Monocyte: A New Player in the Pathophysiology of Herpes Simplex Virus Reactivation in ICU Patients?

Herpes simplex virus (HSV) and cytomegalovirus (CMV) are members of the Herpesviridae family, among which eight may infect humans. In ICU patients, HSV reactivation in the respiratory tract of immunocompetent patients is common; it has been detected in 19–64% of mechanically ventilated patients and may lead to HSV bronchopneumonitis (1, 2). Whereas CMV may be detected in the blood of roughly 30% of CMV-seropositive ICU patients, CMV lung reactivation is occurring less frequently, in 5–6% of mechanically ventilated patients (1, 3, 4). If several factors explaining herpesviridae reactivation in ICU patients (such as immunoparalysis, local microtrauma …) have been suggested (2, 5), the precise mechanisms that may explain herpesviridae reactivation remain to be determined.

In the present study in this issue of the *Journal*, Chaumette and colleagues (pp. 295–310) described immunological changes following acute brain injury, and linked these immunological changes to HSV reactivation and to neurological outcome (6). This study has many strengths: first, the starting point was a large subset of brain-injured patients that were sampled prospectively, and to avoid selection bias they randomly selected the samples used in their analyses; second, they used up-to-date methods and analyses, and followed a rigorous step-by-step process to identify a reorganization of a 721-genes module in the monocytes of brain-injured patients, the brown gene module (which includes PD-L1 and CD80 genes, two proteins involved in T-cell activation [7]), and whose ontogenic analysis found decreased interferon-γ–mediated and antiviral response signaling pathway. At the end, the authors are able to show that HSV reactivation occurs frequently in their brain-injured patients, that patients without HSV reactivation have a particular signature of monocyte's brown gene module (characterized by low CD80 and PD-L1 gene expression, as opposed to patients with HSV reactivation, who have "normal", or less decrease, gene expression), and that this particular signature is associated with 6-month favorable neurological outcome (defined by a Glasgow outcome scale-extended of 7 or 8). They, therefore, hypothesized that after brain injury, CD80 and PD-L1 gene expression is reduced, perhaps in a physiological adaptation way, that helps promote brain recovery, possibly via resistance to interferon-γ; patients without this adaptation may have increased HSV reactivation due to lack of adaptation of the systemic immune system. Since prophylactic or pre-emptive antiviral treatments targeting HSV or CMV failed to demonstrate a positive impact in recent trials (8–12), the present study opens the door of a more targeted approach in a specific population, namely brain-injured patients.

The authors should be congratulated for the huge amount of work they performed, for the number of data presented here, and the rigor they used in their study. However, despite being very impressive and new, the data presented here should be interpreted with caution, since several comments rise from this study.

The first limitation is the interpretation of the association between HSV reactivation and neurological outcome. Although the authors showed that HSV reactivation is independently associated with poor neurological outcome at 6 months, duration of MV and ICU length of stay are shorter in patients without HSV reactivation, which could have biased the results: in other words, patients with good neurological outcome are prone to awake more rapidly; they, therefore, may have shorter duration of MV and thus miss the opportunity of being sampled and detected as HSV reactivators. Although the authors agreed that they are unable to assess whether the association is causative or only an association, to correctly interpret this potential relationship between HSV reactivation and outcome, duration of MV should have been taken into account in this analysis.

The second comment is more a general thought on interpretation of data: although the results presented here are "statistically significant"—namely patients with favorable outcome have more frequently a reduced expression of the brown gene module—this does not give a black-or-white answer for clinicians. In other words, there may be patients with poor neurological outcome but with reduction of CD80 and PD-L1 gene expression. At the patient level, determining who is a true positive, true negative, false positive, or false negative remains challenging, and further studies should determine, if the results are confirmed, how to implement these data in a decision-making process. This thought is not specific to the present study, and clinicians should be aware of that when interpreting results of a study.

One open question raised by the present study is the relationship between brain injury and the immunological changes described here: are they specific of brain injury, or may they be observed in other conditions? Indeed, the reduced expression of the brown module genes described here may be due to ICU-induced immunoparalysis rather than brain injury itself. Although the specific monocyte signature was not found in patients with Coronavirus disease, future studies should explore expression of the brown module genes in other, less specific ICU patients, such as patients with prolonged MV (1, 2), and try to link potential modulations of this brown module with HSV reactivation. If similar results could be described in other patients, the impact of the present study would be potentially amplified.

Last, many obstacles have to be overcome before clinical implications of the present findings could emerge. Indeed, the implementation of systematic and routinely screening of brain-injured patients, looking for CD80 and PD-L1 gene expression is to date challenging, and using HSV reactivation as a surrogate marker for detecting patients with poor outcome might be hazardous.

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Despite these limitations, the data presented here are promising; they put new bricks in the understanding of immunological disorders following brain injury, in the understanding of potential relationship between these disorders and neurological prognosis of brain-injured patients, and in the pathophysiology of HSV reactivation in ICU patients. Moreover, since recent interventional studies targeting HSV or CMV in ICU patients were negative (8–12), the question of a more personalized treatment has been raised; the challenge being to determine which categories of patients may potentially benefit from an antiviral treatment. The present study clearly opens a new door by identifying a potential population that might be targeted for a prophylactic antiviral treatment. ■

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How Should the Effects of CFTR Modulator Therapy on Cystic Fibrosis Lung Disease Be Monitored?

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene leading to structural and/or functional abnormalities of CFTR, an ion channel that regulates transepithelial chloride conductance. CF lung disease is characterized by dehydration of secretions, mucus plugging of airways, inflammation, and infections leading to progressive loss in pulmonary function and, ultimately, respiratory failure (1). The CFTR modulator combination therapy elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) significantly increases CFTR function in patients with one or two CFTR F508del alleles (2) and results in remarkable clinical benefits, including improvements in nutritional status, and in relevant respiratory outcomes (3–6). In CF clinical practice, lung function is traditionally measured by spirometry and expressed as FEV_1, and percent predicted FEV_1 ($ppFEV_1$) improves with effective therapy. However, previous studies have shown that the sensitivity of FEV_1 to detect early CF lung disease is inferior to the lung clearance index (LCI), a measurement of ventilation

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