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The Role of the Membrane-Associated Domain of the Export Apparatus Protein, EscV (SctV), in the Activity of the Type III Secretion System

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Diarrheal diseases remain a major public health concern worldwide. Many of the causative bacterial pathogens that cause these diseases have a specialized protein complex, the type III secretion system (T3SS), which delivers effector proteins directly into host cells. These effectors manipulate host cell processes for the benefit of the infecting bacteria. The T3SS structure resembles a syringe anchored within the bacterial membrane, projecting toward the host cell membrane. The entry port of the T3SS substrates, called the export apparatus, is formed by five integral membrane proteins. Among the export apparatus proteins, EscV is the largest, and as it forms a nonamer, it constitutes the largest portion of the export apparatus complex. While there are considerable data on the soluble cytoplasmic domain of EscV, our knowledge of its membrane-associated section and its transmembrane domains (TMDs) is still very limited. In this study, using an isolated genetic reporter system, we found that TMD5 and TMD6 of EscV mediate strong self-oligomerization. Substituting these TMDs within the full-length protein with a random hydrophobic sequence resulted in a complete loss of function of the T3SS, further suggesting that the EscV TMD5 and TMD6 sequences have a functional role in addition to their structural role as membrane anchors. As we observed only mild reduction in the ability of the TMD-exchanged variants to integrate into the full or intermediate T3SS complexes, we concluded that EscV TMD5 and TMD6 are not crucial for the global assembly or stability of the T3SS complex but are rather involved in promoting the necessary TMD–TMD interactions within the complex and the overall TMD orientation to allow channel opening for the entry of T3SS substrates.

Keywords: type III secretion system, export apparatus, SctV, transmembrane domain, oligomerization

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INTRODUCTION

Diarrheal diseases are a major global health concern and are considered the second leading cause of death in children under the age of five. According to the World Health Organization (WHO), there are nearly 1.7 billion cases of childhood diarrheal disease per year with an estimated 500,000 deaths annually. One of the main infectious agents of pediatric diarrhea is enteropathogenic *Escherichia coli* (EPEC; Clarke et al., 2002). This pathogen was related