Is cytomegalovirus infection causative for coronary heart disease?

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Coronary heart disease (CHD) is the leading cause of death in Australia, representing 16% of all deaths registered in 2009. Atherosclerosis is the major pathological process involved in CHD that usually leads to a clinical condition such as acute myocardial infarction or angina. Epidemiological studies have indicated cigarette smoking, family history, diabetes, hypercholesterolemia and hypertension as independent risk factors for CHD; however, a considerable proportion of patients do not have these classical risk factors. Chronic infections with bacteria and viruses, including cytomegalovirus (CMV), have been proposed to play causative roles in the pathogenesis of CHD. Detection of CMV in atherosclerotic plaques, seroepidemiological data and *in vitro* and animal experiments suggests evidence for a direct role (viral presence in atherosclerotic plaques, increased LDL uptake and proliferative activity in CMV-infected arterial smooth muscle cells, upregulation of inflammatory cytokines in vascular endothelial cells), as well as an indirect role (viral presence in uninvolved aortic tissue of surgical patients, systemic upregulation of cytokines) for CMV infection in the development of CHD.

Several lines of evidence exist that implicate microbial agents, including CMV, in the pathogenesis of CHD. CMV is a highly prevalent herpes virus, with 40–80% of Australians seropositive for the virus, and the prevalence of seropositivity increases with age[1]. Once acquired, CMV can establish a latent infection in the host that persists for a lifetime and may undergo periodic reactivation, especially in immunocompromised individuals[2].

Evidence for CMV as a potential atherogenic agent came from the detection of CMV antigens and virus-specific nucleic acid sequences in cells derived from atherogenic plaques of patients with severe arterial disease[3,4]. This observation was supported by higher prevalence of CMV genome in the coronary arteries of patients with severe atherosclerosis (90%) compared with specimens taken from patients with mild or no atherosclerosis (50%)[5]. Furthermore, CMV DNA was detected in early lesions of atherosclerosis in young trauma victims without symptomatic disease[6]. These observations suggest the human arterial wall might be the site of latency for CMV, and reactivation of the virus could have direct effects on the components of the vascular wall and subsequent development of atherosclerotic lesions. There is supportive evidence for an indirect role of CMV infection in CHD since viral DNA was also detected in uninvolved aortic tissues of patients undergoing surgery for symptomatic atherosclerotic disease as well as in matched controls[7,8]. More recently, Liu and colleagues investigated the coronary plaques of acute CHD patients using CMV-specific immunohistochemical staining and observed a significantly higher number of CMV-positive cells in specimens from patients with severe CHD, compared with patients with stable angina[9], indicating the contribution of CMV infection to the severity of the disease. However, other studies have reported lack of evidence for CMV involvement in atherosclerotic tissue[10,11]. Kol *et al.*[12] assessed the expression of CMV MIE gene mRNA as an early marker for viral replication in coronary atherectomy specimens, but reported the absence of active CMV replication within these tissues, suggesting CMV might be localised within the vessel wall without being involved in the pathogenic process of CHD.

Seroepidemiological studies also suggest that CMV seropositivity is associated with an increased risk of CHD. Danesh and colleagues reviewed several seroepidemiological studies and reported a positive correlation between CMV antibodies and cardiovascular disease[13]. However, evidence for the contribution of CMV to cardiovascular disease in these studies is weakened by small sample sizes, incomplete adjustment for known confounders, as well as focusing mainly on restenosis and transplant atherosclerosis rather than classic CHD. Recent meta-analysis involving six prospective and 49 retrospective case-control studies found that CMV infection was associated with an increased risk for CHD in both prospective and retrospective studies, as well as in Asian and non-Asian

populations[14]. Furthermore, evidence also exists for the measurement of high titre CMV antibodies as a risk factor for increased intimal-medial thickening[15] and increased incidence of coronary artery disease and myocardial infarction[16,17]. Large-scale prospective studies, with careful consideration of confounding factors (other risk factors for CHD) should be carried out to confirm the significance of these earlier findings.

In vitro experiments involving vascular smooth muscle cell (SMC) cultures showed CMV infection was associated with increased uptake of oxidised LDL[18]. Also, CMV infection of human coronary artery SMCs resulted in increased expression of platelet-derived growth factor receptors and increased proliferative activity of SMCs, which could lead to the development of atherosclerotic lesions[19]. In addition, CMV can prevent p53-mediated apoptosis of coronary artery SMCs, leading to accumulation of SMCs[20]. Furthermore, CMV-induced upregulation of intercellular adhesion molecule-1 was demonstrated in human coronary artery endothelial cells, which could facilitate adhesion and migration of macrophages into the vessel wall[21]. CMV infection has also been demonstrated to induce inflammatory cytokines (TNF-α, IL-1β, MCP-1) and trigger procoagulant activity in vascular endothelial cells[22], thereby contributing to proatherosclerotic effects. Elevated cytokine expression, specifically TNF-α, has been well demonstrated to play an important role in reactivation of latent CMV[23], and therefore might lead to increased reactivated virus in the circulation as well as continual reactivation of the virus in the vascular wall for accelerated progression of CHD.

In experiments involving animal models, ApoE knockout mice infected with murine CMV (MCMV) showed larger area lesions in the aortic arch (approximately 2.5 fold at 20 weeks post-infection) compared with mock-infected mice[24]. In addition, increased vascular wall and plasma cytokine (TNF-α, IFN-γ) levels were detected in the infected mice[24–26], which might contribute to the accelerated progression of atherosclerotic process. Induction of local and systemic immune response by MCMV also suggests an indirect effect of the virus on the atherosclerotic process could be equally important as a direct effect observed. In another mouse model, feeding with atherogenic diet and infecting with MCMV resulted in a significant increase in arterial blood pressure, which was independent of atherosclerotic plaque formation in the aorta[27]. Interestingly, Vliegen *et al*. demonstrated that injection of UV-inactivated MCMV was sufficient to aggravate atherosclerosis in hypercholesterolemic mice[28], indicating inflammatory response to viral envelope components rather than active viral replication might contribute to observed atherosclerotic effects. This observation also supports earlier findings that CMV presence in the vascular might be enough to trigger acceleration of atherosclerotic process, without necessarily requiring active viral replication. Taken together, *in vitro* and animal experiments suggest strong molecular evidence for the role of CMV in the major phases of atherosclerosis and CHD. However, the ubiquitous nature of CMV infection means careful interpretation is needed for epidemiological and serological studies in particular. Given the potential impact of CMV on the development of CHD, molecular and pathogenesis research will be of significant interest.

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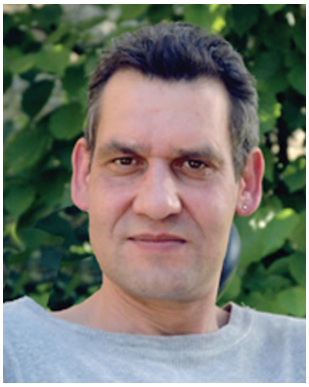
Biography

Zin Naing joined the Virology Research Lab (VRL) in 2007 and completed a year of honours with research into determination of viral and host factors influencing the outcome of human cytomegalovirus (CMV) infection in liver transplant recipients. After completion of his degree, he worked as a full-time research assistant for 3 years at VRL until commencing his PhD. Zin's research is focusing on the role of CMV genetic variation on infection of the human placenta and alteration of immune response within placental tissue. This research will (i) determine the role CMV cellular tropism genes on infection of placental trophoblast cells, and (ii) determine the role of CMV (immediate-early, early, late) gene products on induction of inflammatory cytokines during infection.

Subversion of immunity by schistosomes



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Chronic parasitic disease affects millions of people worldwide. Helminth infections are seldom fatal but cause chronic disease that may range from asymptomatic to debilitating. One of the hallmarks of the immune response to parasitic infections is the tendency to suppress inflammation and control tissue damage. The overall effect of this is not only to reduce or inactivate the activities of the parasite, but even to skew immune responses to other infectious agents. This article discusses the state of our understanding of the complex regulation and control of immune responses induced by schistosomes.

Schistosoma: an important neglected pathogen

With an estimated 1 billion people infected with one or more helminths in the developing world[1], the global burden of helminthic diseases exceeds that of better known infectious diseases like HIV/AIDS (34 million)[2], tuberculosis (9 million)[3] or malaria (225 million)[4]. However, many helminthic diseases are neglected and difficult to control, as available drugs are not always effective and do not provide protection from reinfection. Since 30 January 2012, the London Declaration on Neglected Tropical Diseases[5] represents a new, coordinated programme aiming to control or eliminate 10 neglected diseases by the end of the year 2020.