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Neurite pruning and neuronal cell death: spatial regulation of shared destruction programs

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During development, neurons are initially overproduced and excess neurons are eliminated later on by programmed cell death. In a more refined developmental process termed pruning, excess axons and dendritic branches are removed while the cell body remains intact. In mature animals, axons that become disconnected as a result of injury are eliminated through a series of events collectively known as Wallerian degeneration. Recent evidence points to unexpected similarities between these three types of obliterative processes, as they share common regulators. These findings provide new ideas on how cellular destruction programs are spatially regulated in neurons.

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Introduction

It is well established that regressive processes are important for the establishment of accurate neuronal connections during development [1–3]. However, from a mechanistic point of view our understating of these events lags behind our knowledge of progressive phenomena such as neuronal migration, axon guidance and synapse formation. Unlike other organs and tissues in which cell death accounts for almost all regressive events during development, in many cases, the complex cellular structure of neurons undergoes a more limited refinement. In these cases, the soma is spared but pruning of long neuronal processes and synapse elimination allow the formation of new connections [2,4]. Previous studies suggested that differential genetic programs are employed by the neuron for its death or for pruning of its neurites [2,4,5]. However, recent studies provide evidence indicating that the cell is much more economical, and that neurite pruning and programmed cell death have many shared elements. Therefore, the cellular outcome does not rely on the genetic program that is activated, but rather on how the cell regulates it spatially.

Naturally occurring neuronal cell death and neurite pruning

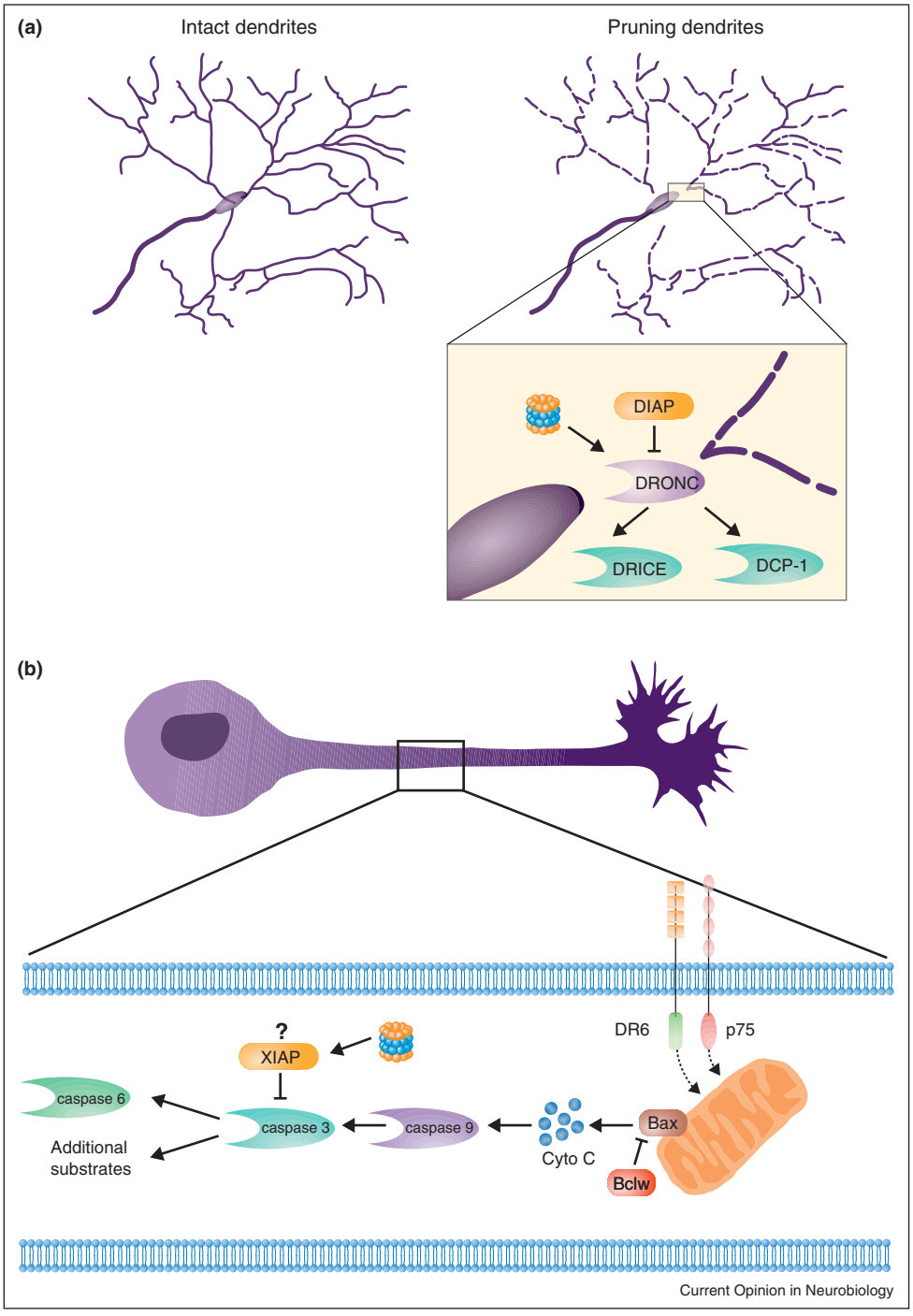
Programmed cell death (PCD) was the first major regressive event that was recognized to shape the nervous system during development. It is now well established that neurons die throughout the vertebrate nervous system at specific developmental stages, resulting in loss of up to 75% of the neurons in certain neuronal nuclei [3]. The roles of PCD during development of the nervous system in multiple model organisms have been extensively reviewed. PCD may act to match the number of neurons to the target field they innervate or to eliminate misguided axons. Notably, however, genetic manipulations of the apoptotic machinery in the mouse resulted in significantly increased numbers of neurons in the CNS, but did not cause severe behavioral abnormalities [3]. This suggested that other forms of PCD may compensate for the apoptotic system, or that other mechanisms allow proper wiring in the face of higher numbers of neurons.

The removal of axonal process and synapses is a widespread developmental phenomenon in vertebrates that ranges from elimination of axonal arbors in the neuromuscular junction (NMJ) to the stereotyped pruning of long axonal projections in the brain [2,4,6]. Interestingly, several cellular mechanisms have been shown to control these events. These include axonal retraction, local degeneration and axosome shedding [7–10]. Most of these processes are not recapitulated by *in vitro* systems, hampering elucidation of the molecular mechanisms that govern them. The most commonly used *in vitro* setup to study axonal pruning is the Campenot chamber. This allows the selective withdrawal of trophic support, mainly NGF (nerve growth factor), from the axons, which results in induction of axonal degeneration without cell death [11]. Remodeling of the *Drosophila* nervous system during metamorphosis provides a unique invertebrate system in which the power of the fly's genetics can be used to uncover the mechanisms of axonal and dendritic pruning. In all of the *Drosophila* studies so far, neuronal process pruning is executed by local degeneration [12–14].

The role of the apoptotic system in neurite pruning

The first indication that the apoptotic system has a role in neurite pruning in addition to its function in PCD came

Figure 1



The apoptotic system regulates neurite pruning in mammals and flies. **(a)** Developmental pruning of sensory neurons dendrites in *Drosophila* is regulated by the apoptotic system. Upon pruning induction, the caspase inhibitor DIAP1 is degraded by the proteasome, which leads to activation of the initiator caspase Dronc. This induces the severing of sensory dendrites from the cell body (arrow heads) and the activation of two effector caspases (DCP-1 and DRICE) that promote the degeneration of the dendrites (arrows). **(b)** Apoptotic machinery executes axonal pruning induced by trophic deprivation and activation of the death receptors DR6 and p75. The pro-apoptotic BAX protein initiates activation of the apoptotic system through release of mitochondrial cytochrome-C, subsequent activation of the initiator caspase-9 and the effector caspase-3, and caspase-6. The anti-apoptotic protein BclW, which binds to BAX, and the caspase-3 inhibitor XIAP, negatively regulate this pathway.

from studies on dendritic pruning of dendritic arborizing (da) sensory neurons in *Drosophila* [15,16] (Figure 1a). These neurons prune their dendrites, but not their axons, first by severing them from the cell bodies; subsequently they degenerate. The initiator caspase Dronc is required for effective dendrite severing and degeneration, while the effector caspases are needed for efficient degeneration [15,17]. Local caspase activity is detected only in dendrites that are degenerating [15–17]. The regulation of Dronc is largely achieved by degradation of its inhibitor, DIAP1, through the ubiquitin proteasome system [15]. The apoptosis protease activating factor 1 (Apaf-1) homolog, ark, a positive regulator of Dronc, may also play a role [16]. Overall, these studies provide clear evidence that the core components of the fly's apoptotic machinery are essential for dendritic pruning.

In mammals, cultured sensory or sympathetic neurons in trophic deprivation models served as platforms to examine the role of the apoptotic system in axonal pruning [17–19] (Figure 1b). Initially there were some discrepancies about the role of different caspases in axonal pruning, due to the use of pharmacological and knockdown approaches [17,18]. These inconsistencies were recently resolved using genetically modified animals [20••,21••]. The emerging picture is that elements of the core apoptotic machinery, caspase-9, caspase-3 and the pro-apoptotic protein BAX are all essential for axonal pruning [17,18,20••,21••]. Caspase-6, which has not been implicated in PCD, operates downstream of caspase-3 and plays a more minor role [20••]. As in the case of *Drosophila*, it was suggested that XIAP, the mammalian homolog of DIAP1, functions as a regulator of caspase-3 [17,21••]. However, the importance of this mechanism is still not clear [20••]. By exploiting the stereotyped pruning of RGCs in the mouse during development, it was further demonstrated that both caspase-3 and caspase-6 are equally required for efficient pruning, *in vivo* [20••]. Nonetheless, in the *in vitro* trophic deprivation model using sensory neurons, caspase-3 plays a more prominent role in the pruning process than caspase-6 [20••]. These differences may be generated by culture conditions or simply by the fact that these are completely different neuronal populations. Whatever the case, these studies highlight the fact that mechanistic extrapolation from one system to another is not always straightforward.

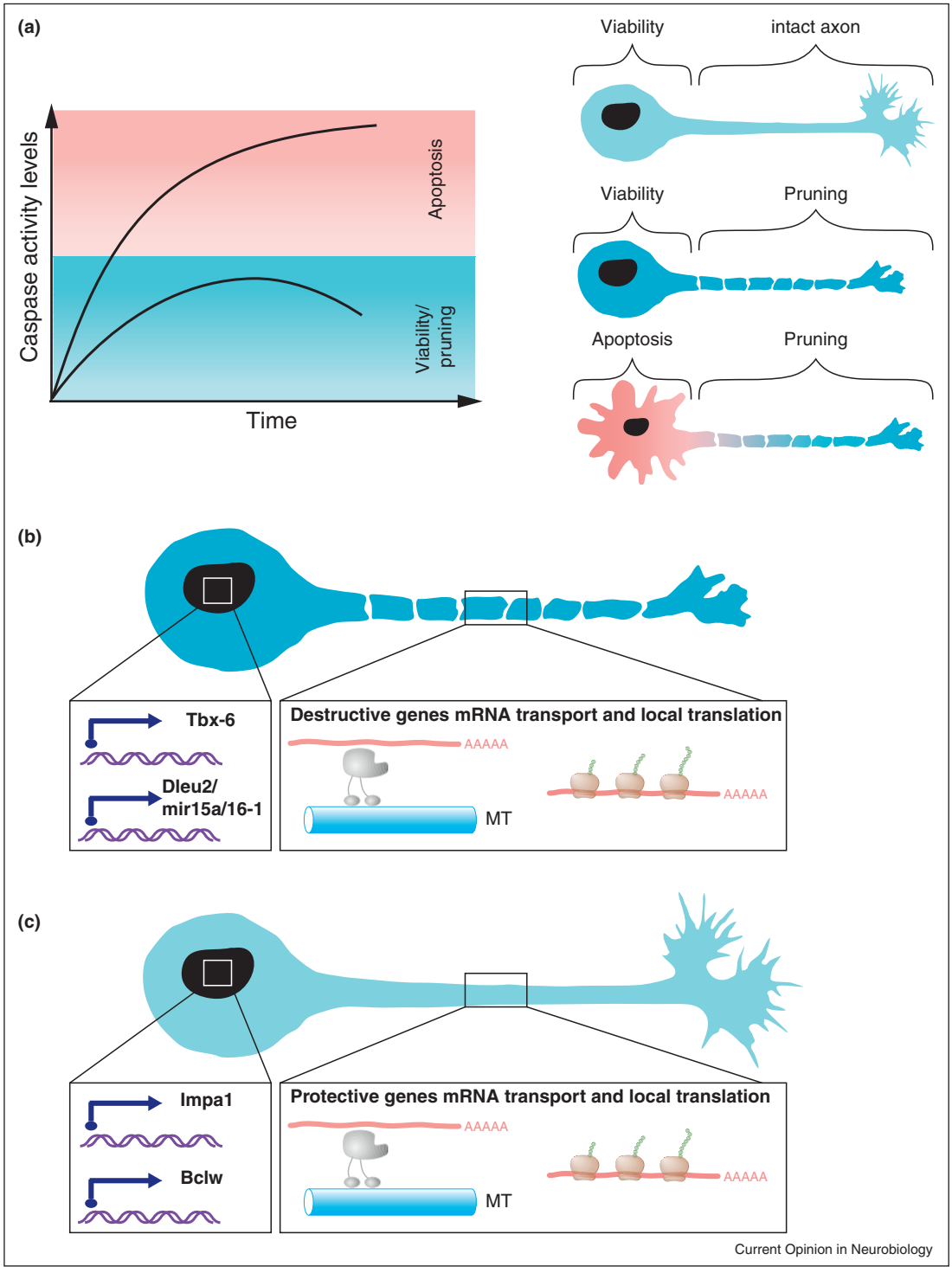
In addition to intracellular apoptotic regulators, two death receptors, DR6 and p75, have been implicated in pruning [18,22,23]. While DR6 is stimulated by N-APP [18], p75 was found to be activated by both BDNF [23] and myelin [22]. The developmental pruning of RGCs was used to show the function of DR6 *in vivo* [18]. The role of the BDNF-p75 pathway has been demonstrated *in vivo* by monitoring the pruning of sympathetic axons that project to the eye, and by genetic manipulation of neuronal activity in the olfactory system [23,24]. In both cases, neuronal activity suppressed the pruning process and allowed the active axons to eliminate the non-active ones through stimulation of p75 by BDNF [23,24]. A similar molecular mechanism has been shown to regulate cell death of sympathetic neurons [25]. However, in this system trophic support rather than neuronal activity suppressed cell death. Mathematical modeling of the death process suggested that combining passive death by trophic deprivation with death induction through p75 by the living neurons generates significantly more efficient neuronal elimination [25]. Whether this is also true for pruning processes remains to be tested.

The signaling mechanisms by which these death receptors ultimately lead to activation of the apoptotic system are still largely elusive [26,27]. Interestingly, it was suggested that DR6 and p75 form a complex [28]. It should be noted that death receptors usually operate through caspase-8 and the extrinsic apoptotic pathway [29]. However, caspase-8 has not been implicated so far in pruning and in contrast BAX, which is a key pruning factor, is a central player in the intrinsic apoptotic pathway [29]. The mechanisms by which these pruning receptors activate the intrinsic pathway may be important for PCD in general and not just in the context of pruning.

Nonapoptotic programmed cell death and Wallerian degeneration share molecular mechanisms

Injured axons degenerate in a process termed Wallerian degeneration, which greatly resembles degeneration during pruning [30]. Multiple studies have demonstrated that the apoptotic system has no role in this degeneration process [17,19,20••,31]. Instead the Wallerian Degeneration Slow (Wld^s)-sensitive pathway was shown to control this type of axonal degeneration both in vertebrates and in invertebrates (for extensive review on this pathway see [32]). Moreover, the Wld^s sensitive pathway does not interfere with apoptotic cell death [17,33]. Therefore, it was postulated that axotomized axons activate a self-destruction program that is distinct from PCD. Recent studies in *Caenorhabditis elegans*, *Drosophila* and mice suggest an intriguing link between axon Wallerian degeneration and non-apoptotic PCD. Genetic screens in *Drosophila* identified the Toll receptor adaptor protein dSarm1 as a key regulator of axonal degeneration after axotomy [34••]. This function of Sarm-1 is conserved in mammals, suggesting that it is part of an ancient axonal self-destruction program [34••]. Studies in *C. elegans* also showed that the worm homolog of Sarm1 (Tir1) is essential to the nonapoptotic cell death of linker cell [35••]. *Tir1* extracts its function in PCD through the p38 MAPK pathway [35••]. Interestingly, inhibition of p38 in axons protects against axonal degeneration upon NGF withdrawal [36•]. An intriguing possibility that arises from these studies is that Wld^s may regulate a nonapoptotic cell death similar to that of the linker cell. This will expand

Figure 2



Spatial regulation of the apoptotic machinery. **(a)** Control of pruning versus cell death by threshold of caspase activity. Low (below the threshold) axonal caspase activity is sufficient to induce pruning but not cell death; once activity levels pass the threshold, death is induced as well. **(b)** Positive regulation of pruning versus cell death by local translation. Axonal pruning induction by trophic withdrawal induces the Dleu2/mir15a/16-1 cluster and the transcription factor Tbx-6. These in turn may activate unknown factors, which are required for pruning but not cell death. The axonal specific activity of these factors may be achieved through mRNA transport and local translation. **(c)** Impa1 and Bclw negatively regulate axonal pruning by local translation. NGF controls transcription of Bclw and translation of Impa; in the presence of NGF their mRNA is transcribed, transported to the axon and locally translated. Bclw inhibits axonal pruning by preventing activation of the apoptotic system through direct binding to the pro-apoptotic BAX. The axonal function of Impa1 is not known but its depletion from axons induces caspase-dependent pruning.

the function of the Wld^s sensitive pathway beyond Wallerian degeneration and may help to uncover its physiological role. Another interesting possible regulator of the linker cell death is the ubiquitin ligase Highwire, which was recently shown to control Wallerian degeneration in *Drosophila* [37].

It is also conceivable that this old destruction program has a physiological role within axons as well. However, the relationship between injury-induced axonal degeneration and developmental pruning is not completely clear. Several studies have shown that the two programs share some elements including the ubiquitin-proteasome system and the two kinases DLK and GSK3β [12,36•,38–41]. Moreover, Wld^s was shown to delay dendritic and axonal pruning [17,42,43]. However, it is clear that not all pruning events are inhibited by the Wld^s protein or in dSarm/Sarm1 mutants [34••,44].

Mechanisms of spatial regulation

The involvement of apoptotic and nonapoptotic cell death programs in axonal destruction raises the question — how does the cell activate these programs without inducing cell death? It seems that at least part of the answer is that it exerts tight spatial control on activation of these systems. One method of spatial control, as demonstrated in *Drosophila* da neurons, is physical detachment of the degenerating neurites from the cell body (Figure 1a). This clearly confines the active death program to the severed neurite [15–17]. In this case, the critical event is the precise severing of the neurite before activation of death programs. This is accomplished by combination of intrinsic regulation of the dendrites cytoskeleton and extrinsic signal from the surrounding glia cells [45,46].

When pruning takes place with the degenerating axon still connected to the cell body, as is true in many mammalian instances of pruning, other mechanisms of spatial regulation must take place. Recent study has demonstrated that Apaf-1 is required for cell death upon trophic deprivation but not axon pruning [21••]. Proposing that caspases are activated through different pathways in the soma and the axons. Work in *Drosophila* has suggested that to induce cell death, caspase activity must exceed a critical threshold [47••]. If pruning can be executed by caspase activity below the death threshold, caspase-dependent pruning could be triggered without cell death as long as there is tight control of expression or activity levels, even if some active caspase leaks to the soma (Figure 2a). In support of this model, it was suggested that much lower level of caspase-3 activity is required for axonal degeneration upon NGF deprivation than the activity that is required for neuronal cell death in the same paradigm [20••]. Moreover, knockout of the anti-apoptotic protein Bclw generates gradual axonal loss without cell death, which is consistent with the idea that axons are much more sensitive than the soma to imbalance in the apoptotic system [48•].

More recently it was suggested that there is differential transcriptional control on the axonal apoptotic program versus the cell body. While neuronal cell death is regulated by the transcription factor c-Jun, the Dleu2/mir15a/16-1 cluster and the transcription factor Tbx-6 regulate the degeneration of sensory axons in Campenot chambers [36•,38] (Figure 2b). How these transcriptional programs are translated into spatial activation of the apoptotic machinery is still elusive. One mechanism that may operate here is mRNA transport and local translation as it is now well established that both dendrites and axons contain a rich repertoire of mRNAs, many of which are translated in response to various stimuli [49]. Although there is currently no evidence that axonal pruning factors are locally translated there is evidence that protective proteins are (Figure 2c). One such factor may be myo-inositol monophosphatase-1 (Impa1), a key enzyme in the inositol cycle [50]. Axonal translation of Impa1 is governed by NGF, and its ablation, specifically from the axons of sympathetic neurons, induces caspase-dependent axonal degeneration. More persuasive evidence for the role of local translation in pruning was discovered recently, when it was shown that NGF also controls transcription of the anti-apoptotic protein Bclw in sensory neurons [51••]. The newly transcribed mRNA of BclW is then trafficked to the axon, locally translated and inhibits pruning through binding to BAX [51••] (Figures 1b and 2c).

Conclusions

In summary while evidence for the usage of shared effectors for cell death, neurite pruning and Wallerian degeneration is accumulating as additional players are discovered, key questions remain. Is all neurite pruning the result of partial or contained activation of cell death pathways? Here, we discussed only a few examples of neurite pruning for which at least some of the executing machinery has been identified. In many other cases, including axosome shedding, retraction of hippocampal axons and pruning of mushroom body axons in *Drosophila*, the underlying machineries are not yet known, thus their relationship to cell death programs has not been determined [2,52]. In addition, there is growing understanding of additional PCD programs not discussed in this review, including necroptosis and autophagy [53]. It will be interesting to test if these programs are involved in neurite pruning and degeneration as well; both genetic and pharmacological tools are available to do this. Despite these caveats, from the available data a picture is emerging of overlapping use of cellular self-destruct programs for cell elimination and for refinement of cellular connectivity, a remarkable efficiency. The mechanisms by which cells achieve such precise regulation of these pathways are of great interest. Our knowledge of the spatial

regulation of the cell death programs is still fragmented and the complete picture is likely to involve interplay between mechanisms discussed here and others that remain to be discovered. We anticipate that future studies that combine robust *in vitro* systems with genetically modified animals will provide new insights into these important questions.

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