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# Ruminococcal cellulosomes: molecular Lego to deconstruct microcrystalline cellulose in human gut

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1 Highlights on: Ben David et al (2015) Ruminococcal cellulosome systems from rumen to  
2 human. Environmental Microbiology

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5 **Ruminococcal cellulosomes: molecular Lego to deconstruct microcrystalline cellulose in**  
6 **human gut**

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1           Plants (and also algae in East Asian cuisine) constitute the bases of human diet. These  
2   photosynthetic organisms are characterized by their abundance in diverse polysaccharides,  
3   which constitute their cell walls and carbon storage (Popper et al., 2011). Paradoxically,  
4   human ability to digest complex carbohydrates is very limited and restricted to the  
5   assimilation of some disaccharides (e.g. lactose, sucrose) and starch. These catabolic  
6   limitations are fortunately compensated by the capacities of symbiotic gastrointestinal  
7   microbes to degrade most dietary polysaccharides (El Kaoutari et al., 2013). Human gut  
8   microbiota is usually dominated by the Firmicutes and the Bacteroidetes form the second  
9   most abundant bacterial group (Ley et al., 2008). Nonetheless, the mechanisms of  
10   polysaccharide assimilation have been mainly studied in gut Bacteroidetes. From the seminal  
11   works of Salyers and coworkers on the starch utilization system (Sus) of *Bacteroides*  
12   *thethaiotaomicron* (Anderson and Salyers, 1989; Cho and Salyers, 2001) has emerged the  
13   more general notion of Polysaccharide Utilization Loci (PUL). These gene clusters encode  
14   most proteins needed for the uptake and degradation of a specific polysaccharide and notably  
15   include the crucial *susC*-like (TonB-dependent transporter) and *susD*-like (an associated  
16   carbohydrate-binding lipoprotein) genes (Koropatkin et al., 2012). In the last years several  
17   PULs with new substrate specificity have been characterized in *Bacteroidetes* such as: plant  
18   fructans (Sonnenburg et al., 2010), porphyrans from red algae (Hehemann et al., 2010),  
19   alginates from brown algae (Thomas et al., 2012), plant xyloglucans (Larsbrink et al., 2014)  
20   and yeast  $\alpha$ -mannans (Cuskin et al., 2015). The frequency of these PULs in the gut  
21   microbiomes tends to correlate with the prevalence of their respective substrate in diet: from  
22   culturally-restricted PULs in the case of porphyrans and alginates to largely distributed PULs  
23   for mannan and xyloglucan (Cuskin et al., 2015).

24           If a polysaccharide could be considered as omnipresent in human diet, it would without  
25   doubt be cellulose, which is conserved from algae to flowering plants (Popper et al., 2011).

1 However cellulose-degrading bacteria in human gut remain relatively unexplored. Cellulolytic  
2 bacteria are present in human gut but their community structure varies with the presence of  
3 methanogen archaea. In non-methane-excreting individuals the cellulolytic community is  
4 dominated by Bacteroidetes species. In methane-excreting individuals the main cellulose-  
5 degrading bacteria are represented by Firmicutes (*Ruminococcus* and *Enterococcus* species)  
6 (Robert and Bernalier-Donadille, 2003; Chassard et al., 2010). The rationale behind this  
7 dichotomy is that cellulose fermentation by the Firmicutes isolates releases large amount of  
8 H<sub>2</sub> which is consumed by methanogens, while the cellulolytic *Bacteroides* strains do not  
9 produce H<sub>2</sub>. This interplay between H<sub>2</sub>-producing and H<sub>2</sub>-consuming microbes seems  
10 essential for an efficient fermentation of cellulose (Robert et al., 2001; Chassard et al., 2010).  
11 In terms of cellulose degradation other points are also essential. The *Bacteroides* isolates,  
12 including the representative species *B. cellulosilyticus* strain CRE21<sup>(T)</sup> (Robert et al., 2007),  
13 are able to degrade native cellulose but not the purified microcrystalline fraction, indicating  
14 that these microorganisms can efficiently degrade only amorphous cellulose. In contrast, the  
15 Firmicutes isolates are able to assimilate all types of cellulose, including microcrystalline  
16 fibers (Chassard et al., 2010). One of these strains defines a new *Ruminococcus* species, *R.*  
17 *champanellensis* (Chassard et al., 2012). So for once, the key carbohydrate degraders in  
18 human gut are not to be found among the Bacteroidetes, but among the Firmicutes! How to  
19 explain such an efficiency difference between cellulolytic Bacteroidetes and Firmicutes?

20 In this issue of Environmental Microbiology Ben David and coworkers give an  
21 exciting answer to this question. An in-depth bioinformatic analysis of *R. champanellensis*  
22 genome has revealed 20 putative cohesin modules (belonging to 11 scaffoldin proteins, from  
23 ScaA to ScaK) and 64 putative dockerin modules, suggesting the existence of cellulosomes in  
24 the human gut ecosystem. Cellulosomes are protein complexes including non-catalytic core-  
25 proteins (scaffoldin) which recruit multiple cellulolytic enzymes through a unique molecular

1 interaction between two protein modules referred to as cohesin and dockerin (Smith and  
2 Bayer, 2013). In the basic structure of a cellulosome, the type-I dockerins of the modular  
3 (hemi)cellulolytic enzymes bind the type-I cohesins of the scaffoldins (Figure 1). Type-II  
4 dockerins are localized in the C-terminal region of the scaffoldins and attach the cellulosome  
5 to the bacterial cell surface through a specific interaction with the type-II cohesin of  
6 anchoring proteins which are themselves covalently bound to the peptidoglycan. The first  
7 cellulosome was discovered in the thermophilic bacterium *Clostridium thermocellum* 30 years  
8 ago (Bayer et al., 1983; Lamed et al., 1983) and similar supramolecular complexes were also  
9 found in the bovine rumen bacterium *Ruminococcus flavefaciens* and extensively  
10 characterized (Flint et al., 2008). To demonstrate the reality of cellulosomes in human gut,  
11 Ben David and coworkers have recombinantly expressed the 20 cohesins of *R.*  
12 *champanellensis* and a representative selection of 24 dockerins. Using an elegant protein  
13 microarray approach, they have identified 64 specific interactions among the 480 possible  
14 interactions. Based on these experimental evidences, the authors have proposed and discussed  
15 a model for the cellulosome complexes of *R. champanellensis*. The most surprising result is  
16 the existence of two types of cellulosomes: (i) cell-attached complexes in which the scaffoldin  
17 ScaE plays a crucial role, due to its C-terminal sortase signal motif and (ii) cell-free minimal  
18 cellulosomes involving the the scaffoldin ScaI which only includes one cohesin module. With  
19 such cellulolytic complexes, *R. champanellensis* is indeed well equipped to take advantage of  
20 dietary cellulose (although the exact function of the cell-free cellulosome is unclear) and to be  
21 a pivotal species for the degradation of microcrystalline cellulose. This remarkable study has  
22 also opened diverse biological questions. Does the degradation of cellulose fibers by *R.*  
23 *champanellensis* and related Firmicutes species provide a significant source of energy to the  
24 human host considering the short time of digesta retention in comparison to the bovine  
25 rumen? Perhaps these Firmicutes play crucial functions more at the community level, opening

1 the way to other cellulolytic bacteria more efficient on amorphous cellulose (for instance *B.*  
2 *cellulosilyticus?*). Such a cooperation between gut *Firmicutes* and *Bacteroides* species is  
3 already known in the case of the degradation of resistant starch (Ze et al., 2012). Finally, the  
4 degradation of microcrystalline cellulose likely alters the integrity of the plant cell wall, and  
5 thus may facilitate the access of other cell wall components to bacteria specialized in the  
6 assimilation of polysaccharides less recalcitrant than cellulose.

7

## 8 **Figure Legends**

### 9 **Figure 1: Example of a cohesin-dockerin complex from *Clostridium thermocellum*.**

10 Cartoon representation of the complex of the type-I dockerin domain from xylanase 10B and  
11 the type-I cohesin 2 from the scaffoldin CipA (PDB code: 1OHZ) (Carvalho et al., 2003). The  
12 dockerin and cohesin are colored in magenta and cyan, respectively. Calcium ions bound to  
13 the dockerin are represented as yellow spheres. This figure was prepared using PyMol.

14

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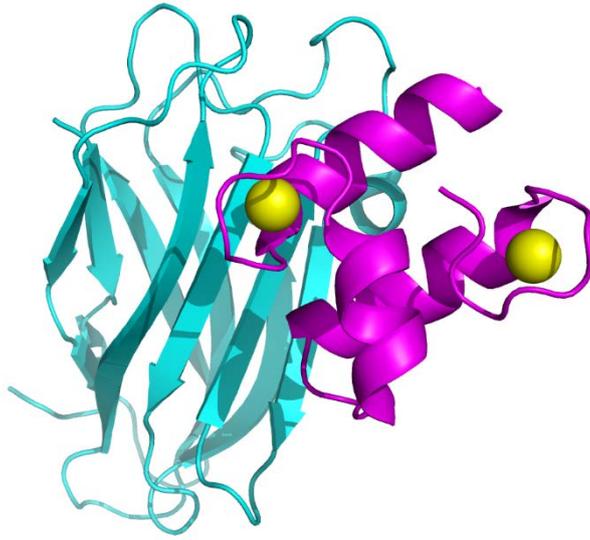


Figure 1

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