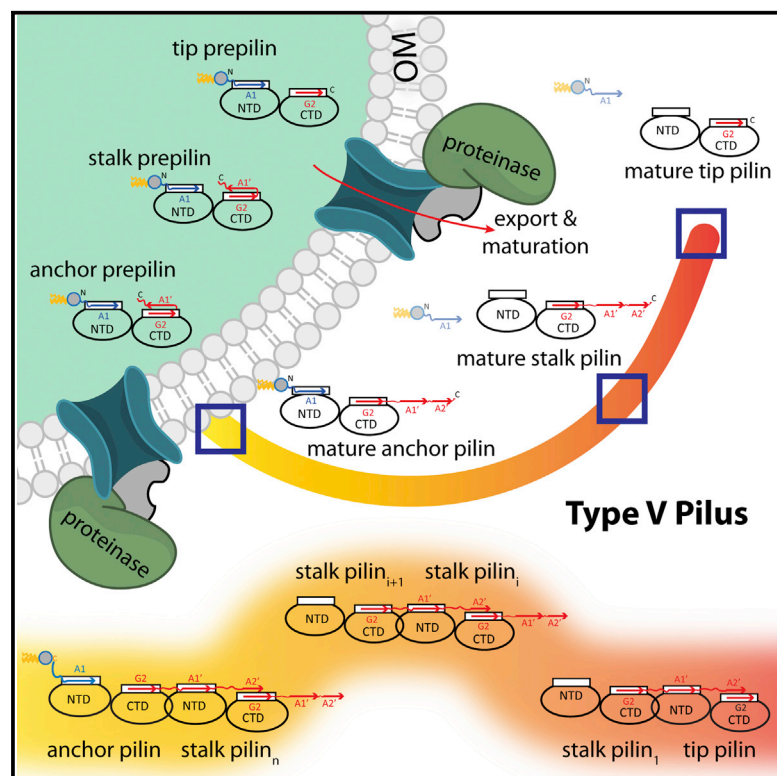


A Distinct Type of Pilus from the Human Microbiome

Graphical Abstract



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In Brief

Structural exploration of the gut microbiome uncovers a new pilin superfamily that is likely critical for microbe-host or microbe-microbe interactions.

Highlights

- A new pilin superfamily uncovered by structural exploration of the gut microbiome
- A distinct mechanism of pilus biogenesis in Bacteroidia of the human microbiome
- Mechanistic insights into proteinase-mediated pilin polymerization
- Key features of the tip, stalk, and anchor subunits of the pilus assembly

Accession Numbers

3LIU 4K4K
4JG5 4QB7
3R4R 4RDB
3UFI 5CAG
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A Distinct Type of Pilus from the Human Microbiome

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SUMMARY

Pili are proteinaceous polymers of linked pilins that protrude from the cell surface of many bacteria and often mediate adherence and virulence. We investigated a set of 20 *Bacteroidia* pilins from the human microbiome whose structures and mechanism of assembly were unknown. Crystal structures and biochemical data revealed a diverse protein superfamily with a common Greek-key β sandwich fold with two transthyretin-like repeats that polymerize into a pilus through a strand-exchange mechanism. The assembly mechanism of the central, structural pilins involves proteinase-assisted removal of their N-terminal β strand, creating an extended hydrophobic groove that binds the C-terminal donor strands of the incoming pilin. Accessory pilins at the tip and base have unique structural features specific to their location, allowing initiation or termination of the assembly. The *Bacteroidia* pilus, therefore, has a biogenesis mechanism that is distinct from other known pili and likely represents a different type of bacterial pilus.

INTRODUCTION

Studies of the human microbiome are uncovering the importance and extent of the complex symbiotic relationships between the human host and the microbiota that inhabit various cavities (e.g., oral, gut, vagina) and exposed surfaces (skin). Many of these colonizing bacteria have long proteinaceous filaments up to several micrometers in length on their cell surface called pili (also known as fimbriae) that serve as probes or anchors for interaction with host cells. These extended appendages also often function as major virulence factors in pathogenic bacteria and are involved in biofilm for-

mation. Structural studies of individual pilin subunits and their assembly have shed significant insights into the mechanism of pilus biogenesis in several model organisms (Allen et al., 2012; Choudhury et al., 1999; Kang et al., 2007; Li et al., 2009; Parge et al., 1995; Proft and Baker, 2009; Sauer et al., 1999). For example, in the well-characterized chaperone-usher pili (type I) of *Escherichia coli*, precursors of the structural subunits are exported to the periplasm where they are processed into their mature forms by signal peptidases. The pilus filaments are then assembled from head-to-tail from the structural subunits (pilins) with the aid of a chaperone and an usher (Allen et al., 2012; Proft and Baker, 2009). In Gram-negative bacteria, pili are assembled via noncovalent interactions and directly inserted into the bacterial cell wall, whereas in Gram-positive bacteria, the pilus subunits are connected by intermolecular isopeptide bonds and the entire assembly tethered to a cell-wall peptidoglycan.

Porphyromonas gingivalis is a major oral pathogen associated with severe adult periodontitis (Holt and Ebersole, 2005). *P. gingivalis* pili are key virulence factors that are essential for host colonization and evasion of innate defenses (Amano, 2010; Hajishengallis et al., 2007, 2008). They are also involved in binding a wide array of oral or epithelial substrates and extracellular matrix proteins (Amano, 2003; Hajishengallis, 2007), in addition to co-aggregation with other pathogens, such as *Streptococcus gordonii* (Park et al., 2005). Two types of morphologically distinct pili have been identified in *P. gingivalis*: major or long (0.3–1.6 μ m) and minor or short (80–120 nm) (Hamada et al., 1996; Yoshimura et al., 1984). These pili are encoded by similar operons (Figure 1A) that contain genes for the main structural pilins (FimA [major] or Mfa1 [minor]) that form the stalk of the pilus (Park et al., 2005; Sojar et al., 1991), followed by genes for the anchors pilins (FimB [major] and Mfa2 [minor]) and other ancillary pilins or regulatory elements (Hasegawa et al., 2009; Nagano et al., 2010). The FimA pilins from various *P. gingivalis* strains are classified into at least five different subtypes (FimA1–FimA5) based on sequence and immunogenic properties. The best characterized FimA1 of strain 33277 (referred to

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