munity exercises greatest control. More potent antimicrobials—defined on the basis of both antibacterial activity and mode of delivery—are less likely to promote the development of resistance than are less potent drugs. The use of macrolides to treat S. pneumoniae infection is one very clear example of this.

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References


Antiviral Pathway Activation in Chronic Fatigue Syndrome and Acute Infection

Sir—We read the very engaging report by Gow et al. [1] with the utmost interest. However, we feel that this article raises more questions than clear-cut answers regarding the hypothesis that motivated the study—that is, that the previously reported activation of the antiviral pathway in chronic fatigue syndrome (CFS) might be linked to infection rather than to CFS specifically. To verify their hypothesis, Gow and colleagues used PCR to measure the genetic expression of 3 IFN-regulated genes—namely, the latent ribonuclease (RNase L), RNA-regulated protein kinase (PKR), 2,5 synthetase, and the RNase L inhibitor (RLI)—in patients with acute infection (in their study, severe gastroenteritis; group 1), patients with CFS (group 2), and healthy control subjects (group 3).

First, surprisingly enough, although they recognized that acute infection is supposed to induce the expression of the genes selected for their study (see figure 1 of [1]), Gow and colleagues failed to find any significant increase in the expression of 2 major genes (RNase L and 2,5 synthetase) in group 1, as compared with groups 2 and 3; they observed only increased mRNA for PKR and RLI. Although it is recognized that genetic expression of PKR, RNase L, and 2,5 synthetase is under the control of interferon, RLI is definitely not [2]. Upregulation of RLI genetic expression with a normal genetic expression of both 2,5 synthetase and RNase L (although PKR is overexpressed!) during acute infection, as was observed in the study of Gow et al. [1], would indicate not only that RNase L is not activated (normal expression of RNase L and, more importantly, of 2,5 synthetase), but that it is further inhibited by an overexpressed RLI [2]. Such a scenario, if verified, would be in complete disagreement with the current understanding of the IFN pathway [3]. Therefore, we cannot help but wonder how Gow and colleagues reconcile their observations with the acute infection status of study group 1. In our view, this inconsistency severely undermines their conclusions.

Second, Gow et al. [1] do not confirm their observations of genetic expression at the translational level, which would have increased the validity of their results. Finally, the authors interchangeably used the terms “genetic expression” and “activation,” which are not necessarily interrelated notions, particularly when research involves enzymes, such as in their study. The level of genetic or protein expression of enzymes (such as PKR, RNase L, and 2,5 synthetase) is indeed not necessarily directly related to their catalytic activation, which requires the further presence of coactivators (2′,5′-oligoadenylates and polynucleotides, in this case). Unfortunately, this aspect was not investigated by Gow et al. [1], and the confusion in the authors’ minds regarding these 2 notions led them to misquote the articles by Suhadolnik et al. [4] and De Meirleir et al. [5].

Over the years, our teams have repeatedly observed an activation at the enzymatic level of the antiviral pathway in subsets of patients with CFS, comitant with the appearance of a truncated 37-kDa RNase L that was produced by proteolytic cleavage and that retains catalytic activity.
[6, 7]. On the basis of their limited observations, Gow et al. [1] challenge our observations and further deny any rational basis to our proposal regarding the use of 37-kDa RNase L detection as a biological marker for CFS [5]. In our study, which they clearly misquoted, we did not measure the enzymatic activity of the fragment and, hence, the 2-5A pathway activation, as Gow and colleagues claimed [1]. Instead, we limited our study to the quantitative detection of the 37-kDa truncated enzyme, as measured by its capacity to bind a radioactive 2-5A probe. We observed a significant increase in the 37-kDa RNase L level in patients with CFS, compared with that observed in healthy control subjects, patients with fibromyalgia, and patients with depression. Both of the latter groups are perhaps as susceptible to chronic infections as are patients with CFS, if not more so [8]. Consequently, this does not support the claim that the presence of the 37-kDa RNase L in CFS could only be imparted to residual nonspecific increases in the antiviral pathway activation [1].

More-recent data from our laboratories [9] extend the implications of our earlier observations of the biological understanding of the CFS immune dysfunction. Our data demonstrate that there is a more-comprehensive downstream cellular role for the signal transduction by IFN in the antiviral pathway [3] than what Gow and colleagues pretend to present to the readers of Clinical Infectious Diseases.

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Reply

Sir—In response to their letter [1] about our article [2], we would like to draw the attention of Dr. De Meirleir and colleagues to the following points.

Chronic fatigue syndrome (CFS) is a common disorder that may be precipitated by viral infections, among other causes [3]. Therefore, the hypothesis that there may be a defect in one of the main antiviral pathways has appeared attractive. Dr. De Meirleir and colleagues, including Dr. Suhadolinck, have addressed this hypothesis elsewhere and have reported positive findings [4, 5]. Their results have potentially huge economic and social consequences, because they provide the basis for development of a diagnostic test and possible therapy.

These researchers have reported 2 key findings, the first of which is activation of the latent ribonuclease (RNase L) antiviral pathway. To identify this activation in patients with CFS, however, it is necessary to include, for comparison, a group of patients with known viral infection. If a comparator group is not included, then changes that may be associated with the other biological roles of the system [6] will be misinterpreted. These researchers have not used such a control group, whereas, in our study, we did.

De Meirleir et al. [1] criticize our results, but it can be seen that our group of infected patients, compared with healthy control subjects, did, in fact, show greater transcription of mRNA coding for RNase L and 2,5A synthetase, with increases of ∼4.9-fold and ∼3.2-fold, respectively. These increases did not satisfy the statistical criteria that we used, but they do not in any way contradict current understanding of the IFN-inducible antiviral pathway. To infer a contradiction from a nonsignificant difference is simply an error of logic.

With regard to the second finding reported by De Meirleir et al. [4] and Suhadolinck et al. [7]—that is, a 37-kDa RNase L product is detectable in patients with CFS—both research groups have also found the protein in up to 32% of healthy control subjects. De Meirleir et al. [4] also detected the protein in 38% of patients with fibromyalgia and in 14% of patients with depression. The contentious statement that the latter groups are more likely to have experienced chronic infections than are patients with CFS is not supported by any evidence, including the findings of the study by Goulding et al. [8] cited in the above letter. The article by Goulding et al. [8] reports the prevalence of fibromyalgia, anxiety, and depression in a group of patients infected with hepatitis C virus, not the prevalence of infections in patients with fibromyalgia and depression. Thus, the interpretation given by De Meirleir and colleagues is also in error.

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