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# **Roles for Cytomegalovirus in infection, inflammation and autoimmunity**

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## **Summary**

Cytomegalovirus is a common herpes virus with a large genome dedicated primarily to immune evasion and manipulation rather than simple viral replication. The range of inflammatory and autoimmune conditions influenced by this virus are explored. Inflammation is explored in detail because the suspicion is that inflammation is in many cases the precursor to autoimmunity. A range of autoimmune and other cases are explored which provide a backdrop for the wide reaching influence of this virus in humans. Somewhat intriguingly a repeating series of infectious-like outbreaks of a subtle condition which creates a set of immune impairments highly reminiscent of the infection, inflammation and autoimmune effects of cytomegalovirus will be explored with a view to providing insights into how the timing of these outbreaks may be relevant to the longitudinal study of autoimmune initiation and symptom exacerbation.

## **Key Words**

Infectious outbreak, cytomegalovirus, CMV, inflammation, immune impairment, autoimmunity, sub-acute infection, endothelial tissue, vitamin D, hospitalization, death, health care costs.

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## **Introduction**

As the chapters in this book amply demonstrate autoimmunity is a multi-factorial issue involving infection, inflammation, genetic and epigenetic factors interacting with the environment. In this respect there is now increasing evidence for a series of infectious-like outbreaks which are largely restricted to a cluster of medical diagnoses centered on immune impairment, namely infection and inflammation and with profound effects upon the health services<sup>1-24</sup> The last three of these outbreaks center around the years 2002, 2007 and 2012 with comprehensive reviews providing greater detail.<sup>1-2</sup>

The ubiquitous herpes virus cytomegalovirus (CMV) has been tentatively implicated in these outbreaks,<sup>1-2</sup> and this adds a further dimension to the accumulating literature dedicated to the formidable array of immune evasive and modulatory effects exerted by this resourceful virus. The inflammatory and autoimmune effects of CMV have already been the topic of three comprehensive reviews<sup>25-27</sup> and the aim of this chapter is to address issues not covered in these reviews.

## **Roles for Cytomegalovirus**

Infection with CMV increases with age, poverty, overcrowding and multiple sexual partners.<sup>28-32</sup> Around 10% of western populations may be resistant to infection, however, this is not the case in Black African, Chinese and Japanese populations, especially in females.<sup>29-32</sup> Until around 5 years ago this virus was considered largely innocuous except to the immune impaired, HIV/AIDS, transplant recipients, the developing fetus, etc. This failed to explain the constant (and increasing) stream of hospital case reports where CMV was directly involved in hospital admission and death in the supposedly immune competent population. The study of Rafailidis et al<sup>33</sup> uncovered some 273 such case studies up to 2007 and the online resource [www.casesdatabase.com](http://www.casesdatabase.com) reports a further 750 case studies between 2009 and 2013. CMV is now widely recognized as a serious risk factor in the intensive care and burns units<sup>34-39</sup> and in those with bacterial sepsis and septic shock.<sup>40-41</sup>

Around 2005 to 2008 several groups started publishing reviews of the evidence for the involvement of CMV in auto-immune disease<sup>25-27,42</sup> and this has since been further augmented.<sup>43-</sup>

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<sup>44</sup> A number of population studies have demonstrated that CMV is associated with >20% increases in mortality, and when accompanied by high antibody levels or elevated markers of inflammation, such as C-reactive protein (CRP) possibly more than a 40% increase in mortality in the elderly.<sup>45-48</sup> Clearly this virus is capable of causing a major infectious outbreak and even if it is not the source of the outbreaks of the infectious immune impairment it is capable of causing serious impairment to health in its own right.

As a focus for the wider discussion in this chapter Table 1 presents a random sample of CMV studies in the areas of infection, inflammation and autoimmunity with a particular emphasis on autoimmunity. Only confirmed autoimmune studies are in the 'Autoimmune' section of Table 1 and it is likely that some of the other studies have an autoimmune component. The studies in this Table are by no means comprehensive; however, they give a rapid overview of the wide-spread impact of this virus as either causative or opportunistic pathogen. The studies have been grouped under section headings for the areas where CMV is most active with a broad outline of the section supplemented by relevant cases. Points to note are widespread infection of multiple variants of endothelial tissue, diseases involving long-term inflammation and the fact that it is sometimes difficult to draw the line between where inflammation ends and autoimmunity begins. Reference back to this table will be made throughout the text. The reader is advised to refer to other reviews covering wider CMV biology.<sup>156-165</sup>

### **Key Features on CMV Biology**

CMV biology has a number of key features which are central to understanding its powerful disease effects. These will now be briefly outlined and are more fully explained elsewhere:<sup>1-2</sup>

1. Action is via multiple strains with different infectious potential.
  - a. Superinfection with multiple strains leads to the worst clinical outcomes.
  - b. Joint infection with other pathogens leads to worse clinical outcomes.
2. These multiple strains exploit multiple immune impairments
  - a. So-called immune competent individuals have multiple (exploitable) temporary through to semi-permanent immune impairments.
  - b. Trauma, wounds, surgery and other infectious agents create a further layer of exploitable immune impairments.

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**Multiple CMV strains**

**All-cause Mortality**

**Immune Modulation**

**Inflammation**

**Autoimmunity**

**Nutrition & Deprivation**

**Race, Genetic & Epigenetic Factors**

**Vitamin D and the Thymus**

**Year-of-birth Effects**

**Disease Time Cascades**

**Role of Gender**

**Conclusions**

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