

Structures of Two Semaphorin-Plexin Complexes Reveal a Basis for Repulsive Guidance Cue Recognition and Viral Mimicry

Semaphorins were discovered as axon guidance molecules that steer the nerve growth cones by repulsion. Over the years, they were found to be path-finding controls for not only the nervous system, but for the vascular system as well, and are critically involved in a wide range of physiological functions in development. There are two families of receptors for Semaphorins: the signaling receptors are called Plexins, and the co-receptors required for the signaling of certain groups of Semaphorins are called Neuropilins. Among the ~30 types of Semaphorins, a subset of Semaphorins are active in the immune system, and are designated as “immune Semaphorins” (for

distinction from Semaphorin’s classical role in the nervous system). Sema7A, one such “immune Semaphorin”, modulate a variety of immune responses ranging from thymic selection to B cell homing [1] through its receptor PlexinC1 [2]. Poxviruses have evolved proteins that engage the immune Semaphorin/Plexin system, presumably to enhance virus survival in the host. The most well characterized examples derive from Vaccinia virus (the virus used as smallpox vaccine) virus, which encode secreted Semaphorin homologues A39R. A39R also binds to, and activate PlexinC1 [3], playing an immunomodulatory role by mimicking Sema7A.

The crystal structures of the Sema7A/PlexinC1 complex, and the free viral Semaphorin A39R, and the A39R/PlexinC1 complex, were determined at 2.0-2.4 Å resolutions using data collected at APS and SSRL.

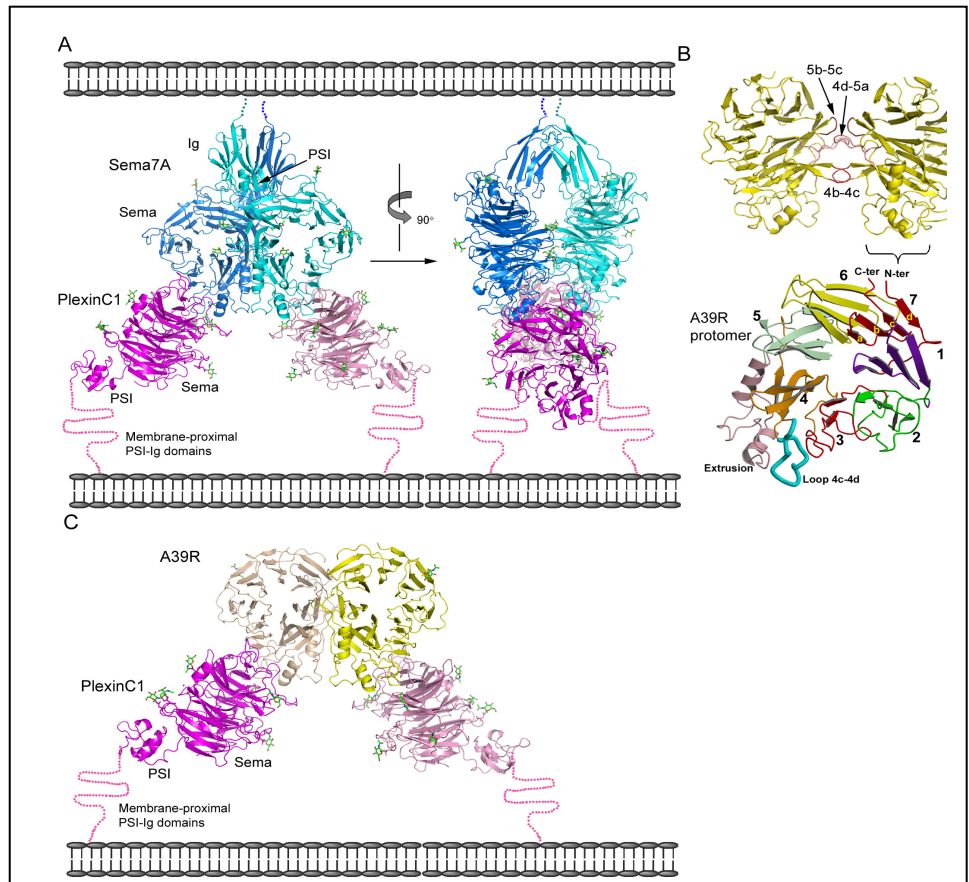


Figure 1. Structures of the Sema7A/PlexinC1 complex, the free viral Semaphorin A39R, and the A39R/PlexinC1 complex. (A) Ribbon models of the Sema7A/PlexinC1 complex in front view (left) and side view (right), with the Sema7A protomers colored in cyan and blue, and the PlexinC1 protomers in pink and magenta. The N-linked glycans are depicted as sticks with carbon atoms colored in green. A cartoon of a membrane is drawn above and below the complex to indicate where the respective proteins would be attached to the cell surfaces. (B) Ribbon model of an A39R dimer (top) and an A39R protomer from the free A39R dimer. (C) Ribbon model of the A39R/PlexinC1-Sema-PSI complex in front view (left) and side view (right), with the A39R protomers colored in yellow and wheat, and the other components colored similarly to panel A.

These structures revealed the basic architecture of a Semaphorin-Plexin recognition complex, which feature a head-to-head docking mode. In the complexes, the Sema domains, the largest domains in both Semaphorins and Plexins, whose shape resembles a 7-bladed propeller, interact "edge-on" using their sides to contact one another, with an orthogonal orientation. The edge-on, orthogonal stacking of the respective propellers in the Semaphorin-Plexins interfaces can be divided into three principal regions: a protruding loop of Semaphorins inserting into the groove on PlexinC1, and two face-to-face contacting areas flanking the "loop-in-groove" interaction.

The structures suggest that the poxvirus Semaphorin A39R, built on a smaller scaffold, has used a limited set of key, highly coincident amino acid contacts to evolve an efficient binding with PlexinC1. There is obvious structural conservation of the centrally located loop-in-groove interaction, and there is mimicry of an array of peripheral interactions, especially a cluster of salt bridges. The improved receptor binding of viral A39R is through both the enhancement of particularly important polar interactions, such as the substitution of A39R Arg207 for the Sema7A Lys280, and slight adjustments of side rotamer and main chain positions throughout the binding surface. These adjustments sum to a substantial optimization of binding energetics (e.g. great binding enthalpy), and a concomitant gain in binding affinity. The poxviruses likely have acquired the A39R gene by hijacking and mutating the Sema7A gene, rather than through convergent evolution. The structures also suggest that Plexins are activated by Semaphorins through dimerization, a knowledge that should help refine the thinking about possible downstream effectors, which are currently not well understood. The structural information can now be used as a template for designing applications modulating Semaphorin-Plexin recognition, such as anti-tumor-progression and directional nerve regeneration.

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