References
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Response to “Which side is nuclear factor-kappa B on in liver injury?”

To the Editors:

We thank Dr. Fujita for raising his questions and carefully explaining his thoughts. We agree with Dr. Fujita’s opinion, because the role for NF-κB activation in liver injury has been a topic of debate and many reports have focused on this issue over the past decade. NF-κB consists of a heterodimer of NF-κB (p50) and RelA (p65), which is found most commonly in the liver. Although Dr. Fujita suggested that NF-κB p50 is a molecular target of therapy, we do not agree with his thought because previous studies have concluded that p65 is the primary activating transcriptional component of NF-κB, and that other NF-κB subunits, such as p50, are expendable for function during inflammatory liver injury.

Two different roles of NF-κB have been reported in models of liver injury. One is to propagate inflammation, and the other is to exert an anti-apoptotic property in hepatocytes. As Dr. Fujita indicated, it was not determined whether suppression of NF-κB activation in response to LPS is directly related to an increase in hepatocyte apoptosis in our study. We showed that the cellular localization of NF-κB activation was identified mainly in hepatocytes by immunohistochemistry for NF-κB p65, and that the decrease in NF-κB activation was observed in hepatocytes in mice with 14 days of obstructive jaundice (OJ14) after LPS administration (LPS OJ14). This finding was consistent with the DNA binding activity and protein expression.

Regarding the pathway leading to hepatocyte apoptosis under this condition, we have reported an important role of increased expression of FasL and subsequent caspase-8 activation. In the study, the gld/gld mouse (FasL knockout) had intermediate survival. This suggests that 14 days of OJ have other effects that induce mortality that are independent of FasL. FasL and tumor necrosis factor-alpha (TNF-α) are the death signals that induce cell apoptosis. Therefore, TNF-α represents a possible candidate to cooperatively enhance apoptosis. Although TNF-α is able to elicit a potent apoptotic response, cells do not undergo apoptosis after TNF-α exposure because NF-κB opposes this response. Thus, in the current study, a decrease in NF-κB activation in LPS OJ14 mice may result in apoptosis after increased TNF-α stimulation.

We previously showed that significant hepatocyte apoptosis combined with ATP depletion caused secondary necrosis in LPS OJ14 mice. Although the question of whether NF-κB activation in hepatocytes is beneficial or harmful under these conditions is still unanswered, experimental data have unequivocally demonstrated that the inflammatory response is detrimental to hepatocytes. Early TNF-α expression and NF-κB activation is likely to lead to resistance against the harmful effects of TNF-α as suggested by Dr. Fujita. However, injured and stressed hepatocytes in LPS OJ14 mice may be less resistant to proinflammatory mediators, such as TNF-α. Therefore, if NF-κB-inducing cytokines are as robust in hepatocytes as in Kupffer cells, the overall liver injury may be increased.

Although Dr. Fujita hypothesized that the Kupffer cell function decreased in this model, previous reports have suggested that this is not the case. In our personal observations, macrophage function from OJ14 mice was not impaired after LPS stimulation in vitro. Taken together,
To the Editors:

I would like to take this opportunity to respond to the comments by Dr. Fujita1 concerning my recent evidence-based surgical hypothesis article, “Reciprocal gut-brain activation in the hepatocytes in LPS OJ14 mice caused massive hepatocyte apoptosis, leading to secondary necrosis.”

First, I would like to thank Dr. Fujita for his thoughtful comments. However, there is a need to correct a number of inaccuracies contained in his letter as well as take issue with his conclusion. Dr. Fujita states, incorrectly, that there is little evidence for cross-talk between the gut and the brain in humans. Although the number of studies in humans examining such cross-talk is small, nevertheless there are a wide and ever increasing number of studies in animals that are elucidating the extraordinary amount of cross-talk that occurs between the gut and brain, with the vagus nerve being the chief conduit of such informational exchange. That there are fewer studies in humans is fully understandable from the vantage point that the demonstration of cross-talk involves experimental manipulation that can only be applied in animal systems. There can be little reason to doubt that the demonstration of cross-talk in animal systems does not extend to humans. Furthermore, Dr. Fujita asserts in his letter that I refer to evolutionary principles applying to information flowing from a “leaky” gut. In fact, nowhere in my hypothesis article do I make this assertion, let alone even use or refer to the term “leaky gut.”

More important, I must as well take exception to Dr. Fujita’s conclusion that “the appropriate treatment of [systemic inflammatory response syndrome] SIRS may not be deducible from evolutionary considerations.” The fundamental defining aspect of SIRS, that postinjury the body initiates a set of responses that seemingly run counter to not only the individual’s own recovery but also the clinician’s sustained efforts at palliative therapy, begs the question of “why” the body would generate and maintain such a response. It would seem a reasonable supposition that, because it is the body that initiates and maintains the inflammatory condition, the answer may lie in the evolutionary programming with which the body deals with injury. As such, the question of “why” becomes paramount and one for which an approach utilizing evolutionary medicine is ideally suited.

Finally, the most salient reason why an evolutionary approach to the management of SIRS, as well as aiding in the design of new therapeutic modalities, should be considered is that the vast majority of current and experimental therapeutic approaches in the treatment of SIRS have not resulted in any major reduction in mortality and morbidity. Current and experimental treatments that are overwhelmingly based on a reductionist approach targeting specific points in the inflammatory response have not been able to circumvent the body’s overall drive to maintain the inflammatory response in the first place. Dr. Fujita’s rationale that “what is functional from an evolutionary perspective is not necessarily functional from the perspective of patients” may have some validity, but in the case of SIRS the continued high mortality and morbidity demand that new approaches be considered. Evolutionary medicine, which seeks to understand the mechanisms governing the body’s programming in response to injury, may provide the theoretical basis for understanding the shortcomings of current therapeutic modalities as well as the design of new ones in the treatment of SIRS.

References


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Response to “Pathophysiology and treatment of the systemic inflammatory response syndrome from the perspective of evolutionary medicine”

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