Transmissible spongiform encephalopathies are accompanied by the accumulation of a pathologic isoform of a host-encoded protein, termed prion protein (PrP). Despite the widespread distribution of the cellular isoform of PrP (protease-sensitive PrP; PrP-sen), the disease-associated isoform (protease-resistant PrP; PrP-res) appears to be primarily restricted to cells of the nervous and lymphoreticular systems. In order to study why scrapie infection appears to be restricted to certain cells, we followed acute and persistent PrP-res formation upon exposure of cells to different scrapie agents. We found that, independent of the cell type and scrapie strain, initial PrP-res formation occurred rapidly in cells. However, sustained generation of PrP-res and persistent infection did not necessarily follow acute PrP-res formation. Persistent PrP-res formation and scrapie infection was restricted to one cell line inoculated with the mouse scrapie strain 22L. In contrast to cells that did not become scrapie-infected, the level of PrP-res in the 22L-infected cells rapidly increased in the absence of a concomitant increase in the number of PrP-res-producing cells. Furthermore, the protein banding pattern of PrP-res in these cells changed over time as the cells became chronically infected. Thus, our results suggest that the events leading to the initial formation of PrP-res may differ from those required for sustained PrP-res formation and infection. This may, at least in part,
explain the observation that not all PrP-sen-expressing cells appear to support transmissible spongiform encephalopathy agent replication.