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Game of Trans-Kingdom Effectors

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1 **Title**

2 **Game of trans-kingdom effectors**

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18 Keywords

19 Type VI secretion system, *Pseudomonas aeruginosa*, trans-kingdom effector, antibacterial,
20 endoplasmic reticulum stress, autophagy

21

22 Abstract

23 TplE, a type VI secreted (phospho)lipase, has been identified as the third trans-
24 kingdom effector of *Pseudomonas aeruginosa*, targeting both prokaryotic and eukaryotic
25 hosts. Indeed, TplE triggers killing of bacterial competitors and promotes autophagy in
26 epithelial cells once localized to the endoplasmic reticulum.

27

28 Main text

29 The type VI secretion systems (T6SSs) are present in more than 25 % of Gram-
30 negative bacteria, making T6SS one of the most widespread protein secretion systems [1]. It
31 functions as a molecular crossbow that mainly delivers toxic effectors into bacterial target
32 cells to antagonize and eliminate competitors in close proximity [1]. Besides the benefits in
33 the environmental habitat, bacteria can use T6SS in the context of eukaryotic host by two
34 divergent routes [1]. On one hand, T6SS can directly target eukaryotic cells through delivery
35 of effectors in their cytosol, highjacking host cellular pathways or triggering toxicity. On the
36 other hand, pathogens which are in close contact with the commensal microbiota while
37 infecting a host, can attack or resist T6SS-dependent attack from commensal microbiota, in
38 order to colonize and/or persist within the host [2,3]. Altogether, T6SSs are key new players
39 in the host-pathogen-microbiota complex interactions, through both anti-eukaryotic and
40 antibacterial activities.

41 T6SS has been the first secretion system shown to mediate interactions with
42 prokaryotic and eukaryotic hosts through dedicated and diverse toxins [1]. The case of
43 *Pseudomonas aeruginosa* is unique in this trait since three T6SS-dependent effectors are
44 capable to target both types of host cells making them the first examples of trans-kingdom
45 effectors [4,5]. Besides being responsible for chronic lung colonization of patients with cystic
46 fibrosis, *P. aeruginosa* is one of the leading causes of hospital-acquired infections. Its genome
47 encodes three independent T6SSs. H1-T6SS is so far exclusively dedicated to antibacterial
48 activity through injection of at least 7 different effectors, whereas H2-T6SS and H3-T6SS
49 have a dual role allowing targeting of both prokaryotic and eukaryotic cells [6]. Even
50 considered an extracellular pathogen, *P. aeruginosa* is able to actively invade non-phagocytic
51 cells, through injection of effectors PldA and VgrG2b via H2-T6SS [4,7], and PldB via H3-
52 T6SS [4] among other factors. On the one hand, PldA and PldB bind the Akt kinase, whose
53 activation together with the recruitment of the PI3K (phosphoinositide 3-kinase) pathway is
54 further required for actin polymerization at the bacterial binding site leading to bacterial
55 invasion [4]. On the other hand, VgrG2b promotes a microtubule-dependent internalization of
56 *P. aeruginosa* through interaction with the gamma-tubulin complex, demonstrating the
57 spectacular ability of *P. aeruginosa* T6SSs to hijack host cellular functions to its own
58 advantage [7].

59 In a recent report from Jiang and colleagues, TplE was identified as the third T6SS
60 trans-kingdom effector of *P. aeruginosa* [5]. Such as PldA and PldB, TplE (formerly called
61 Tle4) belongs to the large antibacterial type VI lipase effector family (Tle) [8]. In agreement
62 with this, its structure exhibits the characteristics of a canonical α/β -hydrolase fold [9].
63 Interestingly, Jiang and colleagues [5] demonstrated that TplE harbors lipase and
64 phospholipase A1 activities *in vitro*. The authors first confirmed that TplE mediates
65 antibacterial activity, by producing TplE and a serine catalytic variant in the periplasm of

66 *Escherichia coli*. Importantly, only wild-type TplE led to bacterial growth inhibition, while
67 the catalytic variant of TplE was not toxic. As previously proposed [8], and consistent with a
68 crab claw-like conformation of TplEi (formerly Tli4) [9], the product of the downstream gene
69 TplEi (TplE immunity), neutralized the TplE toxicity. Indeed, to protect from self or sister
70 cell killing, bacteria produce immunity proteins to counteract their cognate T6SS antibacterial
71 effectors. Authors further demonstrated that TplE lipolytic activity contributes to intra- and
72 inter-species competition once delivered into target bacteria via the H2-T6SS machinery and
73 that TplEi provides protection against TplE.

74 Furthermore, the role of TplE during interaction with eukaryotic target cells was also
75 characterized in this report, by demonstrating the H2-T6SS-dependent translocation of TplE
76 into epithelial cells upon infection with *P. aeruginosa* [5]. Interestingly, TplE contains a
77 eukaryotic PGAP1 (Post GPI Attachment to Proteins 1)-like domain present in proteins
78 localized at endoplasmic reticulum. The targeting of TplE to this compartment was further
79 demonstrated with a combination of *ex vivo* assays (transfection and infection). One can note
80 that the enzymatic activity of TplE was not required for endoplasmic reticulum localization.
81 Nevertheless this targeting led to endoplasmic reticulum disruption, which in this case,
82 involves the lipolytic activity of TplE. The authors also observed that in response to this
83 endoplasmic reticulum stress, TplE activated the unfolded protein response via the XBP1
84 pathway and triggered autophagy, as shown by LC3 conversion and the increase of
85 autophagosomes and autolysosomes. The integrity of the TplE active site was determinant for
86 these two processes. Autophagy is a conserved destructive process allowing degradation of
87 unnecessary, dysfunctional, or undesirable cellular components including organelles (like the
88 endoplasmic reticulum) or intracellular pathogens. In the latter case, autophagy is considered
89 an innate immunity defense mechanism of infected cells against invading bacteria, but
90 intracellular pathogens have evolved mechanisms modulating this host response to their

91 advantage. The autophagy response activated by *P. aeruginosa* highlights the transient but
92 real intracellular lifestyle of this pathogen, still being largely considered an extracellular
93 pathogen.

94 Whereas the competitive advantage towards other bacteria conferred by TplE, PldA
95 and PldB is quite simple, how could their actions towards eukaryotic cells be integrated in a
96 common model? PldA, PldB and VgrG2b contribute to *P. aeruginosa* internalization into
97 epithelial cells that can be view as a strategy to avoid innate immunity. However once
98 intracellular, the destiny of *P. aeruginosa* is still unclear. The pathogen may exploit and
99 benefit the autophagy to acquire nutriments from endoplasmic reticulum degradation and thus
100 promote its own intracellular replication such as *Francisella tularensis* [10]. Consistent with
101 this hypothesis, the H2-T6SS is not cytotoxic towards epithelial cells [4,7]. The use of
102 autophagy modulators may be thus envisioned as a new therapeutic strategy in the fight
103 against *P. aeruginosa* infections. The findings of Jiang and colleagues [5] provide new and
104 important insights in the pathogenesis of *P. aeruginosa* that relies in bacterial competitor as
105 well as in eukaryotic cells in a game of trans-kingdom effectors. Moreover since TplE, PldA
106 and PldB belong to the superfamily of type VI lipase effectors present in various pathogens
107 [8], one can ask whether other trans-kingdom effectors may be discovered in the future.

108

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