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

Thomas Kuri and Friedemann Weber*
Abteilung Virologie; Institut für Medizinische Mikrobiologie und Hygiene; Universität Freiburg; Freiburg, Germany

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.

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 cytoplasmatic 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
likely results in a spatial separation of the viral PAMPs and the cellular PRRs.\textsuperscript{20-22} Furthermore, SARS-CoV actively inhibits the activation of IRF-3.\textsuperscript{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.\textsuperscript{24,26} Moreover, unspecific degradation of host mRNA can also affect IFN induction.\textsuperscript{27,28} As a consequence, tissue cells are not able to launch an antiviral IFN response after being infected with SARS-CoV (Fig. 1).\textsuperscript{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.\textsuperscript{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.\textsuperscript{30} In contrast to tissue cells, pDCs are able to produce large amounts of IFN after infection with SARS-CoV (Fig. 1).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{37} In line with this, SARS-CoV-infected macaques launch an IFN response early after infection.\textsuperscript{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.

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