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Neutralizing antibodies derived from the B cells of 1918 influenza pandemic survivors

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Abstract

Investigation of the human antibody response to influenza virus infection has been largely limited to serology, with relatively little analysis at the molecular level. The 1918 H1N1 influenza virus pandemic was the most severe of the modern era[1]. Recent work has recovered the gene sequences of this unusual strain[2], so that the 1918 pandemic virus could be reconstituted to display its unique virulence phenotypes[3,4]. However, little is known about adaptive immunity to this virus. We took advantage of the 1918 virus sequencing and the resultant production of recombinant 1918 haemagglutinin (HA) protein antigen to characterize at the clonal level neutralizing antibodies induced by natural exposure of survivors to the 1918 pandemic virus. Here we show that of the 32 individuals tested that were born in or before 1915, each showed seroreactivity with the 1918 virus, nearly 90 years after the pandemic. Seven

of the eight donor samples tested had circulating B cells that secreted antibodies that bound the 1918 HA. We isolated B cells from subjects and generated five monoclonal antibodies that showed potent neutralizing activity against 1918 virus from three separate donors. These antibodies also cross-reacted with the genetically similar HA of a 1930 swine H1N1 influenza strain, but did not cross-react with HAs of more contemporary human influenza viruses. The antibody genes had an unusually high degree of somatic mutation. The antibodies bound to the 1918 HA protein with high affinity, had exceptional virus-neutralizing potency and protected mice from lethal infection. Isolation of viruses that escaped inhibition suggested that the antibodies recognize classical antigenic sites on the HA surface. Thus, these studies demonstrate that survivors of the 1918 influenza pandemic possess highly functional, virus-neutralizing antibodies to this uniquely virulent virus, and that humans can sustain circulating B memory cells to viruses for many decades after exposure—well into the tenth decade of life.

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Accession codes

Primary accessions **GenBank/EMBL/DDBJ**

EU169674

EU169679

EU825947

EU825950

Data deposits

Antibody nucleotide sequences have been deposited in GenBank under accession numbers EU169674 to EU169679, and EU825947 to EU825950.

Change history

26 September 2012 Nature 455, 532–536 (2008); doi:10.1038/nature07231 In this Letter, the heavy-chain sequence of 1F1 was in error and has been corrected in GenBank (EU169674.2). Also, the 1947 virus tested that was not inhibited by 1F1 should have been designated A/USA/L3/1947(H1N1) rather than A/Fort Monmouth/1/1947(H1N1).

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Author Contributions X.Y., P.A.M., M.D.H. and F.S.H. made and cloned the monoclonal antibodies, sequenced antibody genes, and performed immunofluorescence experiments. T.T. characterized the interaction of the antibodies with viruses and VLPs and selected for and characterized the escape mutants. C.J.K. performed biosensor studies. T.M.T., C.P. and L.A.P. designed and

performed *in vivo* studies. O.M. sequenced the HA genes of the H1N1 viruses used in this study and performed ELISA assays with these viruses. P.V.A. assisted with HAI and neutralization assays and with cloning of recombinant HA molecules. J.S. and I.A.W. provided recombinant HA. E.L.A. led the clinical recruitment and, together with C.F.B. and J.E.C., conceived of the experimental plan. C.F.B. and J.E.C. wrote the manuscript. All authors discussed the results and commented on the manuscript.

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Supplementary information

Supplementary Information

The file contains Supplementary Tables 1-2 and Supplementary Figures and Legends 1-3. The Supplementary Tables illustrate 1) Serologic data from volunteers of varying ages to 1918 and Sw/30 antigens and viruses, 2) Neutralization or HAI specific activity (μg/mL) of mAbs against representative H1N1 viruses. The Supplementary Figures

illustrate, 1) ELISA binding data for mAbs 1F1, 2D1, and 4D20 to representative 20th century H1N1 viruses, 2) binding of human mAbs to 1918 HA protein in HA transfected cells, and 3) the location of escape mutations in the HA for variant viruses selected with mAbs. *This file was replaced on 27th September 2012 - see Corrigendum* nature11235 *linked to this paper for details.* (PDF 549 kb)

PowerPoint slides

PowerPoint slide for Fig. 1

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