

Title: In-depth 15 H7N9 Human Serum Proteomics Profiling Study

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47

48 **Abstract**

49 **Background.** Human infection by avian influenza viruses is characterized by rapid development of
50 acute respiratory distress and severe pneumonia. However, the underlying host response leading to
51 this severe outcome is not well studied.

52 **Methods.** We conducted mass spectrometry-based serum proteome profiling on 10 healthy controls
53 and 15 H7N9 infected cases with two time points and carried out statistical and biology functional
54 enrichment analysis.

55 **Results.** In total, we identified 647 proteins, 273 proteins were only found in H7N9 infected cases
56 which might generate from cell leakage/death (apoptosis and/or necrosis) and identified 50 proteins
57 with statistically significant difference between healthy control and H7N9 infected cases from 168
58 qualified proteins. We also found that M1 and PB2 tightly associated with the host's HSPA8 (P11142,
59 $p=0.0042$) which plays an important role in the protein quality control system.

60 **Conclusions.** H7N9 infection may increase cell programmed/unprogrammed cell death, and we
61 suggested that upregulated extracellular HSPA8 may suppress the H7N9 virion replication via
62 activation amyloid-beta binding network.

63 **Keywords.** H7N9; avian influenza; cell death; HSPA8; proteomic.

64 **Introduction**

65 As of August 2019, there have been 1568 confirmed human cases and 616 deaths caused by infection
66 with avian H7N9 influenza A viruses in China, with a 39% mortality rate [1]. In April 2019 a fatal
67 case of highly pathogenic avian influenza (HPAI) H7N9 was reported in Inner Mongolia, China,
68 which was associated with severe pneumonia and respiratory failure [2]. Acute respiratory distress
69 syndrome, as observed in the recent human case of HPAI H7N9 infection, may be caused by multiple
70 factors, including higher viral load [3], altered viral tropism and spread in the lower/upper respiratory
71 tract [4], virally-induced host shutoff [5] or hijacking host function [6–9]. Mass spectrometry-based
72 serum proteome profiling has made it possible to conduct extracellular fluid proteins analysis and to

investigate important mediators of intercellular communication and host-viral interactions associated with disease progression, coagulation, communication, inflammation and the immune response. Several studies have been published using mass spectrometry-based proteomics with *in-vitro* assays (Supplementary Table 1)[10–12]. Simon et al. (2015) performed a comparative proteomic study in A549 human cells infected with seasonal H1N1 (sH1N1), pdmH1N1, H7N9 and HPAI H5N1 strains. Using multiplex iTRAQ labelled quantification, they found that NRF2 was associated with infection with HPAI strains of influenza[10]. Ding et al.(2016) carried out similar research work in A549 infected with pdmH1N1 and H7N9 by labelling digested proteins with Cy-dye followed by identification using MALDI-TOF-MS/MS, and found that down-regulation of CAPZA1, OAT, PCBP1, EIF5A were related to the death of cells infected with H7N9, and down-regulation of PAFAH1B2 was related to the later clinical symptoms in patients infected with H7N9[11]. Sadewasser et al.(2017) performed SILAC labelled proteomic assays on human HEK 293T and A549, characterized sets of cellular factors alternatively regulated in cells infected with H3 or H7 AIVs, and suggested that VPRBP(*DCAF1*) was identified as a novel drug target [12]. There has also been a study conducted in humans by Wang et al. (2018), who revealed the differential plasma proteome profiles in two cases of H7N9 infection in a single family[13]. Apolipoproteins appeared to play a critical role in the progression of H7N9 infection and disease. To our knowledge few population-based extracellular fluid proteomic studies on host-viral interactions underlying subtype H7N9 influenza virus infection have been published.

To better understand host's response to H7N9 infection, we carried out serum proteomics profiling on 15 confirmed H7N9 human cases at two time points and compared these with 10 healthy controls. These experiments were performed on LC/MS/MS using labelling by iTRAQ method. We also built a local cloud-based analysis workflow for stable isotopic labelled proteomics study to qualify and quantify proteins and conduct comparative analysis. Our study identified key host responses that may be related to the progression of H7N9 disease.

Materials and Methods

15 patients with laboratory-confirmed, 14 patients in low pathogenic avian influenza A H7N9 infected (LPAI) and one in high pathogenic avian influenza A H7N9 infected (HPAI), were enrolled at First Affiliated Hospital of Guangzhou Medical University, from 2013 to 2017. The clinical history were recorded. The detailed enrollment process has been shown in Figure 1.

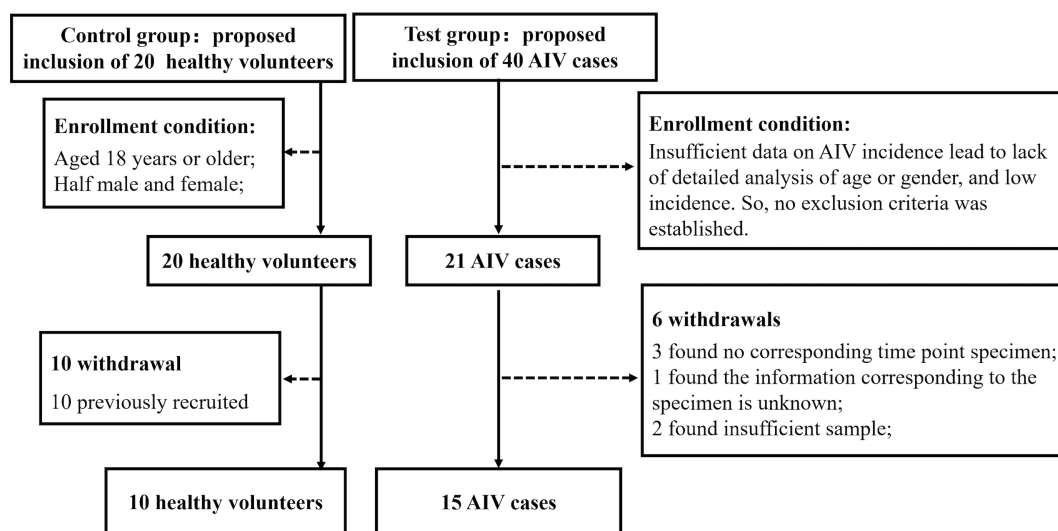


Figure 1: We totally assessed 20 healthy volunteers and 21 H7N9 infected patients, 10 healthy control and 6 H7N9 infected patients withdrawn due to the protocol violations. Finally, 15 patients and 10 healthy volunteers were enrolled in this study.

Earlier time point was defined as the earlier one of the two time points, and Later time point was the later one. The metadata of the patients were tabulated in Supplementary Table 2; and clinical and immunological features of some patients have been reported[3,14]. Ten healthy serum controls were collected from our lab colleagues. Approval for the study was obtained from the ethics committee of the First Affiliated Hospital of Guangzhou Medical University (No.:2016-78) and informed consent was obtained from the patients or their family members.

Proteome profiling of host serum was performed by iTRAQ-based quantitative differential LC/MS/MS, protein identification and quantitation were carried out by in-house workflow deployed in Galaxy framework[15], statistical related analysis was done using MetaboAnalystR (v2.0)[16] in R (v3.6.1), and biological and functional analysis were analyzed by STRING tools[17]. Detailed workflow was provided as supplementary text 1 and showed in Figure 2, we also provided Galaxy workflow for this study as Supplementary workflow 1.

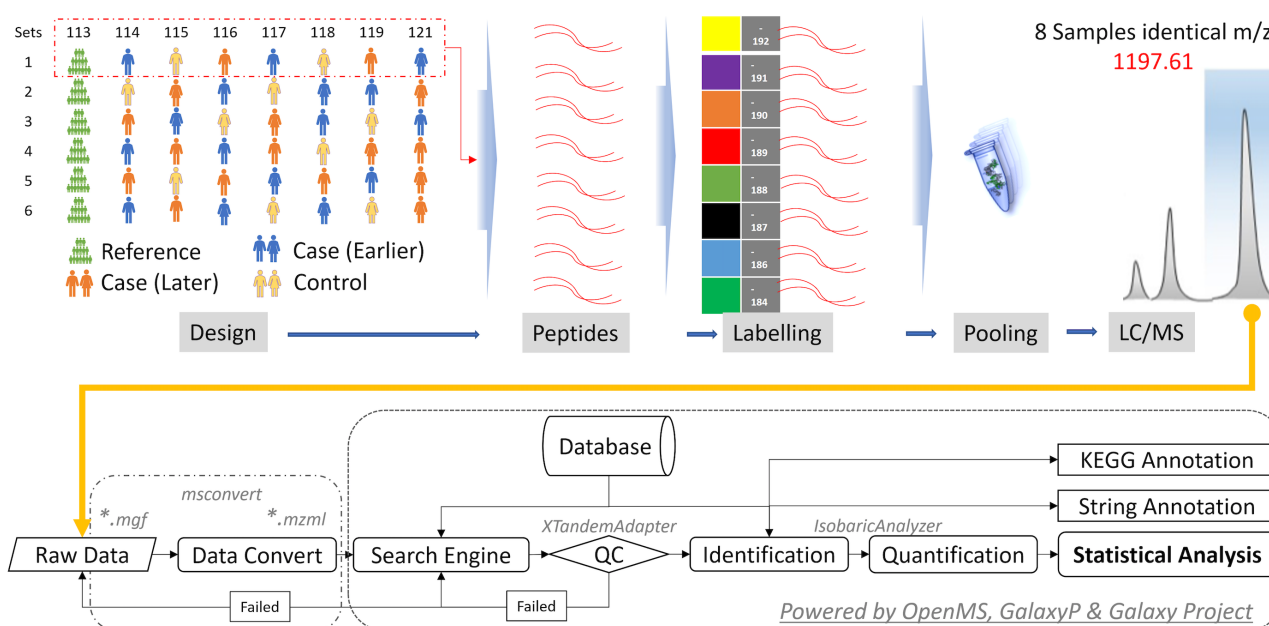


Figure 2. Experimental and analytical scheme of deep depleted serum proteome analysis using

iTRAQ LC/MS. H7N9 infected cases and control samples were extracted, depleted high-abundance protein, digested, labeled and pooled, coupled with high-resolution MALDI-TOF/TOF MS (Bruker Daltonics, Billerica, MA). All data were analyzed by the in-house workflow, which was powered by OpenMS, GalaxyP and Galaxy Project.

Results

Clinical Characteristics Of the Samples

Fifteen H7N9 infected patients were enrolled in this study from 2013 to 2017. Clinical, virologic, and immunological features of each patient were recorded in detail (Supplementary Table 2), including 14 LPAI and one HPAI patients. Five patients (No. 3, 9, 11, 12, and 14) had a fatal outcome, and the remaining patients were discharged. All samples had laboratory confirmed with H7N9 infection by RT-PCR using specific HA primers. The mean age was (28.60 ± 2.79 y) in the control group compared to the case group (49.50 ± 17.83 y) with statistical significantly difference. The viral load was determined from the throat swab (termed as an upper respiratory tract specimen) and from BALF or endotracheal aspirate (termed as lower respiratory tract). The mean URT and LRT viral loads level was 2.40 ± 2.14 (Log10), 4.35 ± 1.62 (Log10) in case's earlier compared to the viral loads 0, 1.04 ± 1.94 (Log10) in later time point with statistical significantly decreased ($p < 0.05$), respectively. We

137 assumed the viral loads in the upper and lower respiratory tracts were zero and the PF ratio ($\text{PaO}_2/\text{FiO}_2$)
 138 values were 450. The mean PF ratio was significantly lower in H7N9 infected cases, and the PF mean
 139 value was significantly upregulated after treatment. Table 1 was listed the characteristics of the 25
 140 participants enrolled in this study, including the 10 healthy controls.

141 **Overview of H7N9 Infected and Healthy Control Sera Proteomics Profiling**

142 Based on 130,325 qualified and quantified MS/MS spectra ($\text{FDR} < 0.01$) in all samples, 36,708 non-
 143 redundant peptide hits were identified. Identification rates were approximately 28.17% and a total of
 144 647 proteins had been annotated. The detailed information regarding the peptide and protein
 145 identification and quantification of six sets generated by X! Tandem and IsobaricAnalyzer are
 146 available in Supplementary Table 3. Data are available via ProteomeXchange with identifier
 147 IPX0001849000.

148 **Differential Expression Profiles of Comparison H7N9 Infected with Healthy Control**

149 We filtered the raw dataset (Supplementary Table 4), and identified 273 features which were only
 150 found in H7N9 infected cases (Supplementary Table 5). Those 273 features which were only found
 151 in H7N9 infected cases were applied proteins interaction analysis by String. The results showed 222
 152 nodes with 798 edges, 7.2 average node degree and 0.426 Avg.Local clustering coefficient with
 153 protein-protein interaction (PPI) enrichment with p -value less than $1.0\text{e-}16$ (Supplementary Table 6).
 154 206 of 273 proteins were annotated to cell part (GO:0044464) from GO Component analysis, and 94
 155 of 273 proteins were from extracellular region (GO:0005576). We then performed Venn diagram
 156 analysis on above two proteins list, and found 85 common proteins that can function on both cellular
 157 position of cell part (GO:0044464) and extracellular region (GO:0005576). The most of 94 proteins
 158 were annotated to immune related pathways by the Reactome database. The top 3 pathways were
 159 immune system (HSA-168256, 43 (45.7%)), innate immune system (HSA-168249, 37 (39.4%)) and
 160 neutrophil degranulation (HSA-6798695, 31 (32.98%)). The fourth and fifth pathways were
 161 metabolism of proteins (HSA-392499, 26 (27.7%)) and post-translational protein modification (HSA-
 162 597592, 20 (21.3%)), respectively. However, those 94 proteins could not be confirmed the source,

163 may be generated from cell death or normally secreted from stressed cells. The remaining 7 singleton
164 proteins were TNFSF12-TNFSF13, AC073610.3 (Novel Protein), C1RL, FBLN2, OLFML3, SBSN
165 and C4orf54. They may play an important role in avian influenza infection, for instance, protein
166 AC073610.3 acts as GTP binding and obsolete signal transducer activity, the most related GGA2
167 protein associated with avian influenza antibody titers[18]. There were still 51 proteins that were not
168 annotated by the String system. Since our study focused on the extracellular biomarkers, we did not
169 do further analysis on those proteins which were only found with H7N9 infected patients.

170 The dataset would be further filtered according to the proportion of the missing value (cut-off: 90%)
171 and got the final qualified dataset for statistical analysis (Supplementary Table 7). We got 168
172 qualified features, and 140 (82.8%) proteins were annotated to the extracellular region (GO:0005576)
173 from GO Component analysis. The qualified dataset was normalized and then applied one-way
174 ANOVA with *post-hoc* tests, we identified 50 features and 4 clinical characters (LRT, URT, PF and
175 TWC) with statistically significant difference (FDR < 0.05; Supplementary Table 8), and HPX
176 (Hemopexin, P02790) was significantly different from each other (FDR = 0.0014, Earlier >> Control,
177 Later >> Control and Earlier >> Later). We performed PPI analysis on those 50 statistically
178 significantly different proteins with all avian influenza A virus proteins, interaction analysis shown
179 50 nodes, 231 edges, 9.24 average node degree and 0.513 Avg.Local clustering coefficient with PPI's
180 enrichment *p*-value less than 1.0e-16 (Figure 3), found that M1 and PB2 tightly linked with host's
181 HSPA8 (P11142, *p* = 0.0042) which plays a core role in the protein quality control system, ensuring
182 the correct folding of proteins, and downregulated in H7N9 infected cases.

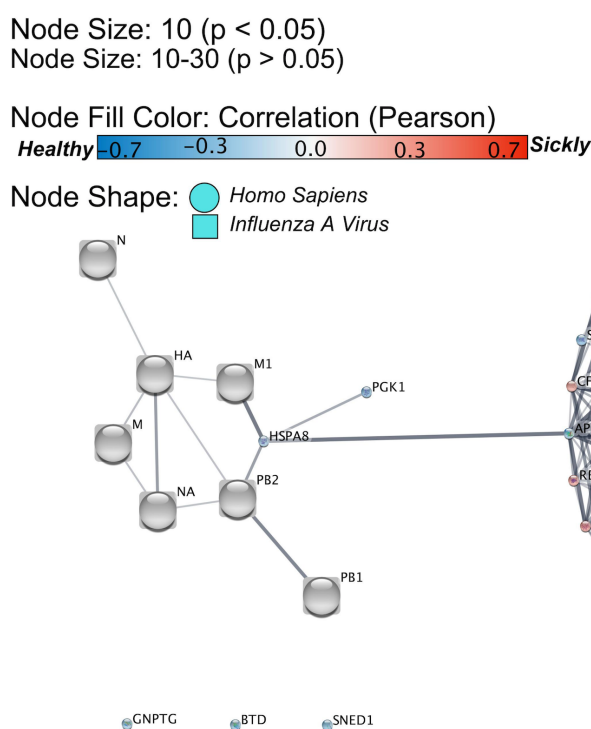


Figure 3. An interaction network between influenza A and extracellular host protein which were significantly different compared to healthy control. We downloaded influenza A proteins from public database using String, and we plotted by using Cytoscape (<http://cytoscape.org/>). Ellipse and round rectangle nodes indicate human proteins and influenza viral proteins, respectively. Node size is 10, means the protein is significantly correlated with disease status, and the node size is between 10 to 30 which means p-value is greater than 0.05, and positively correlated with the node size, node color is red/blue, means the protein positive/negative correlated with H7N9 infectious disease.

The biological function enrichment analysis on those 50 statistically significantly different proteins showed 44 proteins (88.0%) were annotated to extracellular region (GO:0005576) from cellular component analysis, 22 proteins (44.0%) were annotated to immune system (HSA-168256) from Reactome Pathways, 11 proteins (22%) were hit the complement and coagulation cascades pathway (hsa04610) from KEGG pathways annotation, and 9 proteins (18%) were enriched into endopeptidase inhibitor activity (GO:0004866) from GO Function, loss or reduction of endopeptidase inhibitor activity has been reported in vivo in influenza-infected ferrets[19]. The whole functional enrichment output was tabulated in supplementary table 9.

Correlation analysis can be carried out either against features or against a given pattern. The same qualified dataset (Supplementary Table 7) was applied correlation and pattern analysis with the Pearson method ($FDR < 0.05$, $|r| > 0.5$). The correlation of features with the values of different clinical characters, including PF ratio (PaO_2/FiO_2), procalcitonin (PCT), viral loads in the lower (LRT) and upper respiratory tract (URT), leucocyte (TWC), c-reactive protein (CRP), oxygen saturation (SPO_2) and age, were performed by Pearson correlation test (Supplementary Table 10, 11 and [Table 2](#)). The total leucocyte (TWC) significantly negatively correlated with APOF (Q13790, $r = -0.54$), APOA1 (P02647, $r = -0.54$) and C1QC (P02747, $r = -0.53$), and positively correlated with KRT1 (P04264, $r = 0.50$). Oxygen saturation (SPO_2) level has been well confirmed that is associated with lung pathology in influenza infection. SPO_2 level negatively correlated with C4BPA (P04003, $r = -0.53$), F13A1 (P00488, $r = -0.51$), A2M (P01023, $r = -0.55$), PCSK9 (Q8NBP7, $r = -0.51$), PLTP (P55058, $r = -0.52$), APOF (Q13790, $r = -0.56$), APOA1 (P02647, $r = -0.58$) and C1QC (P02747, $r = -0.59$), positively correlated with VTN (P04004, $r = 0.52$), APCS (P02743, $r = 0.52$) and LTF (P02788, $r = 0.50$). To investigate those features correlated with oxygen saturation level, we performed biology functional analysis on those proteins, and found they were highly linked together, and most of them were related with regulation of acute inflammatory response (GO:00002673), regulation of response to external stimulus (GO:0050727) and regulation of defence response (GO:0031347). The PF ratio significantly correlated with CKM (P06732, $r = 0.50$), MBL2 (P11226, $r = 0.50$), CA1 (P00915, $r = 0.50$), CDH5 (P33151, $r = 0.50$), APOE (P02649, $r = 0.52$), CLU (P10909, $r = 0.54$), ITIH2 (P19823, $r = 0.52$) and PLG (P00747, $r = 0.51$). We also performed biology functional analysis on those features and found that those proteins enriched into regulation of response to external stimulus (GO:0032101) and positive regulation of amyloid fibril formation (GO:1905908). Accumulation of beta-amyloid is a clinical sign of Alzheimer's disorder, and Mitchell R. reported beta-amyloid inhibits replication of seasonal and pandemic flu[20].

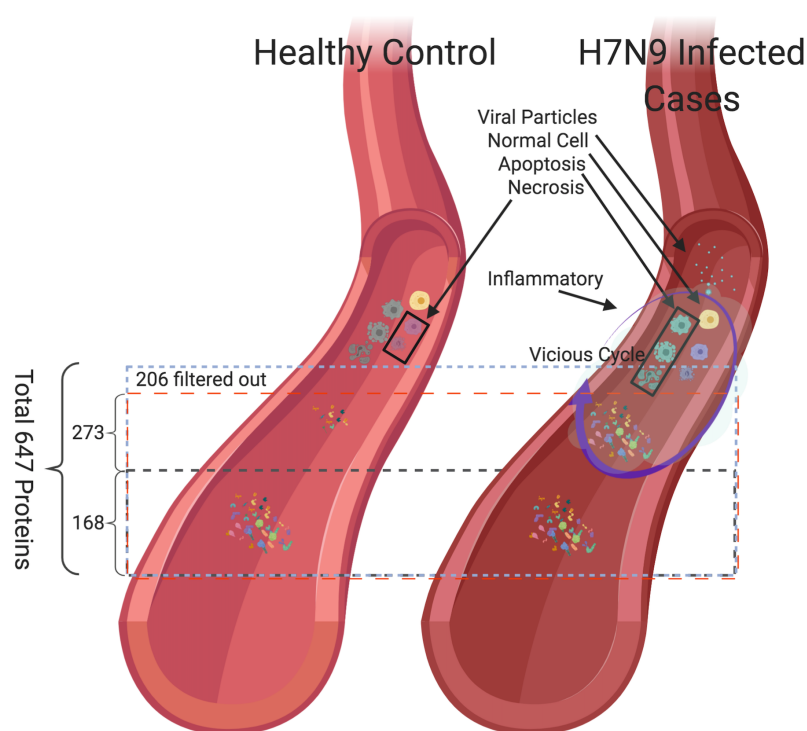
Aim to identify whether the proteins or clinical characters correlated with H7N9 infection. Pattern analysis was performed on the same dataset (Supplementary Table 7), and termed "1-2-3" as the

226 pattern used to search for interesting features that linearly increase with three groups: (Control-
227 Earlier-Later). We identified 112 proteins and 2 clinical characters (URT and PaO₂/FiO₂ ratio)
228 correlated with healthy control status ($r < 0$), and the rest proteins and clinical characters linked to
229 H7N9 infectious status ($r > 0$) (Supplementary Table 12). Sixteen proteins and 1 clinical character
230 (TWC) significantly upregulated in H7N9 infection ($r > 0.39$, FDR < 0.05), and PPI's enrichment
231 analysis showed two separately bins, one bin includes KRT family, KRT1, KRT2 and KRT9, the rest
232 proteins clustered to the 2nd bin. Thirteen of 16 proteins annotated to metabolic process (GO:0008152)
233 by Biological Process database, and 5 of 16 proteins enriched into regulation of protein activation
234 cascade (GO:2000257). FGA (P02671, Fibrinogen alpha chain), significantly positively correlated
235 with H7N9 infectious status ($r = 0.53$, $p = 0.0068$). Fibrinogen was upregulated in a non-specific way
236 in acute inflammatory conditions (infections, rheumatoid arthritis and other inflammations, cancers,
237 etc.). There were 33 proteins significantly downregulated in H7N9 infection status ($r < -0.39$, FDR $<$
238 0.05), and biological function analysis showed those proteins enriched into regulation of proteolysis
239 (GO:0030162), protein processing (GO:0070613) and inflammatory response (GO:0050727).

240 Discussion

241 Clinical laboratory examinations are important for assessing the condition of H7N9 infected patients,
242 however, it is not enough to reveal the etiologic factors that contribute to clinical phenotypes. We
243 tested several clinical factors, including the viral load on upper/lower respiratory tract, the total white
244 cell counts, c-reactive protein, procalcitonin, oxygen saturation (SPO₂) and PaO₂/FiO₂ ratio, which
245 have been correlated with influenza virus infection[3,21]. Influenza virus infection may cause host
246 cells death via several different ways, including apoptosis[22], necroptosis[23] and pyroptosis[24].
247 H5N1 causes mammalian airway epithelial cells death via apoptosis[25]. A study of H7N9 infected
248 CD14⁺ monocytes showed activation of caspases-8, -9 and -3 at 6h post infection, indicating that
249 apoptosis and necroptosis pathways were simultaneously activated[26]. Our data showed that 42.1%
250 of features (273) were only detected in H7N9 infected cases, and 75.5% (206/273) were annotated
251 into cell part (GO:0044464) from GO Component analysis. Among those cell part (GO:0044464)

252 proteins, still have 84 proteins were also expressed in extracellularly (GO:0005576), and biological
 253 function enrichment results showed most of them were annotated into immune response related
 254 pathways by Reactome database. These proteins might be generated by cell leakage/death due to
 255 H7N9 infection. High levels of cell component leakage can aggravate inflammation, and exacerbated
 256 the host immune responses, causing lung pathogenesis leading to acute respiratory distress syndrome
 257 (ARDS) with lower PaO₂/FiO₂ ratio, which correlated with disease severity level (Figure 4). Due to
 258 the limitations of study design, we could not confirm those proteins source, Therefore, they may have
 259 been generated from cell death or normally secreted/leaked from stressed cells.

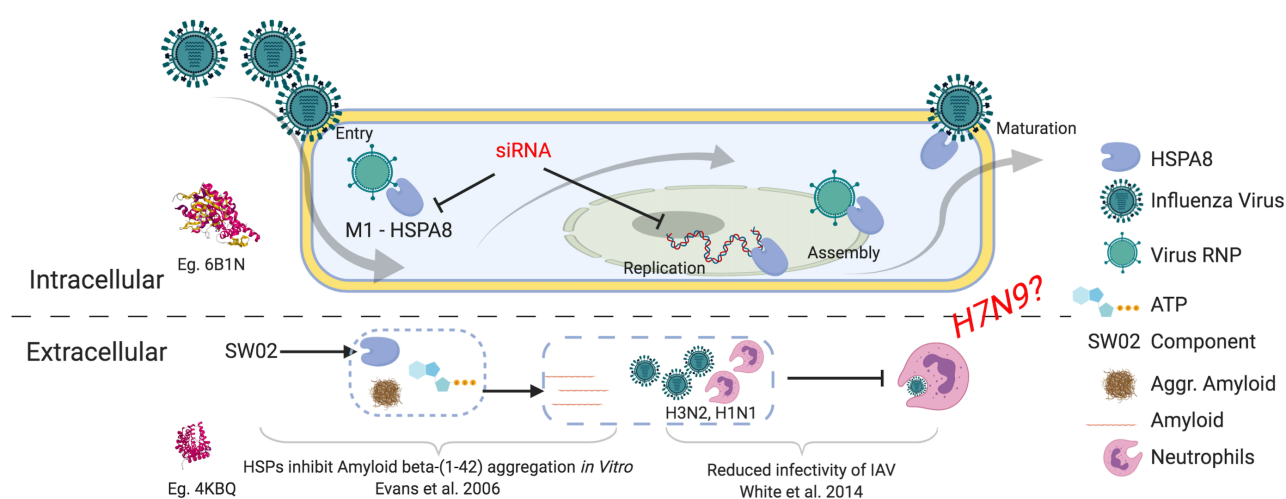


260
 261 Figure 4. Summary of H7N9 infected and healthy control sera proteomics profiling. In total, we
 262 identified 647 proteins, and we dropped 206 proteins with more than 50% missing values in order to
 263 get more reliable results, and also identified 273 proteins were only found in H7N9 infected cases
 264 which might generate from cell leakage/death (apoptosis and/or necrosis), high levels of cell
 265 component leakage can aggravate inflammation, and exacerbated host immune responses caused
 266 lung pathogenesis.

267

268 The Secretory proteins and extracellular vesicles may act via cell-cell communication, delivery
 269 hormones, enzymes, and antimicrobial peptides. Extracellular fluid proteomic profiling might help
 270 understanding the host molecular response to influenza and identifying the novel prophylactic and
 271 therapeutic host biomarkers. In this study, we identified three heat shock proteins, two from the
 272 HSP70 family (HSPA8, HSPA5) and one from the HSP90 family (HSP90B1). The level of HSPA8
 273 in serum may vary in certain pathological states. HSPA8 is widely expressed in the plasma membrane,
 274 extracellularly, in the nucleus and cytosol and the secreted/extracellular HSPA8 has important
 275 metabolic roles[27], acting as a trigger to boost pro-inflammatory cytokines expression, including
 276 TNF-alpha, IL-1beta and IL6[28]. HSPA8 may also regulate the hepatitis C virus replication (via
 277 both positive and negative ways)[29]. Kobayashi's group firstly confirmed that HSPA8 interacts with
 278 Influenza virus matrix protein 1 (M1)'s C terminal domain, which plays a key role in the virion
 279 replication, assembly and maturation. The same research group down-regulated HSPA8 with siRNA
 280 treatment results in reduction of viral load which inhibited the viral M1 and vRNP protein's nuclear
 281 exportation. They also demonstrated that HSP90 associated with the M1 and PA protein, concluding
 282 that HSPA8 and HSP90 may play important roles in various steps of the viral replication, assembly
 283 and maturation[30]. Therefore, Regulating the level of HSPA8 might be a therapeutic host biomarker
 284 for treatment of influenza infectious disease. Judith Frydman group reported that HSP70 family
 285 proteins have been shown to be involved into ZIKV virus replication, and HSP70s inhibitors are
 286 significantly reduced ZIKV replication in human and mosquito cells without appreciable toxicity,
 287 suggesting that HSP70s inhibitor can be used to treat the emergence of drug-resistant virus[31].
 288 However, our result showed that HSPA8 was significantly downregulated in H7N9 infected cases (r
 289 = -0.39, FDR = 0.045), and HSPA8 correlated with APOA1 (P02647, r = 0.35), APOE (P02649, r =
 290 0.26) and CLU (P10909, r = 0.11), which were annotated into amyloid-beta binding (GO:0001540,
 291 FDR = 0.0043). Pattern analysis results showed that APOA1, APOE and CLU were negatively
 292 correlated with H7N9 infection status with r = -0.38, FDR = 0.051; r = -0.46, FDR = 0.017 and r = -
 293 0.41, FDR = 0.036, respectively. APOE is the major genetic risk factor for Alzheimer's disease

294 (AD)[32], and regulation of beta-Amyloid (β A) metabolism, aggregation and deposition.
 295 Upregulation of HSP70/HSP90 has also been shown to slow down Alzheimer disease development
 296 related to β A aggregation[33]. β A has been shown to inhibit growth of bacteria and fungi, and the
 297 replication of seasonal and pandemic strains of H3N2 and H1N1 influenza A virus in vitro[20]. Our
 298 study suggests that HSPA8, through its role in activating the amyloid-beta binding network, may be
 299 important in limiting the pathogenesis of H7N9 infection, although this remains to be proven in future
 300 study (Figure 5). A new compound, SW02, which can specifically upregulated HSP70s has already
 301 been identified[34,35], which may be an entirely novel way to therapeutic intervention of H7N9
 302 infection.



303
 304 Figure 5. Summary of heat shock protein HSPA8 regulate the influenza A virus replication via both
 305 positive and negative way. Intracellular: Down-regulated HSPA8 with siRNA treatment results in
 306 reduction of influenza virus load which inhibited the viral M1 and vRNP proteins nuclear
 307 exportation. Extracellular: Upregulated HSPA8 with SW02 (HSPA8 activator) may active amyloid-
 308 beta binding network, then the activated network regulates the beta-amyloid protein which has been
 309 reported that suppress the H3N2 and H1N1 virion replication, assembly and maturation. Our study
 310 suggests that it may also work for suppression H7N9.

311 In summary, population-based extracellular fluid proteomic profiling was performed on 15 H7N9
 312 infected cases compared to 10 healthy controls. We identified features that were distinct only in H7N9
 313 patients, and most of those features may be from cell leakage/death. We also identified novel

314 candidates that can serve as potential prophylactic and therapeutic host biomarkers. Due to limited
 315 new H7N9 cases (as of October 2017 to now, there were only 4 additional cases[35]), we did not
 316 verify the findings in the same sample sets or apply the verification study on the independent sample
 317 sets. This has limited our study.

318

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327 **Potential conflict of interests**

328 All authors reported no conflicts of interest. All authors have submitted the ICMJE Form for
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434

435 Table 1: Clinical Characteristic of the groups

	Control	Case (Earlier)	Case (Later)
Size (n)	10	15	
Gender [*] (Male)	40%	53.3%	
Age (Year) [†]	28.60 ± 2.79	49.50 ± 17.83	
URT (Log10) [#]	NT	2.40 ± 2.14	0
LRT (Log10) [#]	NT	4.35 ± 1.62	1.04 ± 1.94
TWC (x10 ⁹ cells/L)	NT	11.75 ± 6.55	12.33 ± 8.16
CRP (mg/L)	NT	86.00 ± 44.12	70.69 ± 56.81
Procalcitonin (ng/ml)	NT	1.87 ± 3.68	5.49 ± 14.52
PF [#]	NT	146.79 ± 89.23	228.49 ± 168.07

436 *: Male of total group size (%); Value: mean ± SD; NT: Not Tested; URT: Viral Load on Upper

437 Respiratory Tract; LRT: Viral Load on Lower Respiratory Tract; TWC: Total White Cells; CRP:C-

438 Reactive Protein; PF: PO₂/FiO₂ ratio

439 †: Significantly difference between case and control group with *p* value less than 0.05

440 #: Significantly difference between earlier and later time point in case with *p* value less than 0.05

441 [Go Back To Content](#)

442

443 Table 2: Sensitivity of proteins to clinical characters

Clinical Characters	Protein	Pearson Correlation r	p-value	Protein Name
TWC	Q13790	-0.54409	0.00028447	APOF
	P02647	-0.53654	0.00035842	APOA1
	P02747	-0.52646	0.00048385	C1QC
	P04264	0.50149	0.00097879	KRT1
SPO2	P04003	-0.52895	0.00044974	C4BPA
	P00488	-0.50761	0.00082778	F13A1
	P01023	-0.55056	0.00023238	A2M
	Q8NBP7	-0.50561	0.00087468	PCSK9
	P55058	-0.52354	0.0005269	PLTP
	Q13790	-0.5638	0.00015156	APOF
	P02647	-0.58072	8.54E-05	APOA1
	P02747	-0.59343	5.44E-05	C1QC
	P04004	0.52126	0.00056294	VTN
	P02743	0.52281	0.00053827	APCS
PF	P02788	0.50454	0.00090069	LTF
	P06732	0.5008	0.00099743	CKM
	P11226	0.50253	0.00095164	MBL2
	P00915	0.50188	0.00096852	CA1
	P33151	0.50298	0.00093986	CDH5
	P02649	0.52422	0.00051661	APOE
	P10909	0.54334	0.00029115	CLU
	P19823	0.52297	0.00053578	ITIH2

P00747

0.51514

0.00067033

PLG

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