CHAPTER 3

Structure, Function, and Antigenicity of the Hemagglutinin of Influenza Virus

S. A. WHARTON, W. WEIS, J. J. SKEHEL, AND D. C. WILEY

I. INTRODUCTION

The major surface glycoprotein of influenza virus is hemagglutinin (HA). This chapter reviews the two major functions of HA: (1) its involvement in binding to receptors on cells before their infection, and (2) its role in the fusion of viral and endosomal membranes, necessary for the release of the viral genome into the cell. In addition, HA is the viral antigen that interacts with infectivity-neutralizing antibodies; alterations in the molecule enable the virus to escape immune surveillance and cause epidemics of disease. The nature of these changes in antigenicity is discussed.

II. STRUCTURE OF HEMAGGLUTININ

Hemagglutinin is synthesized in the rough endoplasmic reticulum (RER) of infected cells as an uncleaved precursor, HA₀. During passage to
the plasma membrane, the molecule is glycosylated in several positions (seven in the case of the Hong Kong HA) and is cleaved by unidentified host cell protease(s). Cleavage is essential for infectivity (Klenk et al., 1975) and results in two polypeptides, HA$_1$ (328 residues) and HA$_2$ (221 residues), which are disulfide linked to form subunits associated non-covalently as trimers. The carboxy-terminus of HA$_2$ anchors each monomer in the virus membranes with the 15 C-terminal residues on the cytoplasmic side. It is unclear whether this region is important in controlling intracellular transport (reviewed by Matlin, 1986) or virus assembly. Bromelain digestion cleaves HA on virus membranes at HA$_2$ 175 and results in the release of the entire ectodomain (BHA) as a soluble trimer (Brand and Skehel, 1972). The three-dimensional structure of X31 BHA has been determined to 3 Å by X-ray crystallography (Wilson et al., 1981).