Ageing Research Reviews 96 (2024) 102268

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

Somatic mutations in human ageing: New insights from DNA sequencing and inherited mutations

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ARTICLE INFO

Keywords:
DNA damage
Genome
Longevity
Tumorigenesis

ABSTRACT

The accumulation of somatic mutations is a driver of cancer and has long been associated with ageing. Due to limitations in quantifying mutation burden with age in non-cancerous tissues, the impact of somatic mutations in other ageing phenotypes is unclear. Recent advances in DNA sequencing technologies have allowed the large-scale quantification of somatic mutations in ageing tissues. These studies have revealed a gradual accumulation of mutations in normal tissues with age as well as a substantial clonal expansion driven mostly by cancer-related mutations. Nevertheless, it is difficult to envision how the burden and stochastic nature of age-related somatic mutations identified so far can explain most ageing phenotypes that develop gradually. Studies across species have also found that longer-lived species have lower somatic mutation rates, though these could be due to selective pressures acting on other phenotypes such as perhaps cancer. Recent studies in patients with higher somatic mutation burden and no signs of accelerated ageing further question the role of somatic mutations in ageing. Overall, with a few exceptions like cancer, recent DNA sequencing studies and inherited mutations do not support the idea that somatic mutations accumulating with age drive ageing phenotypes, and the phenotypic role, if any, of somatic mutations in ageing remains unclear.

1. Introduction

As the blueprint to life and cellular functions, one of the primary suspects as a driver of ageing is the gradual accumulation of DNA damage and mutations, a hypothesis first proposed in the late 1950's (Szilard, 1959). Studies in rodents suggest that disruption in DNA repair and DNA damage responses can often result in a short lifespan and phenotypes resembling accelerated ageing, known as 'segmental progeroid syndromes' (Freitas and de Magalhaes, 2011; Vijg, 2021). Human progeroid syndromes, like Werner Syndrome, also originate from inherited mutations in genes involved in DNA damage responses. Evaluating and quantifying DNA damage and mutations in vivo is not straightforward, however, not least because of their random nature. In rodents, gene reporter systems have been used to estimate levels of DNA damage and somatic mutations, showing a gradual increase with age in most (but not all) tissues (Freitas and de Magalhaes, 2011; Ren et al., 2022). Given the age-related incidence of cancer and the higher number of mutations in tumours from older patients (Chatsirisupachai et al., 2021), mutations are expected to accumulate with age in human tissues, but until recently with limited empirical evidence.

Recent advances in high throughput technologies, particularly DNA sequencing, provide new opportunities to investigate and gain insights into ageing and other diseases and processes (de Magalhaes et al., 2010; Ren et al., 2022). Studies during the past few years have revealed the landscape of somatic mutations, particularly single-nucleotide variants (SNVs), in non-cancerous tissues, which we outline below. Recent comparisons in mutation rates across species are also discussed. While somatic mutation burden increases with age in all tissues investigated, the relevance of the mutation accumulation to ageing processes (other than cancer) remains unclear, and we argue that they are unlikely to explain most ageing phenotypes.

2. Somatic mutations accumulate with age in non-cancerous tissues

Several recent studies using genome and transcriptome sequencing have identified somatic mutations in normal human tissues, including strong age-related patterns (Abascal et al., 2021; Blokzijl et al., 2016; Li

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https://doi.org/10.1016/j.arr.2024.102268
Received 23 August 2023; Received in revised form 19 February 2024; Accepted 6 March 2024
Available online 13 March 2024

et al., 2021; Lodato et al., 2018; Martincorena, 2019; Moore et al., 2021; Ren et al., 2022; Rockweiler et al., 2023; Yizhak et al., 2019). Somatic mutations accumulate throughout life and if a given mutation provides a selective advantage to a cell, it will amplify clonally. Unlike in tumours, clonally amplified cells from a single mutant cell typically occur in a small subset of cells within the non-cancerous tissue, making the detection of somatic mutations in normal tissues challenging. Thus, several methods have been developed to overcome this challenge, such as using ultradeep targeted sequencing of a gene panel (Martincorena et al., 2018). Other methods include DNA sequencing on either an *in vitro* single-cell-expanded clone (Blokzijl et al., 2016), which represent a single genome, or laser-captured clonal structures to selectively dissect a small cluster of cells (Lee-Six et al., 2019).

Clearly, the major finding from these sequencing studies is that there is a ubiquitous increase in somatic mutations with age, as observed in various dividing and non-dividing tissues like the brain (Lodato et al., 2018), blood (Genovese et al., 2014; Jaiswal et al., 2014), colon (Lee-Six et al., 2019), heart (Choudhury et al., 2022), oesophagus (Martincorena et al., 2018; Yokoyama et al., 2019), skin (Martincorena et al., 2015), lung (Yoshida et al., 2020), testes (Maher et al., 2018), small intestine (Wang et al., 2023a), liver (Brunner et al., 2019) and others. In addition, recent studies have examined the longitudinal accumulation of somatic mutations across several cell types/organs within the same individuals (Franco et al., 2019; Li et al., 2021; Moore et al., 2021; Park et al., 2021). While numbers of SNVs detected in most tissues were found in a range of a few hundred to several thousand per genome, these numbers vary from tissue to tissue. For example, the highest mutation rate among tissues was found in the small intestine and crypts of the large intestine, with about 50 base substitutions per cell per year, making up a total burden at approximately 5000 SNVs of an 80-year-old individual. Conversely, the mutation rate was lowest in spermatogonia (Moore et al., 2021). Overall, across multiple studies of mutation rates in human tissues with age, SNVs/cell/year varied from ~2.4 in the testis to ~56 in the intestine (Ren et al., 2022).

The major caveat of methods such as deep sequencing of bulk tissues and laser-captured dissection followed by sequencing is that they are only able to detect clonally amplified mutations, precluding the quantification of mutations occurring in only one or a few cells. In addition, *in vitro* single-cell expansion assays can only be performed on mitotically active cell types, are time-consuming, and lead to additional mutations during culturing. Recent studies thus developed single-cell approaches to detect somatic mutations in B lymphocytes (Zhang et al., 2019), hepatocytes (Brazhnik et al., 2020), bronchial epithelial cells (Huang et al., 2022), neurons (Miller et al., 2022), and cardiomyocytes (Choudhury et al., 2022). Not surprisingly, these studies reveal mutation accumulation rates during ageing consistent with those estimated from sequencing of clonally expanded cells. For example, single-cell analysis of bronchial epithelial cells of never-smoker donors revealed an accumulation of ~28 SNVs/cell/year (Huang et al., 2022), similar to ~22 SNVs/cell/year measured from single-cell derived colonies (Yoshida et al., 2020). These rates vary among cell types, however. For example, somatic mutations accumulated ~3 times faster in cardiomyocytes (~60 SNVs/cell/year) than in neurons (~19 SNVs/cell/year) (Choudhury et al., 2022). Also of note, the observation that mutations accumulate with age in non-dividing cells such as neurons argues against the idea of cell division as the key source of somatic mutations (Abascal et al., 2021).

Mutational signature analysis has revealed similarities and differences between the underlying mechanisms across cell types. For instance, age-related increases in the clock-like C>T mutational signature that accumulate consistently like a chronological clock are observed in cardiomyocytes, neurons, lymphocytes, and hepatocytes. Likewise, a C>A signature associated with oxidative damage was also found to increase with age in all these cell types. However, only in cardiomyocytes – where the mismatch repair defect signature, dominated by C>T and T>C mutations but different from the clock-like signature in its trinucleotide context – increases in an age-dependent manner (Choudhury et al., 2022). Interestingly, one study showed that age-related accumulation of somatic mutations in normal neurons is primarily due to the clock-like mutational process, while neurons from Alzheimer's disease patients harboured additional C>A variants associated with an oxidative damage signature as measured via the oxidation product 8-oxoguanine (8-oxoG) (Miller et al., 2022). Somatic mutations in Alzheimer's disease neurons were distributed across the genome and did not overlap with Alzheimer's disease risk loci, suggesting that these mutations were more likely to be a secondary effect caused by a high accumulation of reactive oxygen species (ROS) in neurons from Alzheimer's disease patients (Miller et al., 2022).

Strikingly, recent studies in human tissues indicate that the rate of somatic mutation accumulation with age does not appear to accelerate at older ages. Rather, it accumulates linearly with age and specific C>T clock-like mutational signatures account for most somatic mutations in normal tissues. The mutation rate is relatively high during the first embryonic divisions before dropping considerably, which could relate to the activation timing of more mature DNA repair mechanisms (Coorens et al., 2021). One recent analysis of somatic mutations in human brains found that hypermutable brains were more frequent in individuals over 60 years-old, but when excluding hypermutable samples found no correlation of mutation burden with age, suggesting an early developmental origin of somatic mutations (Bae et al., 2022).

Taken together, these recent results confirm the idea that mutations accumulate with age in most, if not all, human tissues. In addition, there is a very large variation between cells in the mutations detected; even though most mutations will be neutral, all tissues are mosaics made up of genetically diverse individual cells (Mustjoki and Young, 2021). This is unsurprising because mutations are sporadic, and given the size of the genome, mutations will occur in different genomic regions in different cells. If it happens for a mutation to result in increased cell proliferation or somehow improve the fitness of the cell (e.g. mutations in cancer driver genes), then this will result in the expansion of that clone (Martincorena, 2019). Somatic mutations could then predispose to cancer, in line with the multi-hit hypothesis driving cancer. Data from the oesophagus, for instance, supports this concept of clonal expansion (Martincorena et al., 2018; Yokoyama et al., 2019). The degree of clonal expansion depends heavily on the tissue cell dynamics (e.g., whether the tissue self-renews or not) and anatomy. In some tissues, like the oesophagus, clonal expansion can result in large parts of an aged tissue being composed of mutant cell populations. By contrast, in the colon, cells are organized into crypts, with each crypt containing ~2000 cells originating from stem cells at the base of a crypt. Thus, a clonally expanded clone in the colon usually localises within a crypt. As such, tissue anatomy has a major impact on clonal expansion and differences between tissues. Overall, although it may predispose to cancer, the impact of clonal expansion on normal physiology is not clear.

In some cases of stress and pathology, clonal expansions and mutations have been observed, usually predisposing to cancer, though clonal expansions can be protective as well (Kakiuchi and Ogawa, 2021; Ogawa et al., 2022). Liver stress, such as chronic liver disease, can cause mutations in metabolism genes in liver that lead to clonal expansion (Ng et al., 2021), some of which are adaptive and protective (Wang et al., 2023b; Zhu et al., 2019). Mutations and clonal expansion are also selected for in inflammatory bowel disease (Olafsson and Anderson, 2021). Likewise, some stressors can result in a significantly higher somatic mutation accumulation. Of note, mutation accumulation is substantially higher in the lungs of smokers than what is observed in aged non-smokers (Huang et al., 2022; Yoshida et al., 2020). One study found that smoking adds 1000 to >10,000 mutations per cell (Yoshida et al., 2020). More specifically, although single base substitutions accumulate with age in the lung, at an estimated rate of 22 SNVs/cell/year, ex-smokers have an average increased burden of 2330 SNVs per cell and current smokers 5300 more SNVs per cell (Yoshida et al., 2020), which explains the much higher cancer incidence in

smokers.

The above sequencing studies of somatic mutations have limitations. It should be noted that these studies infer the mutation landscape based on only ~5–40 individuals in each study. Furthermore, the difficulties in detecting somatic copy-number alteration (SCNAs) and structural variations (SVs), including insertions, deletions, duplications, inversions, and translocations, mean that current methods may be underestimating the actual number of alterations. Only 2–3 per cent of the elderly contain detectable clonal mosaicism from chromosomal anomalies in blood (Jacobs et al., 2012; Laurie et al., 2012). Recent studies were able to detect, albeit rarely, SCNAs in non-cancerous solid tissues including the oesophagus (Li et al., 2021; Yokoyama et al., 2019), liver (Brunner et al., 2019), colon (Lee-Six et al., 2019), and endometrium (Moore et al., 2020). However, it is expected that the continuous development of sequencing technology will allow a more precise detection of large-scale somatic variants. Indeed, more studies are needed to paint a more complete picture of somatic mutations in normal tissues, in particular regarding other types of mutations than SNVs.

3. Mutation rates, cancer, and ageing across species

Across species, one recent study using cell lines reported that mutagen-induced mutation frequencies inversely correlated with species-specific maximum lifespan (Zhang et al., 2021). Another recent work also reported gradual increases in somatic mutations with age in intestinal crypts in various mammalian species (Cagan et al., 2022). Interestingly, somatic mutation rates inversely correlated with the lifespan of the species, and body mass was less strongly correlated with somatic mutation rates (Cagan et al., 2022). While this result could be interpreted as supporting the somatic mutation theory of ageing (Franco and Eriksson, 2022), there are possible alternative explanations. Given that mutations accumulate from early in development (Coorens et al., 2021), there may be selective pressure for early embryonic DNA sequence fidelity self-check to ensure successful foetal development. It could also be argued that the strong negative association between somatic mutation rate and lifespan could be a result of increased cancer incidence in species with a higher rate of mutation accumulation. Indeed, cancer is widespread among metazoans (Albuquerque et al., 2018; Vincze et al., 2022). As such, selection in mammals to avoid or postpone cancer may result in various adaptations, as previously discovered in whales, elephants and mole-rats (Nery et al., 2022), and one potential adaptation is lower somatic mutation rates (Leroi et al., 2003). Therefore, if the mutation burden necessary to cause cancer is significantly lower than that of other ageing phenotypes, animals may evolve mechanisms to reduce their mutation burden and postpone cancer, resulting in a lower mutation burden than is necessary to drive other ageing phenotypes (de Grey, 2007). In this sense, the lower mutation burden observed in long-lived species may perhaps be explained by the need to reduce cancer risk.

4. Impact of age-related somatic mutation accumulation on human ageing

Recent results showing an increase in somatic mutations with age have been interpreted by some as supporting the idea of a causal role of mutation accumulation in ageing (Vijg and Dong, 2020). On the other hand, it can be argued, as many have before (de Grey, 2007; Maynard Smith, 1959), that the number of mutations observed are too low to explain widespread detrimental effects in tissues. Mutations are nearly always heterozygous and most of them affect non-coding regions with only ~12 mutations in pancreas parenchyma to 76 mutations in liver exomes at older ages (85 – 93 years old) (Li et al. Nature 2021). Further, a study on satellite cells from older individuals (64–78 years old) found an average of 2.25 and 11.5 SNVs per genome in non-coding regulatory regions including promoters and enhancers, respectively (Franco et al., 2018). Besides, patterns of selection in cancer and somatic tissues show that homozygous mutations are much more likely to be detrimental (Martincorena et al., 2017), and the probability of homozygous mutations in the absence of clonal expansion are extremely low – and nearly zero for homozygous mutations in the same gene in two nearby cells. While cancer driver mutations can lead to clonal expansion in tissues and ultimately cancer, no empirical evidence to date supports similar processes leading to degenerative changes during ageing.

Possible mechanisms for how somatic mutations could drive ageing have been proposed, such as mutations in lymphocytes leading to pathogenic autoantibodies that contribute to autoimmune diseases (Singh et al., 2020), and through positive selection on mutations that lead to clonal expansions of phenotypically aberrant cells (Cagan et al., 2022). It has also been suggested that one possible mechanism by which somatic mutations could contribute to ageing is through introducing gene expression noise (Vijg, 2021). Somatic mutations that occur in regulatory regions of the genome could cause dysregulation in the gene regulatory network and aberrant transcription, leading to the physiological decline of tissue functions. Indeed, cell-to-cell variability in gene expression increases with age and correlates with an age-related increase in somatic mutations (Enge et al., 2017; Levy et al., 2020). Moreover, there is likely a mosaic cellular pattern of highly dysfunctional and senescent cells mixed in with normally functioning cells within tissues that increases with age. Secreted signalling factors from a small percentage of highly dysfunctional cells might contribute to tissue dysfunction, though whether mutations drive these dysfunctional cells in ageing remains unknown. Besides, it is unclear how the stochastic nature of mutations and gene expression noise might result in gradual changes during ageing. Even if somatic mutations could contribute to gene expression noise, quantitative analysis is needed to demonstrate how many mutations per genome are required to cause enough noise that impacts cellular phenotypes; and whether this number of mutations is consistent with the observed number of mutations accumulating during ageing. Furthermore, the proportion of cells with altered mutation-created transcriptional noise in a tissue sufficient to disrupt tissue functions is currently unclear. Overall, the phenotypic consequences of mutations in ageing tissues remains unknown.

Ageing, and contrary to cancer, is not a result of the increase of cell proliferation. Quite the opposite, ageing and cancer could be seen as two sides of the same coin in that while cancer increases cell proliferation, ageing often results in a reduced proliferation typically accompanied by a loss of function, cells, and tissue mass. Recent results support this observation and have revealed that ageing and cancer have opposite transcriptional responses in most human tissues (Chatsirisupachai et al., 2019). That said, other ageing diseases besides cancer exhibit stochastic patterns, like clonal haematopoiesis of indeterminate potential, in turn a risk factor for cancer and cardiovascular disease (Jaiswal et al., 2017). Mutations may also drive specific age-related diseases (Mustjoki and Young, 2021), like cerebral cavernous malformations that grow through a three-hit cancer-like mechanism (Ren et al., 2021). Clearly, some ageing phenotypes and diseases are likely driven by mutations. Such cases, other than cancer, appear to be a small subset of ageing phenotypes that are random and of low incidence overall. It does not seem to apply to most ageing phenotypes that are gradual and/or widespread (in most cases inevitable) like sarcopenia, loss of wound healing with age, menopause, ageing of the cardiovascular system, loss of sensory function, hair greying, loss of kidney function, cognitive ageing, thymus involution, loss of lung capacity, etc.

If random events like mutations are driving gradual ageing changes like sarcopenia, cognitive ageing and hair greying then one would expect these phenotypes to be random, to affect different parts of the tissue and/or different parts of the body at different times in different places. But by and large that is not what is observed. With exceptions like the above-mentioned cancers and cavernomas, ageing is fairly regular and consistent. As people age there are gradual changes, such as loss of muscle mass, hair greying and baldness, as well as a gradual loss of function in many organs (e.g. heart, lungs, and kidneys). Although

there is variation in ageing patterns between individuals, they do not tend to vary as much within individuals. As an example, hair greying in the beard of men tends to be symmetrical (Poljsak et al., 2020). Therefore, we speculate that stochastic events like mutations are unlikely to be causal for most ageing phenotypes, in particular in light of their low frequency in coding and regulatory regions, as discussed above. Nonetheless, we acknowledge that whether the number, frequency and impact of mutations observed in recent sequencing studies of aged tissues is sufficient to drive the age-related degeneration of tissues and organs remains a subject of debate. To infer causality of the impact of somatic mutations in ageing one major empirical approach is to determine whether genetic changes in mutation burden impact ageing phenotypes (de Magalhaes, 2024), as discussed below.

5. Causal evidence from inherited mutations in mice and men

Apart from cancer and a small subset of diseases like cerebral cavernous malformations, causal evidence for the role of somatic mutations in human ageing and most age-related diseases is lacking (de Magalhaes, 2024; Olafsson and Anderson, 2021). Serial cloning of mice for over 25 generations did not result in a decrease of cloning efficiency (Wakayama et al., 2013). In contrast, one recent study sequenced the genome of centenarians and revealed genetic variants in genes related to DNA repair as one possible mechanism (Garagnani et al., 2021). It is therefore important to consider the causal evidence of the role of somatic mutations in ageing from specific genetic manipulations in mice and inherited diseases in humans.

Progeroid syndromes, most – but not all (Dolle et al., 2006) – of which in humans and mice are caused by defects in genome maintenance, support the idea that DNA damage is important in ageing (Franco et al., 2022; Vijg, 2021). Nonetheless, some authors have questioned whether progeroid syndromes reflect normal ageing processes (Keshavarz et al., 2023), and the exact molecular mechanisms and specifically a role of somatic mutations in progeroid syndromes remains unclear. Besides, if somatic mutations drive ageing, then one would expect other defects resulting in a higher burden of somatic mutations to result in accelerated ageing. But that is not the case in mice or in humans. Several mouse models with elevated mutations fail to exhibit, apart from enhanced cancer, a clear acceleration of ageing phenotypes (Franco et al., 2022; Kennedy et al., 2012). Examples include *Pms2*-null mice with a 100-fold higher mutation frequency in multiple tissues (Narayanan et al., 1997) and mutator mice with defects in DNA polymerase that have a mutation rate 17 times that of wild-type mice (Uchimura et al., 2015) and do not manifest progeroid symptoms, although they have a higher incidence of cancer and consequently a shorter lifespan (Albertson et al., 2009; Goldsby et al., 2002; Kennedy et al., 2012).

In humans, one recent study showed that individuals with inherited defects in DNA polymerases have more somatic mutations accumulating with age and more cancer, yet do not age faster (Robinson et al., 2021). Another related study also reported that individuals carrying *MUTYH* germline mutations, a gene involved in DNA repair, have 2–4-fold increased somatic single base substitution (SBS) mutation rates (92–193 SBS/year compared with 46 SBS/year in controls) and were predisposed to colorectal cancer. However, these individuals do not show signs of premature ageing, and exhibit a similar rate of telomere shortening between individuals with *MUTYH* mutations and controls (Robinson et al., 2022). Taken together, these studies argue that elevated mutation accumulation alone is unlikely to cause most human ageing-related phenotypes. In addition, while SCNAs and SVs may have a more profound impact than SNVs, they were rarely detected (Robinson et al., 2021, 2022).

6. Concluding remarks

Taken together, recent DNA sequencing experiments focused on quantifying mutations with age reveal a gradual increase in mutations, and widespread evidence of clonal expansion of rapidly dividing mutant clones. These observations are consistent with the age-related increase in cancer observed in most tissues. However, the levels of mutations reported so far are difficult to reconcile with most ageing phenotypes. Whether and how somatic mutations in ageing tissues, affecting mostly non-coding regions and overwhelmingly different genes in different cells, can cause dysfunction is unclear. Likewise, while clonal expansion may be a factor in ageing and result in tissue dysfunction, so far this is not directly supported by experimental data and remains an open question. As such, there is a stark contrast between cancer and ageing: while cancer can originate from mutations in a single cell and subsequent clonal expansion, shown empirically to occur (Evans and DeGregori, 2021), age-related dysfunction would need, we suggest, many mutations in a very large number of cells in a tissue. Evolutionarily this has led others to suggest that the evolutionary pressure to prevent cancer will result in levels of somatic mutations in tissues across the lifespan that will be lower than the number of mutations needed to cause most other age-related conditions (de Grey, 2007).

Recent evidence from inherited mutations in patients with increased somatic mutation burden and no symptoms of accelerated ageing also cast doubt on the role of somatic mutations in most ageing phenotypes – even if it is not well understood why hypermutator phenotypes sometimes do and sometimes do not result in progeroid phenotypes. Perhaps other forms of DNA damage and/or genome instability may accumulate at much greater rates in human tissues, but these have not been studied in detail and have thus far limited empirical support. The impact of clonal expansion, SCNAs, and SVs on ageing phenotypes, in fact, remains to be further investigated. Advances in genome sequencing technology together with the development of computational methods to reliably detect large-scale structural alterations at a single-cell level should shed light on the potential role of SVs and SCNAs on human ageing.

After the idea that somatic mutations could be the main cause of ageing was first proposed in the late 1950's (Szilard, 1959), Maynard-Smith questioned it by arguing that the number of mutations necessary would be too high to be consistent with the data available at the time (Maynard Smith, 1959). Decades and numerous technological advances in genetics and genomics later, which have produced quantitative data on mutation load in aged tissues, and yet we are no closer to empirically showing a role for somatic mutations in ageing and, in fact, have grounds to question it.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: J. P.M. is CSO of YouthBio Therapeutics, an advisor/consultant for the Longevity Vision Fund, 199 Biotechnologies, and NOVOS, and the founder of Magellan Science Ltd, a company providing consulting services in longevity science

Acknowledgements

K.C. was supported by a Mahidol-Liverpool Ph.D. scholarship from Mahidol University, Thailand, and the University of Liverpool, UK. J.P. M. is supported by grants from the Wellcome Trust (208375/Z/17/Z), Longevity Impetus Grants, LongeCity and the Biotechnology and Biological Sciences Research Council (BB/V010123/1). We are also grateful to current and past members of our lab for valuable discussions and suggestions, in particular Blaine van Rensburg and Thomas Duffield.

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