q</b> D <b>V</b> N <b>L</b> H <b>S</b> S <b>R</b> L <b>S</b> <b>F</b>			
4,797	F <b>F</b> K <b>E</b> G <b>S</b> S <b>V</b> E <b>L</b> K <b>H</b> F <b>F</b> <b>F</b>			
4,883	L <b>Y</b> Y <b>D</b> S <b>M</b> S <b>Y</b> E <b>D</b> Q <b>D</b> A <b>L</b> <b>F</b>			
5,198	L <b>P</b> Y <b>E</b> D <b>P</b> S <b>R</b> I <b>L</b> G <b>A</b> G <b>C</b> <b>F</b>			
5,680	A <b>T</b> N <b>Y</b> D <b>L</b> S <b>V</b> V <b>N</b> A <b>R</b> L <b>R</b> A			
5,908	G <b>L</b> F <b>K</b> D <b>C</b> S <b>K</b> I <b>I</b> T <b>G</b> L <b>H</b> P			
6,189	V <b>K</b> R <b>V</b> D <b>W</b> S <b>V</b> E <b>Y</b> P <b>I</b> I <b>G</b> D			
6,314	P <b>G</b> C <b>D</b> G <b>G</b> S <b>L</b> Y <b>V</b> N <b>K</b> H <b>A</b> <b>F</b>			
6,549	T <b>V</b> L <b>F</b> D <b>G</b> R <b>V</b> E <b>G</b> Q <b>V</b> D <b>L</b> <b>F</b>			
6,584	K <b>G</b> P <b>A</b> Q <b>A</b> S <b>V</b> N <b>G</b> V <b>T</b> L <b>I</b> G			
7,017	Y <b>S</b> L <b>F</b> D <b>M</b> S <b>K</b> F <b>P</b> L <b>K</b> L <b>R</b> G			
347	N <b>C</b> V <b>A</b> D <b>Y</b> S <b>V</b> L <b>Y</b> N <b>S</b> T <b>F</b> <b>F</b>	S (Spike) glycoprotein (AAP13441, AAP41037)		
487	T <b>G</b> I <b>G</b> Y <b>Q</b> P <b>Y</b> R <b>V</b> V <b>V</b> L <b>S</b> <b>F</b>			
585	T <b>P</b> G <b>T</b> N <b>A</b> S <b>S</b> E <b>V</b> A <b>V</b> L <b>Y</b> Q			
639	A <b>E</b> H <b>V</b> D <b>T</b> S <b>Y</b> E <b>C</b> D <b>I</b> P <b>I</b> G			
722	M <b>Y</b> I <b>C</b> G <b>D</b> S <b>T</b> E <b>C</b> A <b>N</b> L <b>L</b> L			
1,124	Q <b>P</b> E <b>L</b> D <b>S</b> F <b>K</b> E <b>E</b> L <b>D</b> K <b>Y</b> <b>F</b>			
0	M <b>Y</b> S <b>F</b> V <b>S</b> E <b>E</b> T <b>G</b> T <b>L</b> I <b>V</b>	E (Envelope) protein (AAP13443, AAP41040)		
9	T <b>G</b> T <b>L</b> I <b>V</b> N <b>S</b> V <b>L</b> L <b>F</b> L <b>A</b> <b>F</b>			

Table 1, these antigenically important amino acid positions for mammalian ACTH<sub>25-39</sub> are 26, 29, 31, 33, 37 and 39.

Influenza and SARS contain many examples of amino acid sequences with homology to these probable ACTH key residues (see Table 2). Ex-

actly matching 3 of 6 key residues represents likely antigenic homology, considering that exact matches of only 1 or 2 key residues has been shown to induce significant T cell activation by molecular mimics in other viral agents [4–8]. Since, at this time, it is not possible to predict the degree of antigenic similarity between different sequences, determining which of the likely sequences is actually an ACTH mimic must be accomplished by comparing their activation capabilities in T cell proliferation studies. Furthermore, for the SARS Orf 1AB sequences, it must be shown that the sequences are expressed.

Table 2 lists 34 matches of 3 of 6 of the probable key residues of human ACTH<sub>25–39</sub> in the SARS replicase 1AB protein. There are many matches in the SARS coronavirus for the ACTH of other species as well. For example, there are 38 matches of 3 of 6 of the probable key residues of the rabbit's ACTH<sub>25–39</sub> in the SARS replicase 1AB protein (data not shown). Only one of these is the same as the human matches (at position 2437) as just 3 residues are in common between the probable key residues of rabbit and human ACTH<sub>25–39</sub>.

A high frequency of many mammalian ACTH mimics are also found in the seven currently published complete amino acid sequences of non-SARS coronaviruses. The coronaviruses seem to be repositories of ACTH molecular mimics, probably collected from other viruses. This may partly explain why the coronavirus genomes are so large, being the longest known viral RNA genomes.

Although ACTH molecular mimics appear to be involved in the virulence of the influenza and SARS viruses, the determining factor is not clear. Virulence may relate to the degree of antigenic similarity between ACTH and its molecular mimic or to the number of active molecular mimics that the virus employs.

Evidence of SARS infection has been found in masked palm civets and a Chinese ferret badger for sale in a market in Guangdong, China [9]. Civets, members of the family VIVERRIDAE (mongoose), are weasel-like. Chinese ferret badgers, similar in appearance to civets, are classified in the family MUSTELIDAE (weasel), along with the American mink and the ferret. The ACTH of the American mink has been shown to be identical to human ACTH. Are these animals susceptible to human coronavirus or influenza infection because their ACTH possesses molecular identity to human ACTH? To answer these and other questions, it would be valuable to determine the ACTH amino acid sequences for more species, especially to know the ACTH sequence for more birds.

## Evidence for ACTH antibodies during influenza infection

A systemic stress response normally produces high serum cortisol and ACTH levels. Jefferies et al. [10] reported that influenza-infected patients had normal serum cortisol levels but low ACTH levels. These results are difficult to reconcile unless the patients' serum contained abnormal binding agents to ACTH. For example, if these patients had autoantibodies to ACTH, the antibodies would have interfered with the ACTH immunoassay, especially if the autoantibodies and assay antibodies were competing for the same antigenic region of the ACTH molecule, which is likely. This would result in an erroneously low ACTH reading. The assay would only measure unbound ACTH, as demonstrated in the report by Pranzatelli et al. [11] of a 9-year old boy with opsoclonus–myoclonus who was determined to have ACTH levels of 72 and 4.3 pg/ml using conventional ACTH immunoassay analyses. After solid-phase extraction of the ACTH, the total ACTH level measured by radioimmunoassay was 3000 pg/ml. ACTH antibodies were subsequently detected in the boy's serum. Similarly, Jefferies et al.'s ACTH data only approximates the free ACTH levels. The measurement of subnormal ACTH levels of influenza-infected patients is consistent with the existence of an abnormal binding agent.

Lymphocytes are involved in the pathogenesis of influenza infection [12]. Injections of anti-lymphocytic antibodies increased the survival rate of mice infected with influenza A (H2N2). Mice were infected intranasally with five times a 50% lethal dose of influenza virus. All saline treated mice died within 13 days. 50% of mice treated before and after infection with antilymphocyte serum (ALS) survived more than 15 days after virus infection. The study's authors (Suzuki et al.) conclude, "Assuming that ALS specifically suppresses immune and normal T lymphocytes it can be inferred that some of these lymphocytes participate in the influenza disease manifestations." The results of this study are consistent with influenza causing T lymphocytes to induce the production of ACTH autoantibodies.

There are many symptoms in common between influenza infection and adrenocortical insufficiency: malaise, fatigue, anorexia, myalgia, headache, diarrhea and nausea. If influenza virus stimulates the production of ACTH autoantibodies, after infection, as the autoantibodies interfere with adrenocortical secretion, the infected individual will enter a state of relative adrenocortical insufficiency, where their corticosteroid needs are

greater than their available supply. Furthermore, unlike the increased corticosteroid levels that would be expected during a systemic immune response, influenza-infected patients do not have increased cortisol levels [10]. For example, rats injected with sheep red blood cells demonstrated two to threefold increases in corticosteroid levels [13]. It is reported that during the initial phase, before the onset of respiratory disease, SARS symptoms in adults mimic those of influenza [14]. Therefore, a viral-induced state of relative adrenocortical insufficiency can explain many of the initial symptoms of SARS and influenza.

Influenza virus has been found to be a cytokine dysregulator [15]. The virus induces increased release of inflammatory cytokines, which disrupts the immune response and can lead to multiple organ dysfunction, including acute respiratory distress. A necessary complementary strategy for a cytokine dysregulator would be to inhibit the host's anti-inflammatory response. By stimulating production of ACTH autoantibodies, influenza virus is able to limit the adrenocortical response, allowing the inflammatory cytokine levels to rise unchecked. Pathological findings indicate that SARS also employs a strategy of cytokine dysregulation [16].

Price et al. [17] showed that approximately 48 h after infecting ferrets with influenza, fever declines at about the same time as cytokine levels begin to increase. This relief of fever is unlikely to be due to the host overcoming the infection. Rather, the decrease in body temperature could be due to a lower metabolic rate as a result of relative adrenocortical insufficiency as the infection succeeds in its ACTH mimicry strategy and proceeds to its next phase of cytokine dysregulation.

## Implications for SARS treatment

If ACTH autoantibodies are involved in the pathogenesis of SARS, it indicates why corticosteroid supplements improve the clinical condition of many SARS patients, as reported by numerous clinicians [18–20]. The ACTH autoantibodies interfere with the body's attempt to increase its corticosteroid secretion as part of the body's response to the infection. Treatment with supra-physiological doses of corticosteroids gives the patient the high corticosteroid levels they require to effectively fight the infection and allows the patient to avoid the symptoms associated with the relative adrenocortical deficiency resulting from inadequate corticosteroid levels.

Although many SARS patients were treated with corticosteroids, often only patients with severe, unstable or deteriorating clinical conditions were given corticosteroids. If SARS induces production of ACTH autoantibodies, then all SARS patients should benefit from early, sustained treatment with corticosteroids. If patients exhibiting the first signs of SARS infection are given stress levels of corticosteroids (40–60 mg oral prednisone twice a day for adults), the patients should feel better and the virus will be deprived of its primary immunoevasive strategy, which should make SARS more vulnerable to the immune system. Patients that are already stressed due to an existing medical condition will require higher doses. An initial loading dose of corticosteroids may also prove to be beneficial.

Starting corticosteroid treatment as soon as possible allows using these lower doses of corticosteroids. If corticosteroid treatment is delayed until the patient has become moderately or severely ill, after the infection has established itself, only large doses of corticosteroids may be effective. For example, after the infection has begun to promote the runaway secretion of inflammatory cytokines, higher doses of corticosteroids are required to suppress this dysregulation.

Since corticosteroid supplements compensate for the adrenocortical insufficiency caused by ACTH autoantibodies, the adrenocortical insufficiency symptoms may resolve soon after treatment is begun. If the corticosteroid treatment is decreased or discontinued before the infection has subsided, these symptoms can easily reappear. This may explain the reported relapses and continued fatigue of some SARS patients after decreasing or discontinuing their corticosteroid treatment. Therefore, if the patient becomes symptomatic as the corticosteroid dosage is tapered, the dosage should be immediately raised to a level that was previously effective.

Due to antigenic competition, during the initial phase of SARS infection, the antibody response to ACTH antigen can diminish the SARS antibody response. When interfering ACTH autoantibodies are abundant, ACTH is hypersecreted, as in Pranzatelli et al.'s [11] patient with ACTH antibodies who had total ACTH levels 200 times normal. Since ACTH is more prevalent than SARS antigens, to the immune system, the ACTH invader appears to be the more serious threat, for which a larger proportion of resources must be mobilized. This attenuates the antibody response to SARS. If a sufficient dose of corticosteroids is given, this will significantly suppress the pituitary gland's secretion of ACTH and the ACTH antibody response will abate, which will allow the antibody response to SARS to increase.

Removing the self-antigen and compensating for the lack of effective ACTH allows the immune system to do its job.

Furthermore, short-term use of moderate doses of corticosteroids (40 mg of prednisone per day) may prove to be an effective prophylactic against clinical infection with SARS. If corticosteroids are an effective treatment after infection, they may work in the same manner to avoid clinical infection. An analogy would be the prophylactic use of antibiotics. If SARS's ACTH mimic strategy never has an opportunity to get started, SARS's ability to evade its host's immune system while its viral load is low will be significantly impaired.

The effectiveness of corticosteroids as a prophylactic against influenza A has been demonstrated in mice [21]. Mice were injected with non-lethal doses of influenza A, then treated with single injections of cortisone or daily cortisone treatments. Only the mice given the prolonged cortisone treatment exhibited suppression of neutralizing or hemagglutination-inhibiting antibody. Also, asymptomatic infection while being treated with corticosteroids may confer immunity.

## SARS containment

Much of SARS transmission is within hospitals and from known contact with a SARS-infected individual. If people with known or likely exposure to SARS are treated with moderate doses of corticosteroids, they will not avoid SARS infection, but if infected, they should not become symptomatic or infectious. Prophylactic treatment of these high-risk individuals could significantly decrease the SARS infection rate. New infections will only arise from unidentifiable sources. A reasonable recommended prophylactic corticosteroid dose for adults likely to be exposed to SARS and exposed adults in quarantine is a low supraphysiological dose: 20 mg oral prednisone twice a day. Of course, when discontinuing the corticosteroid treatment, this should be done by tapering the dosage.

It should be emphasized that it would not be advantageous for the general population to employ the use of corticosteroids as a prophylactic against SARS. Only individuals who have been or are likely to be exposed to SARS will truly benefit from short-term use of corticosteroids to avoid SARS symptoms. If there is concern about the duration of prophylactic corticosteroid use by medical personnel, these workers can be rotated out of positions of likely exposure to SARS at appropriate intervals.

There is little or no hazard in the short-term use of moderate doses of corticosteroids (60 mg or less of prednisone per day). The principal adverse effects of corticosteroid use are the development of reversible cushingoid symptoms (rounding of the face, purple striae, hirsutism, easy bruising, increased cervicodorsal fat deposition, thinning skin). These symptoms develop over time and fully resolve upon discontinuation of corticosteroids. Adequate monitoring of treated individuals, that is, regular examinations and interviews, is sufficient to limit any problems arising from the short-term use of moderate doses of corticosteroids.

## Conclusions

As an immunoevasive strategy, the SARS and influenza viruses utilize molecular mimicry to inhibit their host's stress response by inducing the host's immune system to produce ACTH autoantibodies. It is likely that this strategy is utilized by other infectious agents as well. Treatment with corticosteroids seems to be the simplest remedy for counteracting this strategy. Furthermore, short-term, moderate doses of corticosteroids may be effective as a prophylactic against clinical infection with SARS.

Early treatment with corticosteroids should lower the dose necessary to counteract the infection's ACTH autoantibody mechanism. If corticosteroid treatment is delayed until inflammatory cytokine levels are causing serious injury, only high doses of corticosteroids are likely to be effective.

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