SARS: An hypothesis for treatment

Fc Receptors

Leukocyte Fc receptors (FcR) are cell surface glycoproteins that bind the Fc portion of immunoglobulin (Ig), thereby linking antigen recognition by antibodies with cell–based effector mechanisms. Fc receptors for IgG expressed on macrophages and NK cells are important mediators of opsonophagocytosis and Ab-dependent cell-mediated cytotoxicity. Fc receptor-mediated phagocytosis plays a pivotal role in clearance of respiratory virus infections [1].

Influenza A virus infection, for example, induces cross-reactive antibodies that enhance uptake of virus into Fc receptor-bearing cells [2]. Some complex viruses (e.g. Poxviruses, Herpesviruses) may have more than one receptor/receptor-binding protein, therefore, there may be alternative routes of uptake into cells. Specific receptor binding can be side-stepped by antibody-coated virus particles binding to Fc receptor on the surface of monocytes, which results in virus uptake [3]. The expression (or absence) of receptors on the surface of cells largely determines the TROPISM of most viruses, i.e. the type of cell in which they are able to replicate - important factor in pathogenesis. Attachment is in most cases a reversible process - if penetration does not ensue, the virus can elute from the cell surface. Some viruses have specific mechanisms for "detachment" e.g. Influenza neuraminidase protein. BUT: elution from cell often leads to changes in the virus that decrease or eliminate the possibility of attaching to other cells.

SARS coronavirus

The SARS coronavirus is a single-stranded positive (+) sense RNA virus. Polycistronic mRNA, e.g. Picornaviruses and the Flavivirus “Yellow fever virus” (hemorrhagic fever) are also Ssrna+ viruses. The genome RNA of the virus is the mRNA. Translation of the mRNA into DNA results in the formation of a polyprotein product, which is subsequently cleaved to form the mature proteins. [3].

Antibodies and viral infections and Fc Receptors

Specific antibodies are important in and may protect against viral infections. The most effective type of antiviral antibody is "neutralizing" antibody - this is antibody which binds to the virus, usually to the viral envelope or capsid proteins, and which blocks the virus from binding and gaining entry to the host cell. Virus specific antibodies may also act as opsonins in enhancing phagocytosis of virus particles - this effect may be further enhanced by complement activation by antibody-coated virus particles. In addition, in the case of some viral infections, viral proteins are expressed on the surface of the infected cell. These may act as targets for virus-specific antibodies, and may lead to complement-mediated lysis of the infected cell, or may direct a subset of natural killer cells to lyse the infected cell through a process known as antibody-directed cellular cytotoxicity (ADCC). At mucosal surfaces (such as the respiratory and gastrointestinal tracts), virus infection may induce the production of specific antibodies of the IgA isotype, which may be
protective against infection at these surfaces. (This is the basis of immunisation with the current oral polio vaccine) [4]. Not all antibodies to viruses are protective, however, and in certain cases antibody to the virus may facilitate its entry into a cell through Fc receptor-mediated uptake of the antibody coated particle. Such antibodies are called enhancing antibodies. Non-neutralizing antibody has been shown to enhance the virulence of the alpha and flaviviruses by promoting their binding to FC receptors [5].

In murine hepatitis virus, MHV S peplomer protein exhibits Fc IgG binding ability. The SARS coronavirus appears very similar to the murine hepatitis virus though they are not the same [6]. Antigenic variation among murine coronaviruses is associated primarily with the surface peplomer protein E2 (180,000 Da). E2 is responsible for attachment of the virus to the host cell, MHV-induced cell fusion, and eliciting neutralizing antibody. Molecular mimicry exists between E2 and Fc gamma receptor (Fc gamma R) [7]. MHV S peplomer protein expressed by a recombinant vaccinia virus vector exhibits IgG Fc-receptor activity [8].

Polymorphisms of Fc receptors for IgG (Fc gamma R) have been proposed as a genetic factor that influences susceptibility for the human disease, systemic lupus erythematosus (SLE) [9]. Allelic variants of Fc gamma R confer distinct phagocytic capacities providing a mechanism for heritable susceptibility to immune complex disease. Human Fc gamma RIIa has two codominantly expressed alleles, R131 and H131, which differ substantially in their ability to ligate human IgG2. The Fc gamma RIIa-H131 is the only human Fc gamma R which recognizes IgG2 efficiently and optimal IgG2 handling occurs only in the homozygous state [10]. Trend analysis of the genotype distribution showed a highly significant decrease in Fc gamma RIIA-H131 as the likelihood for lupus nephritis increased (P = 0.0004) consistent with a protective effect of the Fc gamma RIIA-H131 gene. The skewing in the distribution of Fc gamma RIIA alleles identifies this gene as a risk factor with pathophysiologic importance for the SLE diathesis in African Americans [11]. An abnormal distribution of Fc gammaRIIa polymorphisms was associated with SLE in Korean patients [12].

One hundred eight Caucasian patients were diagnosed with SLE according to the American College of Rheumatology criteria. The SLE patients and 187 Caucasian controls were genotyped for the FcgammaRIIa polymorphism, and associations between FcgammaRIIa genotypes, selected HLA haplotypes, and clinical as well as laboratory features were analyzed. Results indicated no significant skewing of the FcgammaRIIa polymorphism was observed in the SLE Caucasian cohort. The FcgammaRIIa polymorphism constitutes an additional factor that might influence the clinical manifestations and course of SLE, but does not represent a genetic risk factor for the occurrence of SLE [13].

We see, in the above information, that there appears to be some differences in ethnic groups relative to Fc receptors for IgG. In Systemic Lupus Erythematosus we see skewed Fc receptors for IgG in Africans and Asians but not in Caucasians. You will recall that Fc receptors are cell surface glycoproteins that bind the Fc portion of
immunoglobulin (Ig), thereby linking antigen recognition by antibodies with cell–based effector mechanisms.

Yap (1999) found in their studies, “based on 175 Chinese and 50 Malays SLE patients as well as 108 and 50 ethnically (Chinese and Malays), matched healthy controls for the respective groups in examining Fc Gamma Receptors relative to Lupus (SLE). Analysis of the data (chi2 test with Yates correction factors and odds ratios) revealed that there were no significant differences between SLE patients and controls. We have not found evidence of a protective effect conferred by FcgammaRIIA-H131 in the ethnic groups studied” [14]. Fcgamma receptors (FcgammaRs) are potent initiators of proinflammatory reactions and tissue injury programs through the oxidative burst, degranulation and the production of a variety of proinflammatory cytokines. The well-characterized and functionally important alleles of neutrophil FcgammaR (FcgammaRIIa-H131/R131 and FcgammaRIIIb-NA1/NA2) are possible inheritable genetic elements that may alter disease severity and/or phenotype [15]. Work like this has also been directed toward determining differences between and among, for example, Ethiopians and Norwegians with the observation that “The variation of different polymorphisms both within and between ethnic groups may influence differences in the incidence rates of infectious and autoimmune diseases” [16].

So then, if there are ethnic differences relative to the Fc gamma Receptors associated with IgG and incidence of infectious and autoimmune diseases, might this serve as a basis whereby it might be possible to understand SARS?

Let’s consider the situation in SARS coronavirus and the currently developing pandemic. At this point, there have been over a thousand Chinese infected with SARS and the mortality rate hovers around 5% of that population. In contrast, Caucasian-predominate nations have very few cases of SARS and, for example, in the United States no one has died from SARS. While the disease is not widely spread in Caucasian countries at this time (those infected in Toronto are predominately Chinese), there may be some reason to consider ethnicity and differential immune-system functioning in response to disease.

Might this difference in ethnicity-number-dead-and-infected be a function of an “influencing of differences in the incidence rates of infectious and autoimmune diseases” suggested above? This might depend on whether SARS coronavirus activates Fc gamma Receptors in Asian and Africans who may have a disproportionate proinflammatory reaction to SARS. This remains to be seen as the science progresses. However, we might expect that this potent proinflammatory reaction might be due to the SARS coronavirus and perhaps this potent proinflammatory rection is associated with Fc gamma Receptors. It is a theory worth investigating.

Untried Treatments for SARS?

As indicated above, the coronaviruses related to SARS coronavirus display an “S peplomer protein” that mimicks Fc receptors and the E2 glycoprotein of Murine hepatitis virus, for example, displays Fc receptor-like activity. Perhaps if there was a way to
prevent the “potent proinflammatory response” induced by SARS, a therapeutic treatment may be offered to those in whom the Fc gamma Receptor triggers a profound proinflammatory response. Work suggests that nitric oxide may function in an anti-inflammatory capacity by down-regulating endotoxin-stimulated cytokine production by alveolar macrophages and matured monocytes [17]. Use of a treatment that would prevent the cascade of pro-inflammatory cytokines might prevent further virus uptake and more serious disease as well as offer a treatment for the initial infection itself. There are other anti-inflammatory interventions.

Various efforts to develop cytokine-blocking have been undertaken. Cunard (2002) discusses regulation of cytokine expression by ligands of peroxisome proliferator activated receptors [18]. N-formylmethionylleucylphenylalanine has also been used to inhibit Fc gamma Receptor-dependent functions [19].

Currently, treatments for SARS patients include administration of steroids and ribavirin in China with, as of 4/20/03, questions about the efficacy of such treatments as the number of SARS dead increases in China. There has been nothing stated in any publicly available resource – medical journals, news reports, or elsewhere – of which I am aware of the use of Fc gamma receptor inhibitors / cytokine inhibitors / pro-inflammatory inhibitors (beyond the use of steroids).

It is my suggestion, based on the above information, awareness of the construction of the virus, and many other factors, that consideration be given for treatment of SARS-infected patients which includes:

• Fc gamma Receptor inhibitors
• Cytokine inhibitors
• Pro-inflammatory inhibitors

Possibly there may even be value in the use of immune-system suppression in the treatment of those with the most serious cases of SARS where death-without-a-miracle is impending.

To summarize all of the above data in a few paragraphs, it is my hypothesis that SARS provokes a profound proinflammatory response in infected individuals. Individuals who are susceptible to this type of response, i.e., ethnicities previously noted, may react to SARS coronavirus infection in a cascade of events which generally would include more Fc gamma receptor being produced which leads to more virus being uptaken which leads to more proinflammation which leads to more Fc gamma receptor being produced, etc. in a fatal feedback loop of the immune system.

Treatment of SARS for these individuals might require breaking this feedback loop of the immune system through (a) inhibiting Fc gamma receptors, (b) inhibiting cytokine production, (c) inhibiting proinflammatory responses, and, perhaps, in extreme cases, (d) inducing immune-system suppression.
The theory developed by:

Robert E. Lee, M.S., M.S.W., L.C.S.W.  April 20, 2003

Apologies to those below whom I have quoted liberally…

REFERENCES:


