Review

The role of meiotic drive in hybrid male sterility

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Meiotic drive causes the distortion of allelic segregation away from Mendelian expected ratios, often also reducing fecundity and favouring the evolution of drive suppressors. If different species evolve distinct drive-suppressor systems, then hybrid progeny may be sterile as a result of negative interactions of these systems' components. Although the hypothesis that meiotic drive may contribute to hybrid sterility, and thus species formation, fell out of favour early in the 1990s, recent results showing an association between drive and sterility have resurrected this previously controversial idea. Here, we review the different forms of meiotic drive and their possible roles in speciation. We discuss the recent empirical evidence for a link between drive and hybrid male sterility, also suggesting a possible mechanistic explanation for this link in the context of chromatin remodelling. Finally, we revisit the population genetics of drive that allow it to contribute to speciation.

Keywords: meiotic drive; hybrid sterility; speciation; chromatin remodelling

1. INTRODUCTION

Species formation occurs when gene exchange between two populations has mostly or completely stopped. Gene exchange may be prevented by extrinsic factors, such as geographical isolation, but such extrinsic factors may say little or nothing about the genetic divergence that allows species to coexist without losing their identity. Instead, most studies of 'speciation' focus on intrinsic genetic differences between populations that limit gene exchange. Typical examples of such differences are behavioural mating discrimination and hybrid sterility.

Hybrid sterility and other hybrid incompatibilities have been a focus of genetic studies of speciation. Part of this intensive focus comes from their association with one of the most consistently followed patterns in evolutionary biology: Haldane's rule. This rule states that the heterogametic (XY or ZW) sex is more likely than its counterpart to exhibit F₁ hybrid inviability or sterility (Haldane 1922). Studies mapping the genetic basis of F₁ hybrid male sterility have identified a major cause being interactions between genes on the sex chromosomes and autosomes, and a few of the interacting genes have been cloned in the past few years (see reviews in Noor & Feder 2006; Orr *et al.* 2007; Presgraves 2007).

Despite this progress in mapping the genes and their interactions, researchers have not yet determined whether particular evolutionary or genetic forces disproportionately lead to the evolution of hybrid sterility. Some of the cloned genes associated with

hybrid sterility exhibit a strong signature indicating recent natural selection (Ting *et al.* 1998) while others do not exhibit this pattern (Masly *et al.* 2006; Phadnis & Orr 2009). One hypothesis for a force contributing to hybrid male sterility is meiotic drive, the subject of this review. Most studies of meiotic drive and its association with hybrid male sterility have been performed in *Drosophila*, which potentially limits the scope of the research covered in this review. Such an association has been postulated in other systems, but in those cases meiotic drive could not be distinguished from other genotype frequency distortions in hybrids (e.g. inviability of particular hybrid genotypes) or was not linked to mapped hybrid sterility loci (e.g. *Mimulus*: see Fishman & Willis 2005). The lack of studies of meiotic drive involved in hybrid sterility in other systems presents a large gap in this field that future studies are encouraged to address.

2. FORMS OF MEIOTIC DRIVE AND HOW THEY MAY (OR MAY NOT) CONTRIBUTE TO HYBRID STERILITY

The term 'meiotic drive' can be used in a variety of contexts (described below), though it is generally defined as a distortion of segregation away from Mendelian ratios of allelic inheritance in heterozygotes (Presgraves 2008). Meiotic drive is characterized by the differential formation or success of gametes, and this meiotic or gametic failure may reduce overall fertility. Usually, homologous chromosomes segregate equally (one homologue to each gamete); however, alleles or chromosomes containing a 'drive element' will be transmitted to more than 50 per cent of offspring, at the expense of their homologue. Despite the reduction in fertility of the bearer, the allelic

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transmission advantage can allow the driving chromosome to spread within a species. Driving alleles also tend to be located in inversions or other regions of low recombination, and therefore deleterious mutations linked to the driver may increase in frequency via hitchhiking. Drivers located on the sex chromosomes can strongly distort sex ratios (SRs), which could possibly lead to extinction. These many deleterious effects select for drive suppressors, which have evolved for most known drive systems. We describe two types of meiotic drive that can lead to hybrid sterility: female (chromosomal) and male (genic).

Female or 'chromosomal' drive occurs via competition among oocyte chromosomes for deposition into the resultant egg cell; however, this competition runs an added risk of causing hybrid male sterility. Most *Drosophila* oocytes undergo four rounds of incomplete cytokinesis during meiosis; only one of the resulting cells will become an egg and pass its chromosomes to offspring. Meiotic products may compete for deposition into the egg cell via spindle fibre attachment (Zwick *et al.* 1999; Pardo-Manuel de Villena & Sapienza 2001). Variation in satellite sequences at the centromere (the site of spindle attachment) and numerous replacement polymorphisms at the centromeric histones suggest rapid evolution, and further support the hypothesis of an arms race to be 'chosen' to be relegated to the egg cell (Malik & Henikoff 2001; Malik *et al.* 2002). This arms race for spindle attachment can have negative side effects; centromeric and telomeric sequences in different populations may be divergent enough to cause misalignment of the centromeres, thereby disrupting meiosis in hybrid males and causing sterility (McKee 1998; Zwick *et al.* 1999; Henikoff *et al.* 2001). However, although a possible contributing force, female drive may not provide the single best explanation of Haldane's rule for two reasons: female drive does not explain hybrid inviability and female drive seemingly would not apply to haplodiploid species or species lacking an XY or ZW sex (whereas Haldane's rule still applies to both species types). Further, in haplodiploid or XO species, competition between the two chromosomes would be eliminated and no arms race would occur to increase the chance of hybrid incompatibilities (reviewed further in Coyne & Orr 2004). The remainder of this review will focus mainly on X chromosome male drive and its relevance to speciation.

While chromosomal drive is characterized by a competition between centromeres for spindle fibre attachment, male drive (also called genic drive) is a competition between alleles during sperm development. The mutations caused by this competition may increase divergence between two species and therefore also run the risk of causing hybrid male sterility. During normal spermatogenesis, half of the newly formed haploid sperm cells should contain X chromosomes and the other half should contain Y chromosomes. Deviations from a 50–50 SR in offspring (typically towards females) often indicate genic drive of sex chromosomes in males. Male drive may result from lack of production of Y-bearing sperm or producing Y-bearing sperm rendered incapable of fertilization (§3). In many instances,

sex-chromosome meiotic drive is specifically associated with a particular chromosomal rearrangement (§4) and in *Drosophila*, these rearrangements are dubbed 'SR chromosomes'. While sex-chromosome drive appears more common than autosomal drive, this perception may result from an observational bias: sex-chromosome drive is easily detected by SR disruptions ranging from 60% to 100% female offspring (reviewed in Jaenike 2001, electronic supplementary material). Autosomal drive is more difficult to observe directly unless a visible phenotypic trait difference is closely linked to the driving locus.

Suppressors of meiotic drive are likely to evolve on the autosomes as a response to a change in the SR caused by X-linked drivers, causing them to be observed often in sex-chromosome drive systems. Autosomal suppressors will adjust the SR back to normal; however, they may not spread to fixation quickly. Y-linked suppressors can also restore the SR and will exhibit intense positive selection as non-suppressing Y chromosomes will not appear (Hurst & Pomiankowski 1991; Atlan *et al.* 2003). However, the size, gene content and number of autosomes compared with the Y chromosome provide greater possibility for suppressors to evolve (Hurst & Pomiankowski 1991). Atlan *et al.* (2003) further showed that when the strength of autosomal suppression of drive was substantially greater than Y-linked suppression, autosomal suppressors would spread faster. This observation suggests a reason why autosomal suppressors are observed in so many drive systems and why drive systems that contain Y-linked suppressors nearly always contain autosomal suppressors as well (Stalker 1961; Carvalho & Klaczko 1993, 1994; Jaenike 1999).

Almost 20 years ago, two independent publications discussed the likelihood of mutations in male drive systems explaining hybrid sterility and Haldane's rule in particular (Frank 1991; Hurst & Pomiankowski 1991). These authors described a model where rapid coevolution of drivers and suppressors increases the divergence between species. A reduction in fertility is a common by-product of meiotic drive, and thus accelerated evolution at drive loci may disproportionately impact spermatogenesis genes, inadvertently increasing the chance of hybrid-sterility-causing interactions. The arms race between the evolution of drivers and suppressors is thought to cycle, each triggering evolution in the other (Carvalho *et al.* 1997; Hall 2004). Because distorters may be evolving repeatedly on the X chromosome, this cycle model reinforces the idea that rapid evolution on the sex chromosomes could greatly increase divergence between species and may be a contributor to the large-X effect observed in genetic studies of hybrid sterility (Charlesworth *et al.* 1987; Coyne & Orr 1989; Turelli & Orr 2000; Masly & Presgraves 2007; Tao *et al.* 2007a,b).

However, these meiotic drive theories for hybrid male sterility were quickly criticized for multiple shortcomings (Coyne *et al.* 1991; Charlesworth *et al.* 1993). For example, recombination between distorter alleles and their responders can prevent the spread of new drive systems if the responder allele is recombined onto the same chromosome as the distorter, thereby

causing the distorter to drive against itself (Prout *et al.* 1973; Hartl 1975; Liberman 1976; Thomson & Feldman 1976; Charlesworth & Hartl 1978; Lessard 1985). Because of the absence of crossing over between the X and Y chromosomes, Frank (1991) argues that drivers should evolve faster on the sex chromosomes than autosomes. While Coyne *et al.* (1991) argue that in certain cases, autosomes are actually more likely to evolve drivers, recent empirical studies have repeatedly identified X-linked drivers, including the four discussed in the next section.

Perhaps the strongest criticisms of the meiotic drive models came from the lack of supporting data from empirical studies at the time. Frank's (1991) model assumed that meiotic drive should occur in interspecies crosses, yet early studies failed to detect evidence of meiotic drive in fertile backcross hybrid males (Johnson & Wu 1992; Coyne & Orr 1993). Hurst & Pomiankowski (1991) further predicted that the Y chromosome would play a major role in the association of meiotic drive and hybrid male sterility, but at least some studies of hybrid sterility detected no involvement of the Y chromosome, and Haldane's rule is even observed in species not bearing a Y chromosome (Coyne *et al.* 1991; Charlesworth *et al.* 1993). Despite such arguments against these early meiotic drive hypotheses for causing hybrid sterility, several recent studies have demonstrated compelling links between male drive and hybrid male sterility (see §3).

3. RECENT EMPIRICAL STUDIES LINKING MEIOTIC DRIVE AND SPECIATION

Recently, numerous empirical studies linked drive and sterility in hybrids, yet few have proposed a precise mechanism for this link. Most drive systems are characterized as 'true drive,' where the drive actually takes place during meiosis. This class of drive causes target-carrying sperm never to be produced, as opposed to 'gamete-killing drive,' where the target-carrying sperms are produced but are incapable of fertilization owing to disruptions occurring any time after meiosis. True drive, such as fragmentation of the Y chromosome (Novitski *et al.* 1965), seems to be more common in sex-chromosomal drive systems (see discussion in Montchamp-Moreau 2006), whereas autosomal drive systems, such as segregation distorter (SD) in *Drosophila melanogaster* and the *t*-haplotype in mice, exhibit gamete-killing drive (Kusano *et al.* 2003; Lyon 2003).

Hauschteck-Jungen (1990) identified a link between hybrid sterility and a driving X chromosome derived from one population of *Drosophila subobscura*. Some wild *D. subobscura* males collected from Tunis produced 90 per cent female offspring. These males carried $A_{2+3+5+7}$, an SR arrangement on the X chromosome containing four inversions relative to the standard. Hauschteck-Jungen (1990) further observed that males possessing the Tunis $A_{2+3+5+7}$ X chromosome with autosomes derived from another strain (Küsnacht) were sterile, while males possessing the Küsnacht X chromosome and Tunis autosomes were fertile. Hence, presence of SR X chromosome

arrangement contributed to sterility in hybrids within species when paired with autosomes that had not coevolved with it.

A driving factor also causes sterility in hybrids between *Drosophila simulans* and *D. mauritiana* when made homozygous (Tao *et al.* 2001). Tao *et al.* (2001) introgressed 259 homozygous segments of the *D. mauritiana* third chromosome into *D. simulans* and scored the offspring for fertility and drive. Two segments interact to cause both drive and sterility: *too much yin* (*tmy*) and *broadie*. *Too much yin* (*Tmy*) is presumed to be an autosomal suppressor of X chromosome drive. The *D. simulans* copy of *Tmy* appears to be dominant to the *D. mauritiana* copy (*tmy*), which explains why their study only observed sterility when the *D. mauritiana* introgression was homozygous in the *D. simulans* background. When the *D. simulans* copy was present in the same background, all males were fertile with no SR distortion and the same results were observed for *Tmy/tmy* males. About half of the males homozygous for *D. mauritiana tmy* in a *D. simulans* background were sterile (235/452) while the others were fertile with a strong SR bias. They determined that, while *tmy* alone fails to suppress the SR bias, the added presence of the *broadie* modifier causes complete male sterility. They further fine-mapped *tmy*, narrowing it down to a region spanning 80 kb and demonstrated that recombination cannot separate the two phenotypes (sterility and drive), indicating that *tmy* can act alone to cause both.

Multiple links between meiotic drive and hybrid sterility have been made through genetic mapping studies in the *Drosophila pseudoobscura* species group. The first such link is inferential. Early mapping studies by Wu & Beckenbach (1983) and Orr & Irving (2001) identified effects of the right arm of the X chromosome of *D. persimilis* as contributing to sterility in a *D. pseudoobscura* genetic background. These studies both used strains of *D. persimilis* bearing a SR driving X chromosome. Curiously, the opposite effect was observed by Noor *et al.* (2001), where the same *D. persimilis* X chromosome region derived from non-driving *D. persimilis* X chromosomes reduced hybrid-sterility-conferring interactions elsewhere in the genome when in a *D. pseudoobscura* background. This discrepancy suggests a link between the driving X chromosome and hybrid sterility, but this link is only inferential until more precise mapping is conducted.

More recently, drive and sterility have been directly linked in hybridizations between the *D. pseudoobscura* subspecies. One direction of the subspecies cross (*bogotana* females crossed to *pseudoobscura* males) produces very weakly fertile male progeny (Orr & Irving 2005). Moreover, these hybrid males produce strongly female-biased offspring, a driving effect masked in pure *D. pseudoobscura bogotana* owing to autosomal suppressors. The X-linked factor causing segregation distortion was localized near the *sepia* locus; however, this factor is necessary but not sufficient: distortion requires additional *D. pseudoobscura bogotana* introgressions to exhibit drive. The location implicated here for meiotic drive is the same location mapped in a previous study for hybrid male sterility (Orr & Irving 2001),

leading the authors to suggest that the same factor causes both drive and hybrid male sterility (Orr & Irving 2005). This region was recently mapped further and a gene, *Overdrive*, was identified that is responsible for both phenotypes (Phadnis & Orr 2009). *Overdrive* encodes a protein with a Myb/SANT-like domain in an Adf-1 (MADF) DNA-binding domain. Adf-1 is a transcription factor known to activate genes regulated during *Drosophila* development (England *et al.* 1992).

Some meiotic drive systems and hybrid-sterility-conferring genes share common factors that can be incorporated into a potential single mechanistic explanation for the link between these two phenotypes: chromatin remodelling. Heterochromatin formation was recently implicated in causing hybrid female lethality between *D. melanogaster* males and *D. simulans* females (Ferree & Barbash 2009). In hybrid females, the region of the *D. melanogaster* X chromosomes containing the *Zygotic hybrid rescue* (*Zhr*) gene disrupts separation of chromatids, and the *D. simulans* machinery is unable to compensate. The aforementioned gene *Overdrive*, which contributes to both meiotic drive and hybrid sterility, may also be involved in chromatin remodelling. Further, *Overdrive* is not the only *Drosophila* hybrid-sterility gene to contain a MADF domain; hybrid male rescue (HMR) in *D. melanogaster* contains four MADF domains (Barbash *et al.* 2003; Maheshwari *et al.* 2008). HMR causes hybrid male lethality and hybrid female sterility between *D. melanogaster* and its sibling species, *D. mauritiana*, *D. simulans* and *D. sechellia* (Hutter & Ashburner 1987; Barbash & Ashburner 2003; Barbash *et al.* 2003). Recent studies suggest that some of HMR's MADF domains may be involved in chromatin binding (Barbash & Lorigan 2007; Maheshwari *et al.* 2008), while other studies have also implicated defects in chromatin remodelling as a potential mechanism of meiotic drive (Hauschteck-Jungen & Hartl 1982; Montchamp-Moreau 2006; Tao *et al.* 2007a,b).

Silencing on the X chromosome also involves changes in chromatin states that occur during spermatogenesis. The X chromosome is inactivated in primary spermatocytes during spermatogenesis in *Drosophila*, mammals and nematodes (Lifschytz & Lindsley 1972; Kelly *et al.* 2002; Hense *et al.* 2007). Lifschytz & Lindsley (1972) demonstrated that factors that prevent proper silencing during inactivation may cause sterility. A potential change in chromatin states could result from the different arrangement of the X chromosome in SR *Drosophila*; the rearrangement then causes a failure of the X and Y chromosomes to align during metaphase in hybrids, leading to an arrest of spermatogenesis (McKee 1998). Hence, changes in chromatin states owing to meiotic drivers may also negatively impact X chromosome silencing and therefore fertility. *Drosophila* XO males also undergo X chromosome inactivation, and if such males exhibit disrupted silencing owing to the aforementioned hypothesis, this explanation may address one of the issues raised by Coyne & Orr (2004) regarding the inability of female drive to explain sterility in XO species. Interactions involving chromatin remodelling, and the MADF-binding domain in particular,

may prove to be involved in multiple hybrid incompatibilities.

Finally, our suggestion that changes in chromatin modifications can affect hybrid sterility is further strengthened by a recent finding by Bayes & Malik (2009). The *Drosophila mauritiana* allele of *OdsH* (*OdsH*) contributes to hybrid male sterility when in a *D. simulans* genetic background (Ting *et al.* 1998). The endogenous protein binds to heterochromatin, particularly loci on the X and fourth chromosomes. Coexpression of the *D. mauritiana* and *D. simulans* *OdsH* alleles in sterile hybrids led to anomalous binding of the *D. mauritiana* copy to the Y chromosome, resulting in altered chromosome condensation. Transgenic lines into multiple species also exhibited altered localization of OdsH, reflecting the rapid evolution seen within the *OdsH* homeodomain (Ting *et al.* 1998). These results demonstrate rapid coevolution between a hybrid-sterility gene and its heterochromatic targets across this clade.

4. POPULATION GENETICS OF DRIVE AND SPECIATION

Understanding how drive contributes to speciation requires an understanding of how drive arises and is maintained despite associated fitness detriments. Drive systems on sex chromosomes arise more easily than on autosomes, yet become fixed less easily. This delay between emergence and fixation allows more time for selection to act against sex-chromosome drive systems via recombination, introduction of suppressors and association of unpreferred traits. However, certain effects of drive are also selected, thus causing the cyclical evolution of drivers and suppressors mentioned previously. Again, this cycling can increase the opportunity for hybrid incompatibilities to arise and cause speciation. We discuss each of these processes in this section.

Drive systems are inherently more detectable to investigators when they arise on sex chromosomes than autosomes because of the associated skew in SR. However, despite the observational bias, there are also evolutionary reasons why drive systems would favour the X chromosome. Autosomal drivers must arise on an insensitive chromosome and then drive against a sensitive chromosome (Charlesworth & Hartl 1978). Taking into account the fitness cost (usually a reduction in male fertility) typically associated with drive, Hurst & Pomiankowski (1991) showed that, for autosomal drivers to invade, the frequency of the insensitive chromosome must be low, and the driver must be in strong linkage disequilibrium (LD) with the target. Sex-linked drive systems require fewer starting conditions; as the X and Y chromosomes do not recombine, it is easier to maintain LD between the driver and target (Wu & Hammer 1991). Thus, autosomal drivers must depend on strong LD for invasion, whereas sex-linked drivers rely only on the equilibrium that must be maintained between selection and drive (Hurst & Pomiankowski 1991).

Sex-linked drive systems become fixed less easily than autosomal systems, and this feature may predispose them to acquiring suppressors (Wu 1983;

James & Jaenike 1990; Jaenike 1996, 2001; Capillon & Atlan 1999; Wilkinson & Fry 2001; Taylor & Jaenike 2002; Atlan *et al.* 2004; Wilkinson *et al.* 2006). A system with an X-linked driver will skew the SR of the population such that there is less competition for females, and thus males mate more often (Jaenike 1996). However, driver-carrying males often exhibit reduced fertility (Hartl *et al.* 1967; Beckenbach 1978; Wu 1983; James & Jaenike 1992; Jaenike 1996; Atlan *et al.* 2004; Fry & Wilkinson 2004; Wilkinson *et al.* 2006). Therefore, the driver is held at equilibrium, where selection against it increases as its frequency increases (Wu 1983; James & Jaenike 1990; Jaenike 1996, 2001; Capillon & Atlan 1999; Wilkinson & Fry 2001; Taylor & Jaenike 2002; Atlan *et al.* 2004; Wilkinson *et al.* 2006). This balance between selection and frequency allows greater time for a drive suppressor to evolve, and drivers that skew the SR provoke selection against themselves. Therefore, evolution of suppressors is more likely under X-linked drive systems (Hurst & Pomiankowski 1991).

Non-Mendelian SRs are generally disadvantageous, and thus in sex-linked drive systems, selective pressure is applied that pushes the ratio back to normal (Lyttle 1979). This selective pressure may yield greater probability of inducing the arms race discussed earlier, where rapid evolution at drivers and suppressors increases divergence and thus hybrid incompatibilities are more likely to arise (Frank 1991). Given the fertility reduction in SR males, offspring would be more fit if recombination broke up drivers and their linked targets; however, many drivers are located in inversions, where recombination is prevented. Thus, recombination may prevent drivers from initially fixing, but recombination will have little effect if the drivers are already fixed or have reached a stable equilibrium. Furthermore, in *Drosophila*, where drivers are typically located within inversions, the X chromosome drive loci are thought to have originated prior to the introduction of the inversions (Wu & Beckenbach 1983; Lyttle 1991; Babcock & Anderson 1996). These drive loci would not have been linked without the inversions, and thus no drive would occur. However, as the inversions evolved, more of the X would become linked and eventually the final inversion would have linked the drive loci together causing meiotic drive and increasing the frequency of the inversion arrangement in the population (Babcock & Anderson 1996).

In addition to recombination, the evolution of suppressors will also push the SR back to Fisherian proportions (Lyttle 1979). Continued driver presence will favour the evolution of suppressors; however, once suppressed, a different driver may arise and start the cycle over again (Hall 2004). This cycling hypothesis could explain how meiotic drive is linked to hybrid sterility, where this rapid evolution at different regions of the genome can cause increased divergence and therefore heighten the likelihood of hybrid incompatibilities arising.

Selecting for traits associated with drive can further affect driver frequency, which may induce an arms race between drivers and suppressors. In mice and stalk-eyed flies, females can distinguish between males carrying driving elements and non-driving males

(Lenington & Egid 1985; Wilkinson *et al.* 1998; Carroll *et al.* 2004). In both species, the females actually preferentially mate to non-driving males, and thus drive is selected against (Lenington *et al.* 1992; Wilkinson *et al.* 1998). Females of the stalk-eyed fly species *Cyrtodiopsis dalmanni* and *C. whitei* prefer mates with the longest eye stalks (Burkhardt & de la Motte 1985) and eye span (Burkhardt & de la Motte 1988; Wilkinson & Reillo 1994). However, longer eye stalks are associated with genetic factors that suppress female-biased sex-chromosome drive.

5. CONCLUDING REMARKS

While meiotic drive was not a popular explanation for hybrid sterility just over a decade ago (Johnson & Wu 1992; Coyne & Orr 1993), many recent studies implicating an association between meiotic drive and hybrid male sterility suggest that the community ruled out this possibility too quickly (Wu & Beckenbach 1983; Hauschteck-Jungen 1990; Tao *et al.* 2001; Orr & Irving 2005; Phadnis & Orr 2009). Theoretical studies suggest evolutionary reasons why meiotic drive may contribute to hybrid sterility, and recent empirical studies suggest explicit links between these two phenomena. Furthermore, exploring the genetic architecture of both drive and sterility may provide clues as to the mechanistic basis of an association between them. Future studies of drive and hybrid male sterility should consist of cloning the underlying genes as well as clarifying the role of chromatin remodelling and X chromosome inactivation during spermatogenesis. Overall, this area is ripe for further investigation to help us understand hybrid sterility and the origin of biodiversity.

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