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Review

Understanding and altering cell tropism of vesicular stomatitis virus

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ABSTRACT

Vesicular stomatitis virus (VSV) is a prototypic nonsegmented negative-strand RNA virus. VSV's broad cell tropism makes it a popular model virus for many basic research applications. In addition, a lack of preexisting human immunity against VSV, inherent oncotropism and other features make VSV a widely used platform for vaccine and oncolytic vectors. However, VSV's neurotropism that can result in viral encephalitis in experimental animals needs to be addressed for the use of the virus as a safe vector. Therefore, it is very important to understand the determinants of VSV tropism and develop strategies to alter it. VSV glycoprotein (G) and matrix (M) protein play major roles in its cell tropism. VSV G protein is responsible for VSV broad cell tropism and is often used for pseudotyping other viruses. VSV M affects cell tropism via evasion of antiviral responses, and M mutants can be used to limit cell tropism to cell types defective in interferon signaling. In addition, other VSV proteins and host proteins may function as determinants of VSV cell tropism. Various approaches have been successfully used to alter VSV tropism to benefit basic research and clinically relevant applications.

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1. Introduction

Viral tropism commonly refers to the specificity of a virus for a particular cell type, tissue, organ or species. Here, we define cell tropism as the specificity of VSV for cell types supporting virus infection, replication and production of infectious progeny. Understanding viral tropism is important for basic virology, but also for development of effective gene therapy, vaccines and oncolytic virus therapies. This review focuses on the cellular tropism of vesicular stomatitis virus (VSV), one of the best-studied RNA viruses, which is extensively exploited in various applications.

Studies of virus cell tropism reveal not only viral but also host components, which if present or absent may provide a hospitable environment for the virus life cycle (Fig. 1). Permissive cells usually contain required factors for virus attachment, entry, biosynthesis and exit, but lack effective antiviral mechanisms. The complex interaction of viral and host components determines the rates of infection, replication, and production of progeny. Understanding

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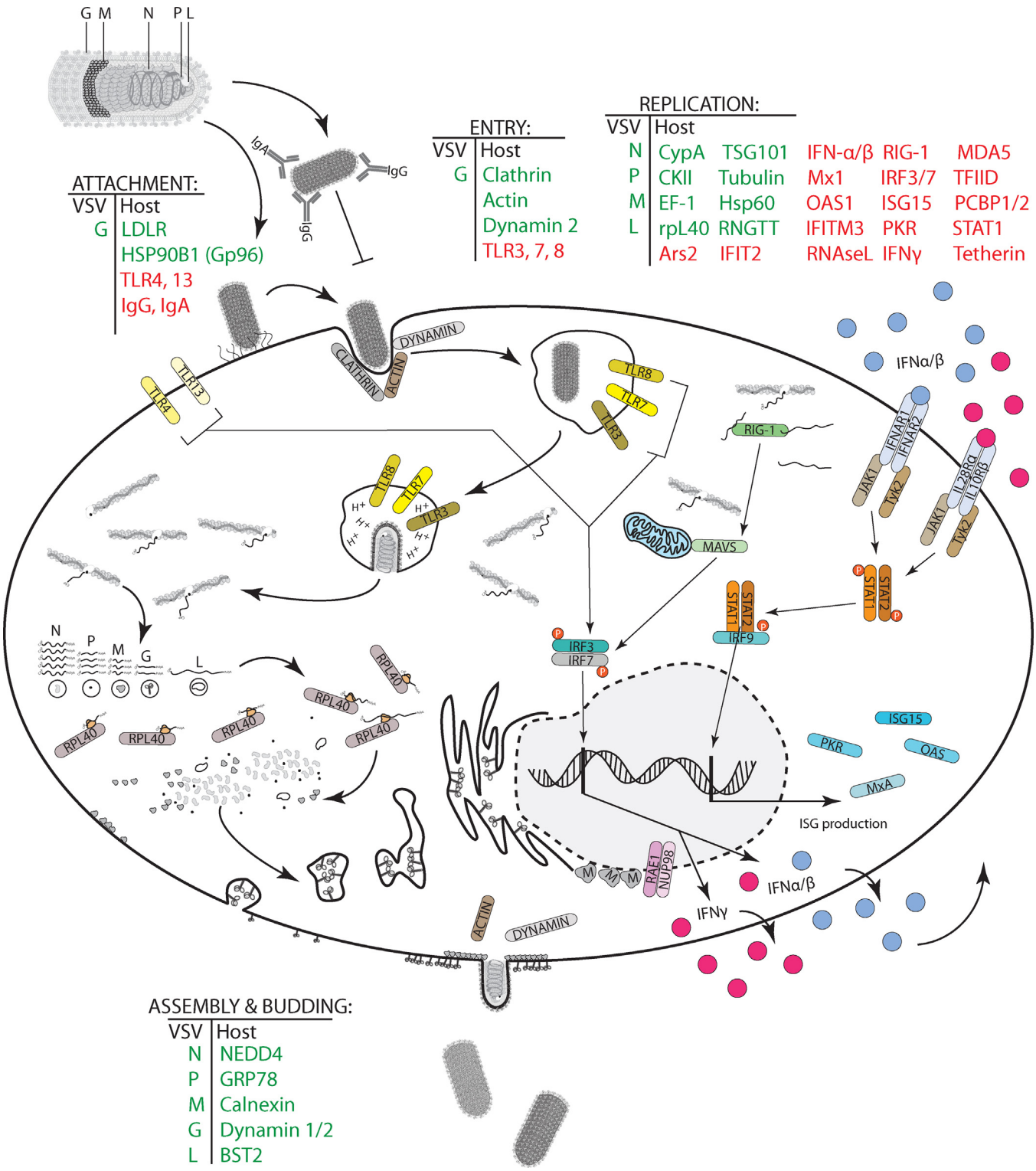

Fig. 1. Known and putative determinants of cell tropism of VSV. Host and viral proteins are involved (positively or negatively) in VSV infection and replication. Different viral and host proteins are involved in VSV attachment, entry, replication, assembly, or release. Proteins known to be involved in the VSV life cycle are shown at each step: green indicates viral or host proteins known to assist VSV while red indicates putative host proteins as well as host proteins responsible for an antiviral response.

these interactions helps to develop various strategies to manipulate VSV tropism.

VSV is a prototypic, non-segmented negative sense RNA virus (order *Mononegavirales*, family *Rhabdoviridae*). Five genes are encoded by the 11-kb VSV genome: nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G), and large polymerase (L). All 5 gene products assemble to create an enveloped, bullet-shaped virion that measures approximately 185 nm × 75 nm (Ge et al., 2010). In addition to G, an attachment protein, that enables infection of very wide range of cells, other VSV proteins may also play roles in directing VSV tropism, including evasion of the innate immune response and interaction with host factors (discussed later). VSV's broad cell tropism, relative independence on cell cycle, rapid replication, high virus yields,