Severe Acute Respiratory Distress Syndrome (SARS)
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1: Cytokine Growth Factor Rev. 2008 Mar 3 [Epub ahead of print]

Interferon and cytokine responses to SARS-coronavirus infection.

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The sudden emergence of severe acute respiratory syndrome (SARS) has boosted research on innate immune responses to coronaviruses. It is now well established that the causative agent, a newly identified coronavirus termed SARS-CoV, employs multiple passive and active mechanisms to avoid induction of the antiviral type I interferons in tissue cells. By contrast, chemokines such as IP-10 or IL-8 are strongly upregulated. The imbalance in the IFN response is thought to contribute to the establishment of viremia early in infection, whereas the production of chemokines by infected organs may be responsible for (i) massive immune cell infiltrations found in the lungs of SARS victims, and (ii) the dysregulation of adaptive immunity. Here, we will review the most recent findings on the interaction of SARS-CoV and related Coronaviridae members with the type I interferon and cytokine responses and discuss implications for pathogenesis and therapy.

PMID: 18321765 [PubMed - as supplied by publisher]

2: Thromb Res. 2008 Feb 29 [Epub ahead of print]

Thrombopoietin levels increased in patients with severe acute respiratory syndrome.

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Hematological changes in patients with Severe Acute Respiratory Syndrome (SARS) are common and frequently include thrombocytopenia. Using a ELISA method, we found an increase in thrombopoietin (TPO) levels in the plasma of convalesced SARS patients (290+/-53 pg/ml) and active SARS patients (251+/-23 pg/ml) comparing to that from normal control patients (228+/-17 pg/ml). In addition, the plasma from active SARS patients had an inhibitory effect on CFU-MK formation,

which could be neutralized by anti-TGF-beta antibodies. In the experiment to determine whether SARS-CoV can directly infect hematopoietic stem cells and megakaryocytic cells, incubation of the cells with SARS-CoV did not show active infection. Our findings of increased TPO levels in the plasma of SARS patients provide a possible explanation for the genesis of thrombocytosis, which frequently develops from thrombocytopenia in SARS patients.

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3: Biochem Pharmacol. 2008 Jan 19 [Epub ahead of print]

Thiopurine analogues inhibit papain-like protease of severe acute respiratory syndrome coronavirus.

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The papain-like protease of severe acute respiratory syndrome coronavirus (PLpro) (EC 3.4.22.46) is essential for the viral life cycle and therefore represents an important antiviral target. We have identified 6MP and 6TG as reversible and slow-binding inhibitors of SARS-CoV PLpro, which is the first report about small molecule reversible inhibitors of PLpro. The inhibition mechanism was investigated by kinetic measurements and computer docking. Both compounds are competitive, selective, and reversible inhibitors of the PLpro with K(is) values approximately 10 to 20muM. A structure-function relationship study has identified the thiocarbonyl moiety of 6MP or 6TG as the active pharmacophore essential for these inhibitions, which has not been reported before. The inhibition is selective because these compounds do not exert significant inhibitory effects against other cysteine proteases, including SARS-CoV 3CLpro and several cathepsins. Thus, our results present the first potential chemical leads against SARS-CoV PLpro, which might be used as lead compounds for further optimization to enhance their potency against SARS-CoV. Both 6MP and 6TG are still used extensively in clinics, especially for children with acute lymphoblastic or myeloblastic leukemia. In light of the possible inhibition against subset of cysteine proteases, our study has emphasized the importance to study in depth these drug actions in vivo.

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4: J Virol. 2008 Feb 27 [Epub ahead of print]

Severe Acute Respiratory Syndrome Coronavirus Nsp1 Suppresses Host Gene Expression, Including Type I Interferon, in Infected Cells.

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Severe acute respiratory syndrome coronavirus (SARS-CoV) nsp1 protein has unique biological functions that have not been described in the viral proteins of any RNA viruses; expressed SARS-CoV nsp1 protein has been found to suppress host gene

expression by promoting host mRNA degradation and inhibiting translation. We have generated an nsp1 mutant (nsp1-mt) that neither promoted host mRNA degradation nor suppressed host protein synthesis in expressing cells. Both a SARS-CoV mutant virus, encoding nsp1-mt protein (SARS-CoV-mt), and a wild-type SCoV (SARS-CoV-WT) replicated efficiently and exhibited similar one-step growth kinetics in susceptible cells. Both viruses accumulated similar amounts of virus-specific mRNAs and nsp1 protein in infected cells, whereas the amounts of endogenous host mRNAs were clearly higher in SARS-CoV-mt-infected cells than in SARS-CoV-WT-infected cells, both in the presence and absence of actinomycin D. Further, SARS-CoV-WT replication strongly inhibited host protein synthesis, whereas host protein synthesis inhibition in SARS-CoV-mt-infected cells was not as efficient as in SARS-CoV-WT-infected cells. These data revealed that nsp1 indeed promoted host mRNA degradation and contributed to host protein translation inhibition in infected cells. Notably, SARS-CoV-mt infection, but not SARS-CoV-WT infection, induced high levels of interferon (IFN) beta mRNA accumulation and high titers of type I IFN production. These data demonstrated that SARS-CoV nsp1 suppressed host innate immune functions, including type I IFN expression, in infected cells, and suggested that SARS-CoV nsp1 most probably plays a critical role in SARS-CoV virulence.

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5: Drugs Today (Barc). 2008 Jan;44(1):63-73.

Development of subunit vaccines against severe acute respiratory syndrome.

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Severe acute respiratory syndrome (SARS) is a novel infectious disease caused by SARS coronavirus (SARS-CoV). Although SARS appears to have been successfully contained, there is still a risk for its reemergence due to sporadic laboratory accidents or the presence of a natural reservoir for SARS-CoV-like virus. Therefore, the development of effective vaccines against SARS-CoV continues to be the current focus of SARS research. This review will first describe the rationale for developing safe and effective SARS vaccines, followed by elucidating viral antigens that could be used as potential vaccine components. After comparing current vaccine categories against SARS, this article will demonstrate the advantages of subunit vaccines, describe the current situation of developing subunit vaccines, and point out the possibility for further improvement of subunit SARS vaccines. This suggests that recombinant protein/peptide-based subunit vaccines containing the spike protein, especially the receptor-bind domain of SARS-CoV, could be developed as safe and effective SARS vaccines.

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