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A Grim Picture Indeed

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Aging is accompanied by numerous functional and phenotypic changes in the immune system that contribute to the increased susceptibility of elderly persons to infectious diseases, vaccine failure, autoimmune disorders, and cancer (1). While innate immunity is better preserved with aging, more detrimental age-related changes occur in the adaptive immune system. In the elderly, due to age-related involution of the thymus, the T cell compartment undergoes the most significant changes with age (2). Elderly patients have decreased numbers of peripheral naïve T cells and an expanded memory T cell population resulting in reduced antigenic diversity, a restricted T cell receptor (TCR) repertoire, reduced interleukin(IL)-2 expression, and impaired T cell expansion and differentiation into effector cells(3,4). Associated with these changes is the loss of co-stimulatory molecules such as CD28 on peripheral T cells as well as an increase in the number of CD25⁺Foxp3⁺ immunosuppressive T regulatory cells (5-7).

In an attempt to better understand the impact of age-related changes in immunity, Inoue and colleagues attempt characterize sepsis-induced changes in peripheral blood T-cell phenotypic markers in elderly patients (>65) and compare these changes to those of a younger cohort of patients (<65). As predicted, the elderly patients have a greater mortality. They find sepsis-induced increased programmed death (PD)-1 receptor expression in CD4⁺ and CD8⁺ T lymphocytes and augmented Foxp3 expression in CD4⁺ cells in elderly septic patients. Interestingly, the greatest increase in T cell PD-1 and Foxp3 expression was seen in elderly non-survivors. T cell functional activity was not evaluated. They conclude that sepsis in the elderly induces a reduction in immunocompetent lymphocytes which may contribute to the increased mortality in elderly patients; however, only age and SOFA II scores were statistically associated with mortality.

PD-1 is a co-inhibitory receptor with two known ligands, PD-L1 and PD-L2, which regulates the balance between T cell activation, tolerance, and immunopathology (8). It appears to be a promising therapeutic target in sepsis. In animal models of sepsis, PD-1 deficiency is protective from CLP-induced mortality by reducing lymphocyte apoptosis, dendritic cell depletion, and reducing IL-10 levels (9). Zhang *et al.* evaluated changes in PD-1 expression in 19 septic patients and demonstrated increased PD-1 expression in CD4⁺ and CD8⁺ lymphocytes in association with accelerated apoptosis in these cell populations (10). They further suggest a mechanism whereby PD-1 expression impacts outcome by blocking PD-1 *in vitro* and found reduced lymphocyte apoptosis. In addition, inhibition of PD-L1 resulted in enhanced macrophage function and reduced IL-10 expression. Similarly, Guignant *et al.* evaluated sepsis-induced changes in PD-1 in 64 septic patients and found

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increased monocyte and CD4+ PD-1 expression in septic patients (11). This study demonstrated impaired T cell proliferative response in septic patients and did not find any correlation between PD-1 expression and age. They concluded that monocyte PD-1 expression had the greatest correlation with IL-10 expression and mortality.

Collectively, these studies establish increased PD-1 expression in monocytes and CD4+ cells in response to sepsis and suggest PD-1 activation during sepsis mediates lymphocyte apoptosis and alters macrophage function. However, the studies by Zhang and Gorgnand do not stratify their patient populations by age at the outset and interestingly, enrolled septic patients in each study have an average age of 59 and 63 respectively. Thus, changes in PD-1 expression may be driven by age as suggested by Inoue and colleagues. Unfortunately, in the present study, no information regarding lymphocyte apoptosis or proliferative activity is provided; furthermore, changes in monocyte functionality are incompletely assessed thus providing an intriguing but partial picture at best. Further investigation into the manner in which aging affects T cell function is required.

CD25⁺Foxp3⁺ T regulatory cells play an important role in developing immunologic tolerance and prevention of autoimmune disease by limiting the activation and expansion of T cells and NKT cells in response to “self” antigens (7). With aging, the T regulator cell pool increases and is believed to detrimentally affect host defense to bacterial infection (12). In studies evaluating changes in T regulatory cells in septic patients, expansion of the T regulatory pool occurs and is associated with reduced lymphoproliferative activity (13,14). In an animal model, siRNA inhibition of Foxp3 restored proliferative activity, suggesting another mechanism whereby lymphocyte apoptosis may be influenced in septic elderly patients. Interestingly, in a study by Monneret et al, differences in T regulatory cells in survivors versus non-survivors became apparent at day 7, which correlates with the change in the survival curve for elderly patients in the present study (14). These T regulatory cell studies also did not segregate patients according to age, making the observations reported in this study by Inoue and colleagues a novel finding.

In conclusion, Inoue and colleagues paint a rather grim picture for elderly patients in whom time may fatigue components of their immune system, making them more susceptible to infection. To compound that matter, it appears sepsis results in a maladaptive response from our T lymphocytes, whereby increased PD-1 and Foxp3 expression results in an immunosuppressed or anergic lymphocyte population that is unable to participate in the fight against invading pathogens. Further investigation regarding sepsis-induced alterations in lymphocyte function over the spectrum of aging are needed to further clarify this picture; however, inhibition of PD-1 or reduction in T regulatory cells appear to be attractive therapeutic targets in the elderly.

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