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INFECTION

Virus boosts protection

> CMV infection seems to improve the serological response to an influenza virus vaccine

Cytomegalovirus (CMV) commonly causes persistent asymptomatic infection in healthy humans; however, in immunocompromised individuals it can reactivate and cause serious illness. The effect of CMV infection on immune responses in healthy individuals is unclear, but it has been suggested to promote immunosenescence. Reporting in *Science Translational Medicine*, Furman *et al.* show that CMV infection does not seem to alter immunity in healthy older individuals, but instead has a beneficial effect on the immune responses of healthy young adults to an influenza virus vaccine.

To investigate the impact of age and CMV infection on immune responses, the authors analysed peripheral blood from 91 healthy young and older individuals, aged 20–30 and 60–89 years, respectively. The changes associated with CMV latency and ageing were determined for 236 immunological parameters. Similar to previous results, ageing was associated with marked down-regulation of cell function, including decreased expression of genes associated with the cell cycle, protein synthesis, and cholesterol and lipid metabolism. However, the immunological profiles of CMV-infected older individuals could not be distinguished from those of uninfected older individuals. By contrast, CMV infection in young adults was associated with an upregulation of immune biomarkers, including interleukin-13 and interferon-γ (IFNγ). Of note, individuals infected with Epstein–Barr virus — which is another herpesvirus — did not show these changes. Thus, CMV infection does not seem to influence immune responses in older individuals, but instead contributes to the activation of immune responses, such as cytokine production, in younger adults.

Vaccination is less effective in elderly people, but whether this is influenced by CMV infection is unclear. To investigate this further, the authors used a seasonal trivalent inactivated influenza virus vaccine and examined the antibody responses to influenza virus at days 0 and 28 post vaccination. As expected, age had a negative effect on antibody responses, but there was no difference between CMV-infected and uninfected individuals. However, in young adults, the antibody responses to the influenza virus vaccine were higher in CMV-infected individuals than in uninfected adults. Hence, CMV infection seems to improve the serological response to an influenza virus vaccine.

Finally, the authors investigated whether their observations could be modelled in mice. Indeed, mice infected with murine CMV (MCMV) for 5–12 weeks before infection with influenza virus showed increased protection compared with mock-infected mice. However, these effects were lost in older mice exposed to long-term (9 months) MCMV infection. The cross-protective effect of MCMV infection in younger mice seems to be mediated by IFNγ, as MCMV-infected IFNγ-deficient mice showed higher influenza virus burdens and lower influenza virus-specific immune responses than control mice.

In summary, this study shows that CMV infection has no apparent effect on immunosenescence or the immune response to influenza virus vaccination in older individuals. Instead, CMV infection enhances the immunity to influenza virus in younger adults and in mice. This could explain why CMV infection is abundant in humans and many other species.

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ORIGINAL RESEARCH PAPER Furman, D. *et al.* Cytomegalovirus infection enhances the immune response to influenza. *Sci. Transl Med.* **7**, 281ra43 (2015)