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Does chronic caregiving stress accelerate T cell immunosenescence?

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It is now well understood that the human immune system undergoes considerable changes, termed immunosenescence, as part of the ageing process, resulting in an increased rate of infections and inflammation. The impact of stress is often studied in the context of such age-related changes, as detailed in this issue by Prather et al., (Prather et al., 2018). In the innate immune system, immunosenescence changes include increased levels of inflammatory cytokines and markers such as CRP, accompanied by decreased anti-inflammatory cytokines; a skewing toward myeloid cell differentiation of haematopoietic stem cells; decreased phagocytosis, intracellular killing and dysregulated chemotaxis in neutrophils and macrophages/monocytes, increased NK and NKT cells but decreased cytotoxicity (Bosch et al., 2013). In the adaptive immune system, these alterations encompass decreased production of naïve T cells, especially cytotoxic CD8+ T cells, due to thymus involution and CMV exposure, decreases in T cell activation, reduced numbers of naïve B cells, and a switch towards accumulation of memory and effector T and B cells (Bosch et al., 2013). Chronic stress is known to exacerbate these changes further and affect a range of immune cells and immune processes such as slower wound healing and reduced antibody response to vaccination (Segerstrom and Miller, 2004).

Chronic stress in ageing is regularly studied using the model of caregiving for a partner/spouse with dementia, showing such outcomes as poorer latent virus control, reduced immune cell function, slower wound healing and a reduced antibody response to vaccination (e.g., (Gouin et al., 2008) for a review) – many of the same changes shown with ageing. This raises the question of whether the chronic stress of caregiving is only observed in the context of immunosenescence, however, others have demonstrated effects on immunity in younger caregivers, specifically parental caregivers of children with developmental disabilities such as Autism (e.g., (Gallagher et al., 2009a)). This shows that the immune impairments associated with caregiving stress are not necessarily age-related and a consequence of immunosenescence, although even in younger caregiving populations, the poorest responses were shown among those at the higher end of the age range (Gallagher et al., 2009b). It is possible that for caregivers, chronic stress and ageing interact to worsen immunity. An alternative rendering of this is that the stress of caregiving actually accelerates immune ageing, such that the immune decrements displayed

are earlier immunosenescence induced by chronic stress. To test this, a range of markers of immunosenescence would need to be examined, in younger caregivers, beyond the immune outcomes known to be dysregulated by chronic stress. Prather et al., (Prather et al., 2018) have conducted such a study on 91 caregiving mothers of children with Autism Spectrum Disorder (ASD) and 88 control mothers. Markers associated with the differentiation and activation levels of CD4+ and CD8+ T cells were examined, which indicate whether such cells are naïve or effector memory cells. The shift towards greater proportions of effector memory cells and fewer naïve cells is associated with ageing, but there are mixed findings in relation to chronic stress. Given the role of CMV exposure to the ratio of naïve to effector cells (Müller and Pawelec, 2013), it is important to adjust for this as well as considering a range of psychosocial characteristics such as perceived stress levels and depressive symptoms, which are typically high but variable among caregivers and can independently relate to differences in immune function beyond caregiving status itself (Vitlic et al., 2016). In age-adjusted analyses, caregivers showed higher percentages of effector memory T cells, and lower percentages of central memory and naïve cells compared to controls, as well as a higher effector to naïve cells ratio for both CD4+ and CD8+ cells. These effects were not driven by CMV serostatus, BMI, race or antidepressant use. Although perceived stress and depression were related to caregiver group but not immune outcomes, a strong positive association for self-reported parental stress and CD4+ effector memory cells withstood adjustment for covariates, although it was not revealed to be a significant mediator.

What these findings imply is that, independent of age itself, the chronic stress of caregiving is sufficient to progress some indicators of immunosenescence among younger caregivers. This accumulation of these cell types potentially means that their immune system is less well equipped to respond to novel antigens (Grubeck-Loebenstein et al., 2009), which ties in with observations in other studies of younger parental caregivers (Gallagher et al., 2009a,b). This finding is novel, given that earlier research in this group has focused on older caregivers who already have immunosenescence. The higher numbers of central memory cells in caregivers is less clear, although it could potentially indicate fewer cells available to differentiate into effector cells, which might reduce the ability to fight infection, and certainly implies that the majority of T cells within caregivers are further down the

differentiation pathway, as would be expected in an older population. Caution must be taken when examining changes in cell numbers, as these do not necessarily reflect lower availability, but possibly a change in circulation and distribution of cell subtypes. However, such changes do still indicate a shift similar to that observed with immunosenescence alone.

Further, it seems that it is the impact of the specific stress experienced by caregivers which was associated with this shift, such that parental stress attenuated the association between caregiver status and effector cell number. This moderation by parental stress adds to our understanding of how specific aspects of caregiving influence immunity, given that other studies of younger caregivers have shown immune effects to be mediated or moderated to an extent by child challenging behaviours (Gallagher et al., 2009b). It is possible that the exact psychosocial mechanism of how caregiving influences immunity differs across sub-populations, and that other key factors also play a role such as reduced social support. Measurement of these factors gives direction for potential interventions to ameliorate these immune effects. Further, to fully support the notion that younger caregivers' stress puts them at risk of earlier indications of immunosenescence, the measurement of markers of further ageing and differentiation of T cells, such as the loss of CD28, as well as functional measures, such as T-cell proliferative ability, would be important to study in parallel.

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