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MOLECULAR BASES OF SENDAI VIRUS PATHOGENICITY: HOST PROTEASES FOR PROTEOLYTIC ACTIVATION OF PROGENY VIRUSES AND VIRUS BUDDING DOMAIN AT THE PRIMARY INFECTION SITE

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Sendai virus is a murine parainfluenza virus type 1. Post-translational proteolytic cleavage of the F protein by host protease is required for Sendai virus to express infectivity. Progeny virus produced in tissues where suitable protease(s) is present regains infectivity and subsequently undergoes multiple cycles of replication, leading to pathological changes. If such a protease is not available, progeny virus remains noninfectious. Therefore, tissue tropism and pathogenicity of Sendai virus is determined by availability of such proteases in a given organ.

Wild-type Sendai virus (WT) is exclusively pneumotropic in rodents. WT progeny virus recovered from the lung is in the activated form with cleaved F protein, indicating that a virus-activating protease is present in the lung. We have found that tryptase Clara, a trypsin-like protease secreted by the Clara cells of rat bronchial epitheliums to the airway lumen, is a principal protease for activation of WT virus. Together with the fact that progeny viruses produced in various organ culture systems remain nonactivated, tryptase Clara, that is restricted to the bronchial epithelium, is a host factor responsible for pneumotropism and pulmonary pathogenicity of WT Sendai virus.

On the other hand, pulmonary surfactant, a phospholipoprotein complex also secreted by the Clara cells as well as type II alveolar cells, is a specific inhibitor of tryptase Clara. Intranasal infection of rats with Sendai virus was found to stimulate secretion of the protease and to decrease the amount of surfactant in the bronchial lumen within 12 h p.i. These results suggest that viral infections produce a condition favorable for activation and multiplication of progeny virus in the lung. Such regulation of host factors might be involved in pulmonary pathogenesis of Sendai virus infection.

We have isolated a protease-activation mutant, F1-R, of Sendai virus. In contrast to pneumotropism of WT virus, F1-R causes a systemic infection in rodents. Whereas the F protein of WT can be cleaved by tryptase Clara present only in the lungs, F1-R F was cleaved by ubiquitous host proteases in various organs due to an amino

acid exchange, S(115) to P, at the cleavage site. The enhanced cleavability of F protein is, therefore, a determinant for pantropic property of F1-R.

Budding of WT is restricted to the apical domain of the bronchial epithelium, whereas F1-R buds bipolarly at the apical and basolateral domains. The latter has been attributed to mutations in the M protein, resulting in impairment of cellular polarity due to disruption of microtubule network. Comparative analyses of WT, F1-R and mutants with various combinations of phenotypes (cleavability of the F protein and budding domain) revealed that apical budding by WT is responsible for the localized infection in the lungs, while bipolar budding by F1-R is required for the systemic spread of the virus. Therefore, budding polarity at the primary target of infection is an additional important determinant of organ tropism of Sendai virus in rodents.

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