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Centriole length control

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Centrioles are microtubule-based structures involved in cell division and ciliogenesis. Centriole formation is a highly regulated cellular process and aberrations in centriole structure, size or numbers have implications in multiple human pathologies. In this review, we propose that the proteins that control centriole length can be subdivided into two classes based on their antagonistic activities on centriolar microtubules, which we refer to as 'centriole elongation activators' (CEAs) and 'centriole elongation inhibitors' (CEIs). We discuss and illustrate the structure-function relationship of CEAs and CEIs as well as their interaction networks. Based on our current knowledge, we formulate some outstanding open questions in the field and present possible routes for future studies.

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Introduction

Centrosomes are organelles that act as major microtubule-organising centres in all animal cells. An archetypal vertebrate centrosome is composed of a pair of orthogonally arranged centrioles that are surrounded by proteinous pericentriolar material. Furthermore, most of these centrioles display a characteristic ninefold symmetrical 'cartwheel' structure at their base, which is connected to nine peripheral microtubule-triplet blades (reviewed in Ref. [1]). Centrioles can be interconverted to basal bodies, which are required for the formation of cilia and flagella.

The overall structure and size of centrioles are quite variable between different species as well as between different cell types within a species [2]. Despite this variability, the length of a centriole is tightly controlled within a given cell type [3]. Since microtubules lie at the core of the centriole architecture, the regulation of the centriole length is tightly coupled to the regulation of the length of their constituent centriolar microtubules. In support of this conclusion, overexpression of proteins that either stabilize or destabilize centriolar microtubules directly impact centriole length [4]. Remarkably, centriolar microtubules display distinct properties compared to the highly dynamic cytoplasmic microtubules: they exhibit exceptionally slow growth rates (approximately four orders of magnitude slower) and retain remarkable stability after their formation [5]. These peculiar biochemical and biophysical properties of centriolar microtubules are in part due to their specific posttranslation modifications (reviewed in Ref. [6]) and to the activity of centriolar microtubule-associated proteins.

Recent work on a number of centriolar microtubule-associated proteins has highlighted their importance in controlling centriole length. However, our understanding of the molecular machinery that regulates this complex process is still fragmented. In this review, we present an overview of the proteins and their interaction networks that are involved in controlling the length of centrioles and briefly discuss their structure-function relationships. Finally, we formulate some outstanding open questions and present possible routes for future studies aimed at understanding the enigmatic molecular mechanisms underlying centriole length control.

Proteins involved in centriole length control

The initiation of a new daughter centriole at the proximal end of a mother centriole critically depends on the activities of the Polo-like kinase Plk4, the cartwheel proteins SAS-6 and STIL, the microtubule minus-end binding protein γ-tubulin, and the protein Cep135 that links the cartwheel to the microtubule triplet blades (reviewed in Ref. [7]). However, the actual formation of the centriolar microtubule wall that founds the core of a centriole is orchestrated by a set of centriolar proteins that we here propose to subdivide into two classes based on their antagonistic activities on centriolar microtubules, which we refer to as 'centriole elongation activators' (CEAs) and 'centriole elongation inhibitors' (CEIs). CEAs are proteins that bind microtubules or their αβ-tubulin heterodimer building blocks and which upon overexpression lead to overly elongated centrioles. Accessory CEAs (aCEAs) do not directly bind tubulin or microtubules but promote centriole microtubule growth by regulating the activity of CEAs. CEIs, on the other

hand, are proteins that upon overexpression lead to shorter centrioles by counteracting the activity of CEAs. Similar to aCEAs, accessory CEIs (aCEIs) regulate the activity of CEIs. The precise balance between the activities of CEAs and CEIs ultimately defines the proper length of a centriole [4].

In the following and in Table 1, we briefly describe and summarize, respectively, our current knowledge on the functions and mechanisms of the various CEAs and CEIs as well as on their accessory proteins. The domain organization, available structural information and known protein interaction sites of CEAs and CEIs are illustrated in Figure 1.

CEAs and their accessory proteins

CPAP (centrosomal P4.1 associated protein; SAS-4 in *Caenorhabditis elegans*). CPAP/SAS-4 is perhaps the best-characterized protein involved in centriole length control to date. It contains an N-terminal αβ-tubulin-binding domain, denoted PN2-3 [8], a positively charged unstructured microtubule-binding domain [9], a coiled-coil dimerization domain [10], and a C-terminal G-box domain [10]. In addition to being important for centriole elongation [4,11,12], CPAP plays a role in pericentriolar material recruitment [13,14] and might be involved in connecting the cartwheel to the microtubule-triplet blades [10]. The G-box domain of CPAP has the capacity to self-assemble into a fibrillar structure *in vitro*, which displays a ~8 nm axial periodicity; it has been speculated that such fibrils may act as 'molecular rulers' for centriole formation [10]. However, the C-terminus of CPAP encompassing the coiled coil and G-box domains can also form dynamic oligomers [15].

CPAP, whose function is regulated by phosphorylation [16], localizes and tracks growing microtubule plus ends by recognizing their exposed β-tubulin subunits through its PN2-3 domain [17••,18••]. Binding of CPAP to growing plus ends causes a peculiar slow and processive growth of microtubules *in vitro* reminiscent of centriolar-microtubule growth rates in cells [18••]. In this context, the PN2-3 domain of CPAP presumably dampens microtubule dynamics by acting as a 'leaky lid' that stabilizes microtubule protofilaments and controls the addition of tubulin dimers at microtubule plus ends [18••]. The centriolar localization of CPAP depends on its binding to Cep152 [19], PPP1R35 [20] and Centrobin [21]; the latter protein also prevents the proteasome-mediated degradation of CPAP [22]. Furthermore, SPICE1 is required for the centriole elongation activity of CPAP [23]. Two CPAP disease-related mutations have been reported so far: the Seckel syndrome 4 [24] and the autosomal recessive primary microcephaly disorder [25]. Interestingly, a conditional CPAP knockout mouse shows developmental defects in the brain mimicking human microcephaly, which could provide new insights into the role of CPAP in brain development [26].

Cep120 (centrosomal protein of 120 kDa). Cep120 contains three consecutive N-terminal C2 domains (C2A, C2B and C2C) followed by a coiled-coil dimerization domain [27•,28•]. The C2A domain of Cep120 binds tubulin and microtubules and enhances microtubule formation and stability *in vitro* [27•]. Two ciliopathy-

Table 1

CEAs and CEIs and their associated proteins

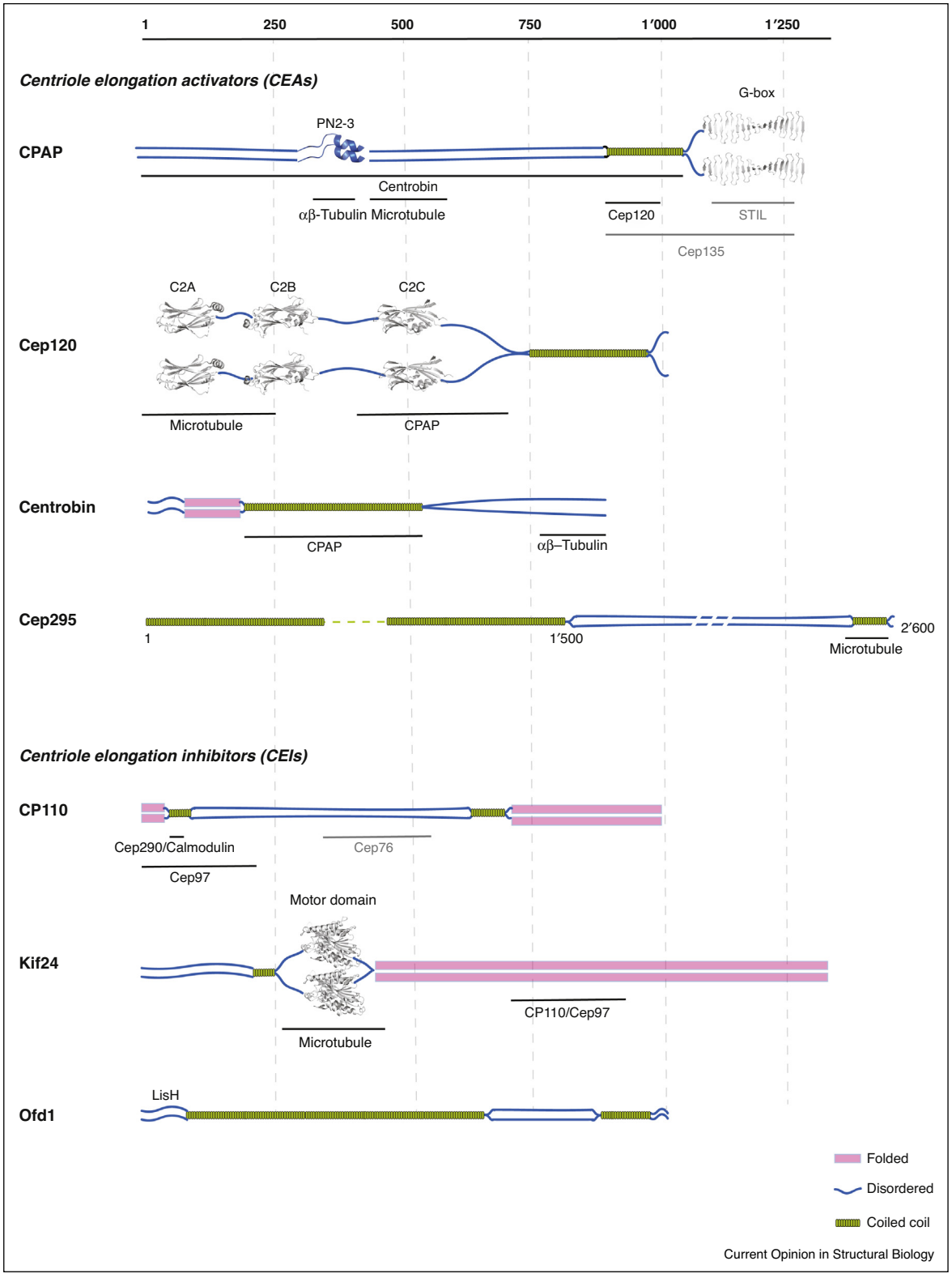
CEA	Effects on MTs	Functions[a]	aCEA
CPAP	MT plus-end tracking [18••], promotion of slow and processive MT growth [18••]	Recruitment of pericentriolar material [13,14], centriole scaffold-MT connection [10], brain development [26]	Cep152 [19] SPICE1 [23]
Cep120	Enhancement of MT formation and stability [27•]	Centriole appendage assembly [30••]	SPICE1 [23] Talpid3 [29] C2CD3 [30••]
Centrobin	Unknown	C-tubule assembly in primary spermatocytes [34]	Cep152 [19]
Cep295	Unknown	Required for CPAP-induced and Cep120-induced centriole elongation [35•], posttranslational acetylation and glutamylation of centriolar MTs [35•]	Rotatin [36•]

CEI	Effects on MTs	Functions[a]	aCEI
CP110	Unknown	Ciliogenesis inhibition [38,41,48•]	Cep290 [39], Calmodulin [45], Cep97 [38], Cep104 [46], Centrin2 [44]
Kif24	MT depolymerization [41]	Ciliogenesis regulation [41]	Cep97 [38,48•]
Ofd1	Unknown	Recruitment of distal appendage proteins [50], intraflagellar transport and ciliogenesis [50]	

The most commonly used names for the human proteins are given. CEA, centriole elongation activator; aCEA, accessory CEA; CEI, centriole elongation inhibitor; aCEI, accessory CEI; MT, microtubule.

[a] Additional functions besides regulation of centriole length.

Figure 1



Relative sizes, domain organization, structural information and known protein interaction sites of CEAs and CEIs.
Predicted secondary structural elements are depicted as follows: pink, folded region; blue, disordered region; green, coiled-coil region. The ruler on top indicates amino acid positions (except for Cep295 that is much longer than the other CEAs and for which amino acid boundaries are given directly in the schematic representation). Tubulin-binding, microtubule-binding, aCEA-binding and aCEI-binding regions are highlighted with black

associated point mutations in C2B destabilize this domain, reduce cellular and centrosomal Cep120 levels, and impede centriole function and cilia formation (Short-rib thoracic dysplasia 13 and the Joubert syndrome 31; [28•]). Cep120 is asymmetrically localized to daughter centrioles through its interaction with Talpid3 [29]. Cep120 binding to C2CD3 and Talpid3 is required for the assembly of centriolar appendages [30••]. Furthermore, loss of Cep120 produces short centrioles with no apparent distal and subdistal appendages essential for proper cilia assembly [30••]. Cep120 interacts with SPICE1 and CPAP, which is crucial for the protein's centriole elongation activity [23,31]. In addition, Cep120 helps to maintain centrosome homeostasis by inhibiting the maturation of daughter centrioles [32].

Centrobin. Centrobin is a coiled-coil protein harboring a tubulin-binding domain at its C-terminus [21]. Overexpression of this domain leads to centriole destabilization in normal and CPAP overexpressing cells and disrupts centriole localization of the endogenous protein [33]. Centrobin is required in primary spermatocytes for their basal bodies to achieve normal length and for the assembly of the C-tubule of centriolar microtubule triplets [34]. Centrobin overexpression is linked to an increased cellular level of CPAP, which could be partly responsible for its centriole elongation activity [22]. The centrosomal localization of Centrobin is dependent on the cartwheel proteins SAS-6 [33] and Cep152 [21].

Cep295 (centrosomal protein of 295 kDa, Ana1 in *D. melanogaster*). Cep295 contains mainly predicted coiled coils at its N-terminus followed by an unfolded stretch and a C-terminal, microtubule-binding coiled-coil domain. It localizes at the proximal end of the centriole wall and is required for CPAP-induced and Cep120-induced centriole elongation, as well as for the posttranslational acetylation and glutamylation of centriolar microtubules [35•]. The centriolar localization of Cep295 is dependent on the accessory protein Rotatin [36•].

CEIs and their accessory proteins

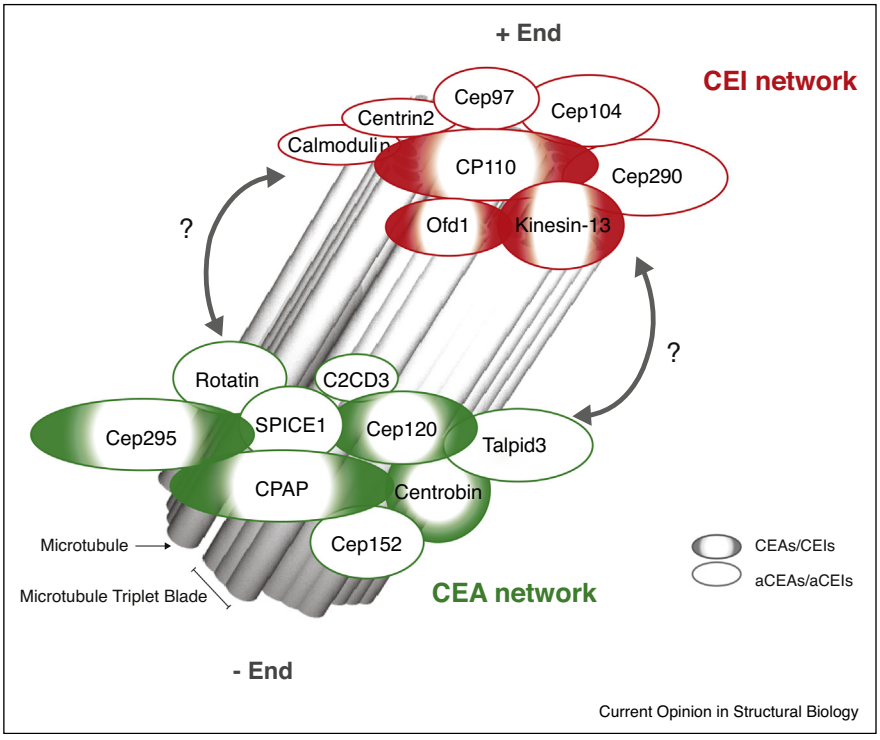
CP110 (centrosomal protein of 110 kDa). CP110 localizes to the distal plus ends of both the static mother and growing daughter centrioles where it seems to act as a 'plug' [37]. Overexpression of CP110 supresses the centriole elongation activity of CPAP [4]. Its depletion in mammalian cells, on the other hand, causes the extension of centriolar microtubules from the distal ends of centrioles [4] and leads to the formation of primary cilia [38]. CP110 controls primary cilia formation through its interaction with Cep290 in dividing cells until they are ready to undergo ciliogenesis [39]. In *Drosophila*, however, depletion of CP110 leads to centriole shortening apparently via the microtubule-depolymerizing activity of the CP110-associated kinesin-13 family member Klp10A [40]. The recruitment of CP110 to centrioles depends on Cep97, Kif24 and Centrobin [33,38,41]. CP110 protein levels are controlled in cells by the antagonistic activity of the ubiquitin ligase $SCF^{cyclin\text{-}F}$ [42] and by USP33-mediated deubiquitination [43]. The centriole-localized CP110 pool exists as part of a multiprotein complex involving Cep97 [38], Kif24 [41], Centrin2 [44], Calmodulin [45], Cep290 [39], and Cep104 [46]. Kif24 recruits M-phase phosphoprotein 9 (MPP9) to centrioles, which in turn recruits the CP110-Cep97 complex via direct binding to Cep97 [47•]. In addition, Cep97 is involved in the stabilization of centriolar microtubules by regulating their posttranslational modifications [48•].

Kinesin-13 family members. Mammalian Kif24 and drosophila Klp10A are two kinesin-13 family proteins whose members act as microtubule depolymerases by inducing and/or stabilizing a curved conformation of tubulin at microtubule ends [49]. Kif24 specifically depolymerizes centriolar microtubules with little effects on cytoplasmic microtubule dynamics [41]; in contrast, Klp10A destabilizes both cytoplasmic and centriolar microtubules [40]. Kif24 associates with the CP110-Cep97 complex and preferentially localizes to the mother centriole; however, the centriole localization of Kif24 is independent of its CP110-Cep97 binding activity [41]. Ablation of Kif24 promotes ciliogenesis whereas its overexpression supresses centriole elongation upon Cep97 depletion [41].

Ofd1 (orofaciodigital syndrome 1 protein). Ofd1 localizes to the distal ends of centrioles, in close proximity to the centriolar microtubule wall. Loss of Ofd1 leads to overelongated centrioles containing destabilized microtubules [50]. Ofd1 is involved in the recruitment of distal appendage proteins as well as in intraflagellar transport and ciliogenesis [50]. Unlike CPAP overexpression or CP110 depletion leading to procentriole elongation, the depletetion of Ofd1 leads to elongation of the distal region of centrioles [50]. Ofd1 and the CPAP-CP110 module might thus be involved in the regulation of distinct centriole regions. Since the distal regions of centrioles contain microtubule doublets, it remains to be investigated whether Ofd1 could specifically act on microtubule doublets. Mutations in Ofd1 leads to multiple human pathologies like, for example, the orofaciodigital syndrome [51].

(Figure 1 Legend Continued) bars; other centriolar binding partners are highlighted with grey bars. Available structures of domains are depicted in cartoon representation. They were prepared using PyMol (Schrodinger LLC) using the following Protein Data Bank (PDB) entries: CPAP G-box, 4BXP; CPAP PN2-3, 5ITZ; Cep120 C2A, 6FLJ; Cep120 C2B, 6EWG; Cep120 C2C, 6FLK; Klp10A motor domain, 6B0C.

Figure 2



CEA and CEI interaction networks.
CEA and CEI network components are highlighted in green and red, respectively. '−End' and '+End' indicate the polarity of the microtubules in the centriole (−End, microtubule minus-ends; +End, microtubule plus-ends). The double arrows highlight the potential crosstalk between the CEA and CEI networks.

CEA and CEI networks and their possible crosstalk

As described above, CEAs and CEIs do not act in isolation but collaborate together with their accessory proteins to execute their functions (Figure 2). This interdependence is required for proper protein localization (Cep120-CPAP [31]; CP110-Kif24 [41]), stability (Centrobin-CPAP [22]), or activity (Cep120-CPAP-SPICE1 [23]). Thus, both CEAs and CEIs seem to act as protein network machineries that either activate or inhibit centriolar microtubule growth to control precisely the length of centrioles. Whether there is a functionally relevant crosstalk between the CEA and CEI networks remains to be investigated — the observation that the CEI CP110 localizes to the growing procentriole adjacent to the CEA CPAP/SAS-4 [37] and that it interacts with the CEA Centrobin [52•] indicates that this may indeed be the case.

Concluding remarks and future perspectives

Why is it important to understand the molecular mechanisms underlying centriole length control? Mutations in proteins controlling centriole length often lead to ciliopathies and developmental disorders [24]. Furthermore, elongated centrioles can lead to centrosome amplification, enhanced centrosome activity and chromosome segregation defects, all factors that contribute to tumorigenesis [53]. Thus, besides representing a fundamental open basic research question in biology, understanding the formation and architecture of centrioles may hold the key for developing strategies against multiple severe human pathologies.

Microtubules are the major structural components of centrioles and hence play a key role in defining centriole length. In this review, we categorized the proteins that control centriole length into two classes, CEAs and CEIs, based on their antagonistic activities on the growth of centriolar microtubules. We recently started to get first glimpses on how these proteins and their networks affect the formation of centriolar microtubules and how their activities are regulated by accessory proteins, by post-translational modifications or by controlling their intracellular levels. Immediate open questions emerging from recent studies are: What are the modes of action of the CEAs and CEIs networks on microtubule dynamics, stability and length? Can CEA and CEI networks specifically recognize centriolar microtubules and if so how? Is

there a functional crosstalk between the CEA and CEI networks and if so what is its underlying mechanism(s) and how is it regulated?

One possible route to start answering these questions is to understand how CEA and CEI network components specifically localise to, recognize and affect centriolar microtubules. Detailed structural and biochemical investigations on CEAs and CEIs may reveal novel tubulin-binding and microtubule-binding domains as well as their specificity determinants towards centriolar microtubules. In this context and based on previous observations [41], it is expected that centriole-specific tubulin isotypes or tubulin posttranslational modifications of the C-terminal tubulin tails [6] will play a major role in imparting binding specificity. Another possible route would be to systematically test whether CEA and CEI network components interact with each other and how interfering with such interactions affects centriole length. On a more long-term perspective, reconstituting and imaging of the CEA and CEI networks together with microtubules will reveal a comprehensive picture of the processes governing the length of the fascinating centriole organelle.

Conflict of interest statement

Nothing declared.

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