Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Structural Biology

# Towards a complete structural deciphering of Type VI secretion system

Van Son Nguyen[1,2], Badreddine Douzi[1,2,4], Eric Durand[1,2,3], Alain Roussel[1,2], Eric Cascales[3] and Christian Cambillau[1,2]

The Type VI secretion system (T6SS) is a dynamic nanomachine present in many Gram-negative bacteria. Using a contraction mechanism similar to that of myophages, bacteriocins or anti-feeding prophages, it injects toxic effectors into both eukaryotic and prokaryotic cells. T6SS assembles three large ensembles: the trans-membrane complex (TMC), the baseplate and the tail. Recently, the tail structure has been elucidated by cryo electron microscopy (cryoEM) in extended and contracted forms. The structure of the trans-membrane complex has been deciphered using a combination of X-ray crystallography and EM. However, the structural characterisation of the baseplate lags behind and should be the target of future studies. Finally, cryo-tomography should provide low/medium resolution maps allowing to assemble the different parts ultimately leading to a complete structural description of T6SS.

**Addresses**
[1] Architecture et Fonction des Macromolécules Biologiques, Aix-Marseille Université, Campus de Luminy, Case 932, 13288 Marseille Cedex 09, France
[2] Architecture et Fonction des Macromolécules Biologiques, Centre National de la Recherche Scientifique (CNRS), Campus de Luminy, Case 932, 13288 Marseille Cedex 09, France
[3] Laboratoire d'Ingénierie des Systèmes Macromoléculaires, Institut de Microbiologie de la Méditerranée, Aix-Marseille Univ. – Centre National de la Recherche Scientifique (UMR7255), 31 Chemin Joseph Aiguier, 13402 Marseille Cedex 20, France

Corresponding author: Cambillau, Christian (cambillau@afmb.univ-mrs.fr)
[4] Present address: Laboratoire d'Ingénierie des Systèmes Macromoléculaires, Institut de Microbiologie de la Méditerranée, Aix-Marseille Univ. – Centre National de la Recherche Scientifique (UMR7255), 31 Chemin Joseph Aiguier, 13402 Marseille Cedex 20, France.

**Current Opinion in Structural Biology** 2018, **49**:77–84

This review comes from a themed issue on **Macromolecular assemblies**

Edited by **Kira Weissman** and **Timm Maier**

https://doi.org/10.1016/j.sbi.2018.01.007



## Introduction

The first report on components of the cluster that would become T6SS appeared more than 15 years ago. It was only in 2006 that the identification of a secreted tube component, Hcp, established that the identified cluster was a secretion system [1]. It was coined Type VI Secretion System (T6SS) the following year [2]. The structure of Hcp together with the determination of the crystal structure of the tube tip, VgrG, established the common evolutionary origin of T6SS and myophages (e.g. T4 or Mu) contractile tail [1,3], leading to the vision that T6SS could be some kind of tamed phage. Later on, this hypothesis was completed when T6SS tail sheath proteins VipA and VipB (TssB and TssC) were found to share structural and functional homology with those of myophages, and were at the origin of tail's contraction [4]. Contrary to what occurs for all other contractile machineries, T6SS tail is recycled after contraction thanks to an ATPase, ClpV, that disassembles the tail sheath into monomeric components, TssB and TssC [5]. This tail sheath recycling constitutes a hallmark of T6SS. A group of proteins were found to be attached or embedded in both IM or OM. One of them, TssM, shares sequence identity with the T4SS component IcmF. This finding completed the view of T6SS as being a phage-like machinery, attached to a secretion membrane system. Between them, another ensemble constitutes the baseplate, which was found to share some similarity with that of myophages.

In 2012, a tomography electron microscopy (EM) examination of T6SS yielded the first complete topology and dynamics of the system. It visualized the three domains of T6SS, TMC, baseplate and tail, and revealed that the tail crosses completely the cell's cytoplasm. Furthermore, analysis of tail's dynamics established that elongation takes tens of seconds, while contraction is very fast (<5 ms) [6,7].

T6SS is able to kill both prokaryotic or eukaryotic cells [8,9]. To this end, deadly effectors can be loaded at different positions: inside Hcp, docked to VgrG via PAAR module, or can be part of evolved Hcp or VgrGs. These effectors have been the subject of several reviews and are not part of this account [10,11].

## The trans-membrane complex spans between cytoplasm and outer membrane

Of the 13 proteins conserved in the T6SS cluster (Figure 1a,b), four have been shown to be inserted in