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Interferon interplay helps tissue cells to cope with SARS-coronavirus infection

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SARS coronavirus (SARS-CoV), the causative agent of severe acute respiratory syndrome, is a versatile pathogen armed with a host of factors countering the antiviral type I interferon (IFN) system. Hence, tissue cells infected with SARS-CoV are unable to launch an IFN response. Plasmacytoid dendritic cells, however, produce high levels of IFN after infection. We recently demonstrated that minute amounts of IFN applied before infection (IFN priming) can ameliorate the IFN response of tissue cells to SARS-CoV. IFN priming of SARS-CoV-infected cells activated genes for IFN transcription, IFN signaling, antiviral effector proteins, ubiquitinylation and ISGylation, antigen presentation, and other cytokines and chemokines, whereas IFN treatment or infection alone had no major effect. Thus, the IFN which is produced by plasmacytoid dendritic cells could enable tissue cells to at least partially overturn the SARS-CoV-induced block in innate immune activation.

Key words: SARS, interferon antagonism, plasmacytoid dendritic cells, interferon priming, interferon induction

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In 2002, the first epidemic of the new millenium was provoked by an emerging virus which caused severe acute respiratory syndrome (SARS). The outbreak quickly spread in 28 countries around the globe and resulted in 8,000 infected people of which approximately 10% had a fatal course.[1] The causative agent was found to be a coronavirus subsequently named SARS-CoV.[2-5] There is evidence that bats are the reservoir host of this virus, since sequences of closely related viruses were found in these animals.[6-8] Most probably, SARS-CoV initially spilled over from bats to humans via an intermediate host like palm civets.

In order to establish infection and accomplish spread from one subject or even species to another, viruses have to cope with a range of antiviral mechanisms. The type I interferon (IFNα/β) system marks the first line of defence with potent antiviral activity and therefore represents a powerful part of the innate immune system of vertebrates.[9,10] Depending on the cell type and on the pathogen, the IFN system can be activated by different pathways. IFN production in tissue cells is preferentially induced after an infection was recognized by cytoplasmic pattern recognition receptors (PRRs) which sense so-called pathogen associated molecular patterns (PAMP). Prominent virus PAMPs are double-stranded RNA and 5'triphosphorylated RNA.[11,12] Activated PRRs trigger a signaling cascade which leads to the induction and secretion of IFNs, finally resulting in the upregulation of IFN-stimulated genes (ISG) and in the establishment of an antiviral state in uninfected neighbouring cells. Crucial transcription factors involved in the induction of IFN are members of the IFN-regulatory factor (IRF) family. The activation of IRF-3 represents a pivotal step of IFN induction in cells of non-lymphoid origin, like tissue cells.[13]

SARS-CoV displays a certain IFN sensitivity. Pre-treatment of cell culture or animals with ectopic IFN decreases virus titers and relieves pathogenesis.[14-17] However, SARS-CoV employs several strategies to prevent the activation of the IFN system.[18,19] Firstly, SARS-CoV replicates in cytoplasmic compartments surrounded by a double-layer of membranes. This intracellular hiding most

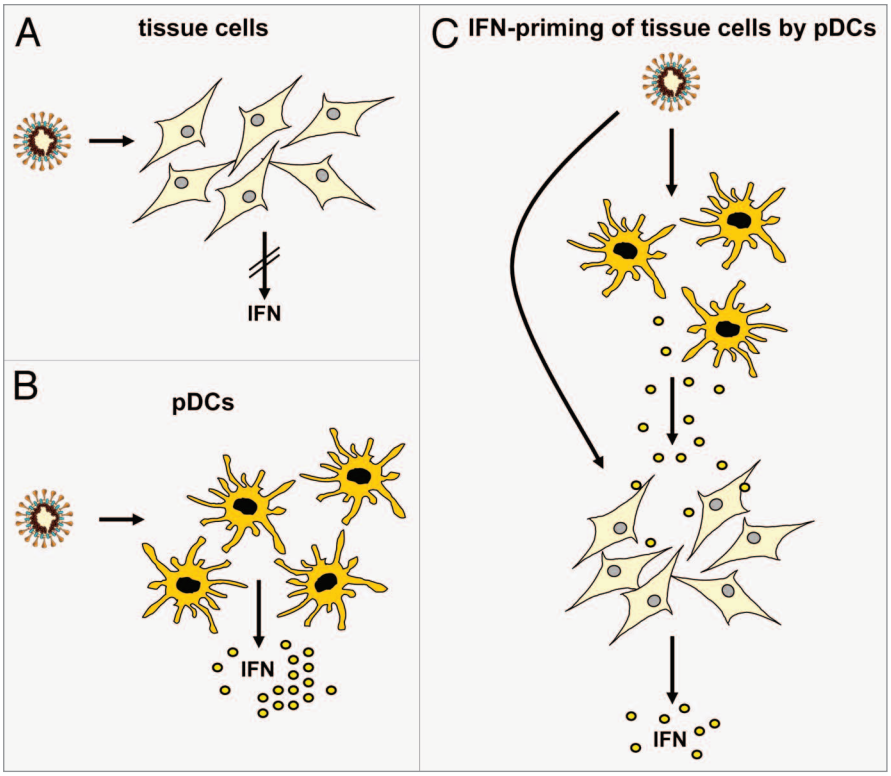

Figure 1. IFN production after infection with SARS-CoV in cells of different origin. (A) Non-lymphatic tissue cells are not able to produce IFN after infection with SARS-CoV. (B) pDCs can respond to SARS-CoV and secrete robust amounts of IFN. (C) After being sensitized by low amounts of IFN, tissue cells are able to respond to an infection with SARS-CoV.

likely results in a spatial separation of the viral PAMPs and the cellular PRRs.[20-22] Furthermore, SARS-CoV actively inhibits the activation of IRF-3.[23] To date, five different proteins of this particular virus have been shown to target IRF-3, in order to prevent the activation of the IFN system.[24-26] Moreover, unspecific degradation of host mRNA can also affect IFN induction.[27,28] As a consequence, tissue cells are not able to launch an antiviral IFN response after being infected with SARS-CoV (**Fig. 1**).[23]

Plasmacytoid dendritic cells (pDCs) are so-called 'professional' IFN-producing cells. These cells utilize Toll-like receptors (TLRs) and IRF-7 to recognize pathogen structures and induce IFN transcription, respectively.[29] The TLRs of pDCs are located in endosomes and are pre-associated with adaptor and signaling molecules in order to launch an antiviral response quickly after an invading pathogen has been detected.[30] In contrast to tissue cells, pDC are able to produce large amounts of IFN after infection with SARS-CoV (**Fig. 1**).[31]

It is long known that cells which came in contact with small amounts of IFN ('priming'), are able to enhance their response to virus infection.[32-34] This set-up resembles the assumed in vivo situation in which IFN produced by SARS-CoV-infected pDCs may be influencing the surrounding tissue cells. Therefore, in our recent study we investigated how IFN priming alters the transcriptional response of tissue cells to SARS-CoV infection.[35] Global gene expression profiles and specific analysis of selected genes revealed that IFN-primed cells infected with SARS-CoV not only upregulated the genes for IFNβ itself, but also those for IFN transcription factors, IFN signalling components, antiviral effector proteins, ubiquitinylation and ISGylation machineries, antigen presentation, and other cytokines and chemokines. Thus, despite the presence of several anti-IFN strategies employed by SARS-CoV, activation of the innate immune response can be restored by IFN priming to some extent.

SARS-CoV massively remodels the endoplasmatic reticulum (ER)—Golgi compartment in order to establish sites for viral replication and budding.[20,21,36] Surprisingly, these rearrangements had no influence on protein secretion, since primed cells secreted exactly the amounts of IFN which were expected from the measured IFNβ mRNA levels. However, despite the clear transcriptional response after IFN priming and SARS-CoV infection, neither IRF-3 nor IRF-7 were visibly activated. This may indicate that IRF-3 and IRF-7 can be active at sub-detectable levels which are sufficient to launch an IFN response.

In a patient study which examined 40 clinically well-defined human SARS cases, high levels of IFN were found in pre-crisis patients, but not in crisis patients, and early production of IFN correlated with a beneficial outcome for the infected individuals.[37] In line with this, SARS-CoV-infected macaques launch an IFN response early after infection.[38] Several IFN-producing cells were found which were not identified, but it is likely that this might have been pDCs. Collectively these data indicate that SARS-CoV infected pDCs produce IFN which spreads via the bloodstream and primes tissue cells to prepare them for infection. It is likely that such an interplay between professional IFN producing cells and tissue cells is a common mechanism that allows an improved response against viruses.

References

1. WHO. Summary table of SARS cases by country, 1 November 2002–26 September 2003. http://wwwwhoint/csr/sars/country/table2004_04_21/en/indexhtml 2004.
2. Drosten C, Gunther S, Preiser W, van der Werf S, Brodt HR, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. N Engl J Med 2003; 348:1967-76.
3. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003; 348:1953-66.
4. Kuiken T, Fouchier RA, Schutten M, Rimmelzwaan GF, van Amerongen G, van Riel D, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003; 362:263-70.
5. Peiris JS, Lai ST, Poon LL, Guan Y, Yam LY, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. Lancet 2003; 361:1319-25.
6. Lau SK, Woo PC, Li KS, Huang Y, Tsoi HW, Wong BH, et al. Severe acute respiratory syndrome coronavirus-like virus in Chinese horseshoe bats. Proc Natl Acad Sci USA 2005; 102:14040-5.

7. Li W, Shi Z, Yu M, Ren W, Smith C, Epstein JH, et al. Bats are natural reservoirs of SARS-like coronaviruses. Science 2005; 310:676-9.
8. Pfefferle S, Oppong S, Drexler JF, Gloza-Rausch F, Ipsen A, Seebens A, et al. Distant relatives of severe acute respiratory syndrome coronavirus and close relatives of human coronavirus 229E in bats, Ghana. Emerging infectious diseases 2009; 15:1377-84.
9. Haller O, Kochs G, Weber F. Interferon, Mx and viral countermeasures. Cytokine Growth Factor Rev 2007; 18:425-33.
10. Samuel CE. Antiviral actions of interferons. Clin Microbiol Rev 2001; 14:778-809.
11. Pichlmair A, Reis e Sousa C. Innate recognition of viruses. Immunity 2007; 27:370-83.
12. Yoneyama M, Fujita T. Structural mechanism of RNA recognition by the RIG-I-like receptors. Immunity 2008; 29:178-81.
13. Hiscott J. Triggering the innate antiviral response through IRF-3 activation. J Biol Chem 2007; 282:15325-9.
14. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. Lancet 2003; 362:293-4.
15. Haagmans BL, Kuiken T, Martina BE, Fouchier RA, Rimmelzwaan GF, Van Amerongen G, et al. Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. Nat Med 2004; 10:290-3.
16. Spiegel M, Pichlmair A, Mühlberger E, Haller O, Weber F. The antiviral effect of interferon-beta against SARS-Coronavirus is not mediated by MxA. J Clinical Virol 2004; 30:211-3.
17. Stroher U, DiCaro A, Li Y, Strong JE, Aoki F, Plummer F, et al. Severe acute respiratory syndrome-related coronavirus is inhibited by interferon-alpha. J Infect Dis 2004; 189:1164-7.
18. Frieman M, Heise M, Baric R. SARS coronavirus and innate immunity. Virus Res 2007.
19. Thiel V, Weber F. Interferon and cytokine responses to SARS-coronavirus infection. Cytokine Growth Factor Rev 2008; 19:121-32.
20. Stertz S, Reichelt M, Spiegel M, Kuri T, Martinez-Sobrido L, Garcia-Sastre A, et al. The intracellular sites of early replication and budding of SARS-coronavirus. Virology 2007; 361:304-15.
21. Knoops K, Kikkert M, Worm SH, Zevenhoven-Dobbe JC, van der Meer Y, Koster AJ, et al. SARS-coronavirus replication is supported by a reticulovesicular network of modified endoplasmic reticulum. PLoS Biol 2008; 6:226.
22. Versteeg GA, Bredenbeek PJ, van den Worm SH, Spaan WJ. Group 2 coronaviruses prevent immediate early interferon induction by protection of viral RNA from host cell recognition. Virology 2007; 361:18-26.
23. Spiegel M, Pichlmair A, Martinez-Sobrido L, Cros J, Garcia-Sastre A, Haller O, Weber F. Inhibition of Beta interferon induction by severe acute respiratory syndrome coronavirus suggests a two-step model for activation of interferon regulatory factor 3. J Virol 2005; 79:2079-86.
24. Devaraj SG, Wang N, Chen Z, Chen Z, Tseng M, Barretto N, et al. Regulation of IRF-3-dependent innate immunity by the papain-like protease domain of the severe acute respiratory syndrome coronavirus. J Biol Chem 2007; 282:32208-21.
25. Kopecky-Bromberg SA, Martinez-Sobrido L, Frieman M, Baric RA, Palese P. Severe acute respiratory syndrome coronavirus open reading frame (ORF) 3b, ORF 6, and nucleocapsid proteins function as interferon antagonists. J Virol 2007; 81:548-57.
26. Siu KL, Kok KH, Ng MH, Poon VK, Yuen KY, Zheng BJ, Jin DY. Severe acute respiratory syndrome coronavirus M protein inhibits type I interferon production by impeding the formation of TRAF3.TANK.TBK1/IKKepsilon complex. J Biol Chem 2009; 284:16202-9.
27. Kamitani W, Narayanan K, Huang C, Lokugamage K, Ikegami T, Ito N, et al. Severe acute respiratory syndrome coronavirus nsp1 protein suppresses host gene expression by promoting host mRNA degradation. Proc Natl Acad Sci USA 2006; 103:12885-90.
28. Wathelet MG, Orr M, Frieman MB, Baric RS. Severe acute respiratory syndrome coronavirus evades antiviral signaling: role of nsp1 and rational design of an attenuated strain. J Virol 2007; 81:11620-33.
29. Barchet W, Cella M, Colonna M. Plasmacytoid dendritic cells—virus experts of innate immunity. Seminars in immunology 2005; 17:253-61.
30. Takeuchi O, Akira S. Innate immunity to virus infection. Immunol Rev 2009; 227:75-86.
31. Cervantes-Barragan L, Zust R, Weber F, Spiegel M, Lang KS, Akira S, et al. Control of coronavirus infection through plasmacytoid dendritic-cell-derived type I interferon. Blood 2007; 109:1131-7.
32. Erlandsson L, Blumenthal R, Eloranta ML, Engel H, Alm G, Weiss S, Leanderson T. Interferon-beta is required for interferon-alpha production in mouse fibroblasts. Curr Biol 1998; 8:223-6.
33. Phipps-Yonas H, Seto J, Sealfon SC, Moran TM, Fernandez-Sesma A. Interferon-beta pretreatment of conventional and plasmacytoid human dendritic cells enhances their activation by influenza virus. PLoS Pathog 2008; 4:1000193.
34. Stewart WE, 2nd, Gosser LB, Lockart RZ Jr. Priming: a nonantiviral function of interferon. J Virol 1971; 7:792-801.
35. Kuri T, Zhang X, Habjan M, Martinez-Sobrido L, Garcia-Sastre A, Yuan Z, Weber F. Interferon priming enables cells to partially overturn the SARS-Coronavirus-induced block in innate immune activation. J Gen Virol 2009; 90:2686-94.
36. He B. Viruses, endoplasmic reticulum stress and interferon responses. Cell Death Differ 2006; 13:393-403.
37. Cameron MJ, Ran L, Xu L, Danesh A, Bermejo-Martin JF, Cameron CM, et al. Interferon-mediated immunopathological events are associated with atypical innate and adaptive immune responses in severe acute respiratory syndrome (SARS) patients. J Virol 2007; 81:8692-706.
38. de Lang A, Baas T, Teal T, Leijten LM, Rain B, Osterhaus AD, et al. Functional Genomics Highlights Differential Induction of Antiviral Pathways in the Lungs of SARS-CoV Infected Macaques. PLoS Pathogens 2007; 3:112.