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Cellulosome assembly: paradigms are meant to be broken!

Pedro Bule[1], Virgínia MR Pires[1], Carlos MGA Fontes[1,2] and Victor D Alves[1]

Cohesin–Dockerin interactions are at the core of cellulosomal assembly and organization. They are highly specific and form stable complexes, allowing cellulosomes to adopt distinct conformations. Each cellulosomal system seems to have a particular organizational strategy that can vary in complexity according to the nature of its Cohesin–Dockerin interactions. Hence, several efforts have been undertaken to reveal the mechanisms that govern the specificity, affinity and flexibility of these protein–protein interactions. Here we review the most recent studies that have focused on the structural aspects of Cohesin–Dockerin recognition. They reveal an ever-increasing number of subtle intricacies suggesting that cellulosome assembly is more complex than was initially thought.

Addresses
[1] CIISA – Faculdade de Medicina Veterinária, ULisboa, Pólo Universitário do Alto da Ajuda, Avenida da Universidade Técnica, 1300-477 Lisboa, Portugal
[2] NZYTech genes & enzymes, Estrada do Paço do Lumiar, 1649-038 Lisboa, Portugal

Corresponding authors: Bule, Pedro (pedrobuleg@gmail.com), Alves, Victor D (vdalves@fmv.ulisboa.pt)

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Introduction

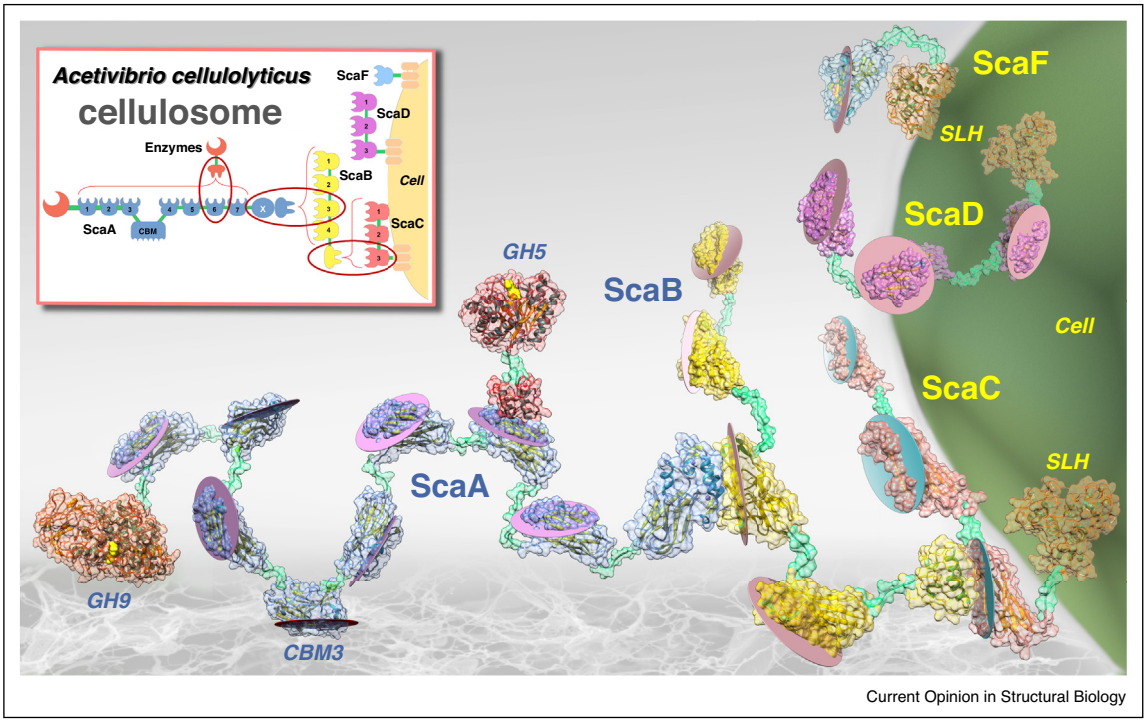
The cellulosome is one of Nature's most intricate nanomachines. It consists of a multi-modular enzymatic complex produced by anaerobic cellulolytic microorganisms in order to process recalcitrant polysaccharide substrates to generate simple sugars that are used as energy source. Central to cellulosome assembly is the high affinity protein–protein interaction established between cohesins (Coh) and dockerins (Doc). Cohs are present in non-catalytic structural proteins, called scaffoldins, which serve as the backbone on to which the enzymes will bind through their appended Doc modules. It is now apparent that different species have evolved cellulosomes with distinct conformations depending on the number of enzymes and Coh–Doc interactions each system possesses (Figures 1 and 2). Cellulosomes that assemble via a single primary scaffoldin are characteristic of most mesophilic *Clostridia*, such as *C. cellulolyticum*, *C. josui* and *C. cellulovorans*. These are the simplest cellulosomes thus far identified [1,2] and their structural resemblance suggest a common evolutionary origin [3•]. In more elaborate cellulosomes the primary scaffoldin contains a C-terminal Doc usually associated to an X-module (XDoc), which tenaciously interacts with the Coh of a cell bound anchoring scaffoldin, thus providing a mechanism for cellulosome cell surface attachment [4]. More complex cellulosomes have adaptor scaffoldins that either connect two scaffoldins or a scaffoldin and enzyme(s) (Figures 1 and 2). Understanding the mechanism of cellulosome assembly requires elucidating the mechanisms modulating the specificity and affinity of different Coh–Doc interactions. Recently, a comprehensive set of studies clarified the intricacies of the Coh–Doc interaction at a structural level, suggesting a diversity of mechanisms fine-tuning specificity, affinity and flexibility. The recent structural advances on the Coh–Doc interaction are revisited here.

Cellulosome architecture

Cellulosome producing organisms inhabit a wide range of ecological niches, from sewage sludge and soil to the gastrointestinal compartments of herbivores and even the human gut. Since these highly elaborate cellulolytic systems were first described, only around 20 species were identified as cellulosome secretors suggesting that the cellulosome is not as prevalent in nature as it was initially thought [5]. Nevertheless, with the increased availability of genomic and metagenomic information, cellulosome diversity is expanding and is likely to increase as new species emerge [6•].

The cellulosome of *Clostridium (Ruminiclostridium) thermocellum* was the first to be described and remains as the archetype example [7]. It is now well established that the basis for its architecture relies on two different Coh–Doc interactions: type I, which allows the recruitment of enzymes into the primary scaffoldin ScaA; and type II, that attaches ScaA to a cell surface anchoring scaffoldin, tethering the cellulosome to the bacteria (Figure 2). Extensive structural and biochemical studies revealed that *C. thermocellum* type I Docs display a dual-binding

Figure 1



Acetivibrio cellulolyticum cellulosome — a structure-based concept art illustration. The cellulosome architecture is organized around the non-catalytic primary scaffoldin (ScaA), a unique adaptor scaffoldin (ScaB) and several anchoring scaffoldins (ScaC, ScaD and ScaF). ScaA bears 7 cohesin (Coh) modules that congregate the catalytic enzymes via their appended dockerin (Doc) modules, it also can bind the carbohydrate substrate through a carbohydrate binding module (CBM) and it is crowned by a N-terminal glycoside hydrolase (GH) and by a C-terminal XDoc that enables the anchoring of the cellulosome to the bacterial cell-wall. The schematic cellulosome in the small image insert is color-coded according to the main 3D image representation, but does not reflect the diverse specificities of Coh–Doc possible pairings, which can be seen in Figure 2. The structures of 3 Coh–Doc complexes (circled in red), *Ac*CohScaA-DocCel5 (PDB 5nrm/5nrk), *Ac*CohScaB-XDocScaA (PDB 4u3s/4wi0) and *Ac*CohScaC-DocScaB (PDB 4uyp/4uyq) completed the full picture of *A. cellulolyticus* cellulosome assembly and cell-wall anchoring. All the depicted Coh modules display a distinct colored disk plane highlighting the Coh binding platform, and a similar representation was used for the CBM's binding site. An 'artistic' rendering of the unstructured linkers between all the modules is shown in green color. The structure artwork was done in UCSF Chimera [44].

mode [8]. Due to the characteristic internal symmetry of Docs, they possess the ability to bind the cognate Coh in two different orientations by rotating ~180° with respect to its protein ligand, resulting in two different Coh–Doc conformations. Although the dual binding mode was initially visualized in a series of seminal Coh–Doc structures, the two ingenious Coh–Doc binding modes were recently corroborated with single-molecule force methodologies [9,10].

As the number of known cellulosome producing species grows, systems with increased complexity start to emerge. The finding of adaptor scaffoldins, such as ScaB from *Acetivibrio cellulolyticus*, revealed a new mechanism to improve the intricacy of cellulosome architecture by enlarging the capacity to incorporate a large number of enzymes with diverse substrate specificities [11,12]. One of the most complex cellulosomes presently known is that from *Ruminococcus flavefaciens*. Over 200 Doc-containing proteins and 21 Cohs were identified in this species' proteome (Figure 2) [13]. Interestingly, the vast majority of these Cohs and Docs were structurally divergent from the classic types I and II described in *C. thermocellum* and were therefore classified as type III. This system also introduced us to monovalent adaptor scaffoldins: proteins with a single Coh whose specificity diverges from its C-terminal Doc. It is believed that this simpler adaptor scaffoldins act as a 'switch' that changes the Coh specificity of the primary scaffoldin and therefore the type of enzyme that is integrated into the cellulosome [14]. These scaffoldins may have a regulatory role in determining the assembly and composition of a cellulosome complex, depending on the available substrate.

The recent near complete sequencing of *Bacteroides (Pseudobacteroides) cellulosolvens* genome has revealed what is now the most complex cellulosome described to date. With an impressive 212 Doc-containing proteins and 78 Cohs scattered across 31 different scaffoldins, this cellulosome can adopt numerous conformations,

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