Mononucleosis in the Laboratory

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(See the articles by Balfour et al. and Woodberry et al., on pages 1505–12 and 1513–24, respectively.)

Laboratory investigation of infectious mononucleosis long preceded any knowledge of the etiologic virus [1]. The characteristic mononuclear leukocytosis associated with Pfeiffer glandular fever was reported in 1920. Heterophile antibodies were recognized 12 years later [2]. A specific viral link was established only after the serendipitous observation that a technician recovering from infectious mononucleosis had seroconverted to Epstein-Barr virus (EBV) [3]. A series of studies shortly thereafter confirmed the association.

In more recent years, a great deal of effort has focused on the viral genome, structure and function of the virion, and aspects of gene regulation, particularly lymphocyte-immortalizing and growth-transforming properties and association with various types of tumors—including Burkitt lymphoma, nasopharyngeal carcinoma, posttransplantation lymphoma, Hodgkin lymphoma, AIDS lymphoma, nasal lymphoma, leiomyosarcoma in immunocompromised patients, and gastric carcinoma [4]. In this issue of the Journal of Infectious Diseases, 2 investigations of the laboratory correlates of infectious mononucleosis are presented. One is focused on measurement of viral copy number [5], and the other is focused on the cellular immune response to viral antigens [6].

In considering the study by Balfour et al. [5] of viral copy number in association with infectious mononucleosis, it must be remembered that measurements of viral copy number may reflect the presence of latent or lytic infection or both (figure 1). Thus, latently infected B cells harbor double-stranded viral episomes, and the measurement of viral copy number in blood may simply reflect the number of latent episomes in B cells. But B cells may also support lytic cycle replication, and viral copy number may therefore reflect virion production. In cell-free blood (serum or plasma), encapsidated viral genomes (virus) may be detected. But viral DNA may be also be released without the protective virion capsid or envelope from latently infected cells, most notably tumor cells undergoing apoptosis.

In patients with nasopharyngeal carcinoma, EBV DNA is detected in high copy numbers in serum or plasma but not in mononuclear cells [7–11]. Pretreatment viral copy number in cell-free blood is an important adverse prognostic factor, as is the persistence or recrudescence of high copy numbers of viral DNA in serum or plasma. Evidence that the viral DNA in serum or plasma is predominantly tumor derived includes its rapid disappearance after surgical excision of the tumor (a rare procedure) and its somewhat slower disappearance, after a transient increase, with radiation therapy (a standard approach). Sensitivity to DNase digestion suggests that the DNA is not encapsidated, and its fragmentation pattern suggests that it is released from cells undergoing apoptosis. The situation in nasal lymphoma, gastric carcinoma, and Hodgkin disease appears to be similar.

In posttransplantation lymphoproliferative disease, viral DNA is also detected in high copy numbers in peripheral blood mononuclear cells (PBMCs) and in cell-free blood [11–13]. Viral copy numbers in PBMCs are accounted for by a large increase in the number of latently infected
lysis of oropharyngeal epithelial cells, an inflammatory response to viral infection, or both is not clear. Similarly, whether the hepatitis that commonly accompanies infectious mononucleosis is caused by an infection of hepatocytes or misguided immune responses is unknown.

The immune response during infectious mononucleosis is characterized by the presence of activated lymphocytes (primarily CD8+ cytotoxic T lymphocytes). Although the possibility that this expansion might be the result of a superantigen-driven process has been entertained, analysis of the diversity of antigen receptors favors the idea that these T cells are antigen specific [15]. Woodberry et al. [6] present what is to date the most comprehensive study of the evolution of the cellular immune response over time and comparisons of the response in HLA-matched siblings with and without a history of infectious mononucleosis. Their results point to no sustained difference in the cellular immune response that accompanies symptomatic primary EBV infection, although, as they acknowledge, there is much more work to be done.

References