Physiological Mechanisms of Stress-Induced Evolution

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Summary statement

This article presents five mechanisms that eukaryotes can employ when experiencing stress to accelerate the process of adaptation. These mechanisms are outlined with emphasis on examples in animals.

Abstract

Organisms mount the cellular stress response (CSR) whenever environmental parameters exceed the range that is conducive to maintaining homeostasis. This response is critical for survival in emergency situations because it protects macromolecular integrity and, therefore, cell/organismal function. From an evolutionary perspective, the cellular stress response counteracts severe stress by accelerating adaptation via a process called stress-induced evolution (SIE). In this review, we summarize five key physiological mechanisms of stress-induced evolution. Namely, these are stress-induced changes in 1) mutation rates, 2) histone post-translational modifications, 3) DNA methylation, 4) chromoanagenesis, and 5) transposable element activity. Through each of these mechanisms, organisms rapidly generate heritable phenotypes that may be adaptive, maladaptive, or neutral in specific contexts. Regardless of their consequences to individual fitness, these mechanisms produce phenotypic variation at the population level. Because variation fuels natural selection, the physiological mechanisms of stress-induced evolution increase the likelihood that populations can avoid extirpation and instead adapt under the stress of new environmental conditions.

Introduction

All living organisms exist under the stress of their environment. Stress, in this sense, refers to any environmental parameter exerting strain on biological systems (Kültz, 2020a). When organisms are well-adapted to their environments, they harbor mechanisms that counteract imposed strain and therefore maintain homeostasis. Whenever environmental parameters change, organisms must adjust these mechanisms to uphold the balance between stress and the forces that oppose it. If the change in stress is minor enough, only the cellular homeostasis response (CHR) is needed for this adjustment. However, the capacity of the CHR may be exceeded depending on the magnitude of stress and how rapidly it arises. This threshold for stress tolerance is termed the "elastic limit," and once it is surpassed, organisms must activate the cellular stress response

(CSR) in order to survive (Kültz, 2020a; Call et al., 2017; Tian et al., 2012). Stress of this degree is becoming increasingly relevant and concerning to life on Earth amid climate change. As the atmosphere continues to collect greenhouse gases, numerous environmental factors, including the temperature, salinity, and acidity of water, change globally and much more rapidly than during previous geological periods (Cheng et al., 2020; Hoegh-Guldberg et al., 2007; Karger et al., 2020). When populations are limited in their ability to migrate to more suitable environments, they must somehow adapt in order to remain viable.

Under these circumstances, the CSR can employ physiological mechanisms of stress-induced evolution (SIE). These are strategies by which individuals rapidly generate new heritable phenotypes. At the population level, SIE produces widespread phenotypic variation and therefore accelerates evolutionary processes. In one mechanism, stress triggers mutagenesis by causing both increased DNA damage and decreased DNA repair fidelity (Chatterjee and Walker, 2017). In a more flexible response, stress induces the alteration of epigenetic marks, including histone post-translational modifications (PTMs) and DNA methylation. These epigenetic marks modify the expression patterns of DNA. Therefore, even if an individual's sequence of DNA remains unchanged, expression patterns (and corresponding phenotypes) can be passed through generations. In a more radical response, stress can prompt the formation of structural genomic variants through either chromoanagenesis or transposable element (TE) activity. These processes can produce especially distinctive phenotypes by reorganizing gene regulatory networks, e.g., via activation or inhibition of *cis*-regulatory elements (CREs), modifying gene products, and creating and deleting genes (Lanciano and Mirouze, 2018; Mérot et al., 2020; Pellestor and Gatinois, 2020; Ye et al., 2018).

In this review, we will summarize key physiological mechanisms of SIE in eukaryotes. An emphasis will be placed on animals for supporting examples. Throughout the article, we will demonstrate on a molecular level how life experience can alter the phenotype of an individual and its progeny. Notably, these mechanisms may or may not increase an individual's fitness; oftentimes, they result in disease or sterility. Nonetheless, they facilitate the generation of phenotypic variation within populations, where individuals may develop novel solutions to compensate for stress. In doing so, these mechanisms increase the likelihood that populations will adapt under stress.

Stress triggers mutagenesis through increased DNA damage and decreased DNA repair fidelity

DNA damage is an unavoidable part of life. Even under ideal environmental conditions, DNA is continuously damaged by spontaneous alkylation, strand breaks, hydrolytic loss of nitrogenous bases, and base conversion (Chakarov et al., 2014). In humans, it is estimated that 2 x 10^4 events of DNA damage take place every day in each cell (Barzilai and Yamamoto, 2004). Damage, however, is not always detrimental, as the DNA damage response network has evolved to either repair DNA damage or tolerate it (Pilzecker et al., 2019). Only a fraction of DNA damage events lead to mutations that are retained and potentially inherited. In humans, despite the high frequency of DNA damage, rates of retained mutation are about 2.8 x 10^{-7} per base pair in somatic cells and 1.2 x 10^{-8} per base pair in the germline (Milholland et al., 2017).

Stress increases the rate of DNA damage, and therefore the rate of mutation, beyond what happens spontaneously. Diverse cellular stresses achieve this either directly or by secondarily stimulating the production of reactive oxygen species (ROS) in cells (Chakarov et al., 2014; Cheng et al., 2018; Kültz, 2005; Kültz, 2020b). ROS can damage DNA by causing strand breaks or oxidizing nucleotides into a plethora of compounds, including thymine glycol and 8-oxo-deoxyguanosine (Grollman and Moriya, 1993; Honda et al., 2001; Sallmyr et al., 2008). Through alternative routes, stress can damage DNA by producing single-strand breaks (SSBs), double-strand breaks (DSBs), apurinic (AP) sites, deaminated cytosine, cyclobutane pyrimidine dimers (CPD), and pyrimidine-pyrimidone photoproducts (6-4PP). In Table 1, we outline specific stresses that can produce these DNA lesions.

Cells attempt to repair all types of stress-induced DNA lesions. The strategy to repair DNA strand breaks depends on whether they are SSBs or DSBs. DSBs are especially mutagenic. When cells attempt to repair them, they can use the high-fidelity process of homologous recombination (HR), but most often they use the error-prone process of non-homologous end joining (NHEJ) (Chang et al., 2017). To address oxidized nucleotides, cells initiate base excision repair (BER) (Chatterjee and Walker, 2017). Nonetheless, approximately 2-5% of these lesions escape repair, and when they do, they often cause mutations from G:C to A:T (Chatterjee and Walker, 2017; Grollman and Moriya, 1993; Moriya, 1993). The remaining stress-induced lesions are often repaired through a combination of BER and nucleotide excision repair (NER). However, if the cell cycle progresses into S phase before the lesions can be repaired, DNA

damage tolerance pathways are activated instead (Chatterjee and Walker, 2017; Duncan and Miller, 1980; Pilzecker and Jacobs, 2019). Translesion DNA synthesis (TLS) is a prominent mechanism of the DNA damage tolerance pathway, and it functions to ensure that DNA replication can proceed even when DNA lesions are present. TLS promotes mutagenesis by using low-fidelity DNA polymerases that lack corrective exonuclease activity (Gerlach et al., 1999; Masuda et al., 2016).

While DNA repair is naturally fallible, stress can further reduce its fidelity and thereby increase the retention of mutations. Heat stress, for example, can inhibit both the BER and NER systems (Kantidze et al., 2016). This inhibition compromises the repair of DNA damage inflicted by stress. Similarly, proteins required for mismatch repair are downregulated under the stresses of both hypoxia and toxins (Chatterjee and Walker, 2017; Mihaylova et al., 2003). The mechanism of DSB repair can also be altered by stress, ensuring that low-fidelity NHEJ is used for repair, e.g., during hypoxia and heat stresses (Galhardo et al., 2007; Kantidze et al., 2016).

Through these and many other mechanisms, stress increases the incidence and retention of mutations. Stress-induced mutagenesis is likely an adaptive strategy as it provides an avenue for a maladapted population to accumulate genetic diversity in response to environmental change. Selection can act on the resulting genetic variation, enabling the population to become better suited for stressful environments. These mutations are not entirely random. Stress-induced mutations accumulate at different rates in transcriptionally active versus silent genes since the susceptibility to DNA damage differs between corresponding eu- and hetero-chromatin (Makova and Hardison, 2015). This effect can accelerate evolution in genes that are actively involved in defining the phenotype of a specific cell type in a specific context. Altered cellular phenotypes, in turn, influence phenotypes at higher levels of organization, including the whole organism level.

Stress causes heritable (epigenetic) changes in histone post-translational modifications

In the nucleus of eukaryotic organisms, DNA wraps around an octamer of the four core histones: H2A, H2B, H3, and H4 (Luger et al., 1997). These proteins are subject to a wide variety of post-translational modifications (PTMs) (Zhao and Garcia, 2015). Histone PTMs are epigenetic marks that can modify the state of chromatin and influence gene expression. They can do this by altering the manner in which DNA is packaged, thus changing the accessibility of the

DNA for proteins involved in transcription and repair (Norton et al., 1989). Histone PTMs also modulate the recruitment of histone reader proteins to specific genetic loci to carry out physiological functions, such as DNA repair, replication, transcription, and chromosome condensation (Kouzarides, 2007).

Stress can alter the histone PTM landscape, which is the relative abundance and genomic distribution of all histone PTMs in a cell (Table 2). Histone PTMs are "written" and "erased" by histone modifying enzymes, but the catalytic activity of these enzymes can be modified under stress, e.g., through chemical inhibition or alteration of cosubstrate availability (Fan et al., 2015). Both of these strategies apply to the histone demethylase enzyme JmjC. Oxidative stress causes the iron in its catalytic center to be oxidized from Fe(II) to Fe(III), which inhibits its function and leads to histone hypermethylation (García-Giménez et al., 2021). Interestingly, hypoxia also represses the activity of this demethylase because JmjC requires oxygen as a cosubstrate (Hsu et al., 2021). At the same time, however, hypoxia-inducible factors transcriptionally upregulate JmjC to fine-tune the overall histone demethylation activity (Hsu et al., 2021). This example illustrates that the effects of stress on the regulation of histone PTMs are pervasive and highly complex.

By modifying the histone PTM landscape, stress can facilitate an appropriate physiological response, e.g., during temperature and salinity stresses. Heat stress increases the relative abundance of H3K27me3 in the adrenal gland of chickens (*Gallus gallus domesticus*) (Zheng et al., 2021). This epigenetic response is associated with increased glucocorticoid production, which assists in heat dissipation (Zheng et al., 2021). During cold stress, the relative abundance of H3K27me3 decreases in thale cress (*Arabidopsis thaliana*), and it does so specifically at the loci of two cold stress genes, leading to their activation (Yuan et al., 2013). On the contrary, stress-induced histone PTMs can be associated with maladaptive phenotypes. For example, people working in steel plants breathe in toxic particulate matter. As their time of employment increases, their levels of H3K4me2 and H3K9ac also increase. In this case, the histone PTM landscape is associated with an increased risk for lung cancer (Cantone et al., 2011).

Even once the stress has subsided, induced histone PTMs can be retained within individuals, via "intragenerational" inheritance by mitosis (Alabert and Groth, 2012). When stress causes changes to histone PTMs in the germline, the epigenetic marks can be retained

across generations (Figure 1). This retention can occur through different processes. In one process sometimes called "intergenerational" inheritance, stress directly induces histone PTMs in the gametes of exposed parents. Upon fertilization, gametes that carry the directly induced epigenetic marks become the next generation. In a second process often called "transgenerational" inheritance, induced histone PTMs travel across multiple generations without the need for individuals inheriting them to be directly exposed to stress (Bošković and Rando, 2018; Mørkve Knudsen et al., 2018; Perez and Lehner, 2019; Woodhouse and Ashe, 2020). Transgenerational inheritance is especially relevant for stress-induced evolution as it extends the time that natural selection can act on epigenetically mediated phenotypic variation. Heat stress, for example, was shown to increase the global acetylation levels of histones H3 and H4 in the brine shrimp (*Artemia spec.*). After heat stress subsided, the induced histone PTM landscape could be transmitted through three subsequent generations, and it was associated with enhanced tolerance to severe heat stress in the progeny (Norouzitallab et al., 2014).

While the mechanism of transgenerational epigenetic inheritance is not yet fully elucidated, individuals can directly receive modified histones from the gametes that form them. This process is relatively straightforward regarding maternal transfer, but epigenetic reprogramming represents a hurdle to paternal transfer. During spermatogenesis, histone proteins are replaced with protamines for an even tighter packaging of DNA (Bao and Bedford, 2016). Some species such as mice only retain 1-2% of histones in sperm; however, this value is widely variable between species (Champroux et al., 2018). For example, the percentage of retained histones is approximately 5-10% in humans (Champroux et al., 2018), 37% in nematode worms (Samson et al., 2014), 45% in marsupials (Soon et al., 1997), and 100% in lampreys and hagfish (Saperas et al., 1997). In this way, it is possible that some species have a much higher propensity for the transgenerational inheritance of histone PTMs.

Histone PTMs offer individuals a mechanism to rapidly modify gene expression patterns and their phenotypes to better tolerate their environment. Such altered phenotypes (and the underlying genotypes of corresponding individuals) are acted upon by natural selection and, therefore, represent targets of stress-induced adaptation. Selection on these targets may be prolonged over multiple generations since individuals exposed to stress can transmit histone PTMs, gene expression patterns, and the resulting phenotypes they acquire to their progeny. The adaptive value of retaining phenotypes that confer tolerance to short periods of stress in the

absence of persistent stress may seem questionable (Nilsson et al., 2018). However, what natural selection favors under such conditions are individuals with the ability to tolerate transient periods of stress best while also performing best during intermittent periods of low stress. For this reason, histone PTMs and corresponding gene expression patterns and phenotypes are reversible, and their persistence within a lineage can depend on the intensity and duration of stress experienced by their ancestors. In this way, epigenetic mechanisms can facilitate trial runs of new phenotypes and integrate stochasticity and periodicity in environmental conditions into the process of natural selection (Burggren, 2016; Walker and Burggren, 2020). Through this mechanism (and epigenetic inheritance of DNA methylation), natural selection assesses the adaptive value of corresponding phenotype variants in a particular lineage under variable environmental conditions over longer periods of time.

Stress alters heritable (epigenetic) DNA methylation patterns

DNA methylation is a heritable epigenetic mark characterized as a methyl group attached to the fifth carbon of cytosine. When DNA methylation occurs in a promoter, it typically silences the gene by preventing the binding of transcription factors and prompting the formation of heterochromatin. Conversely, when methylation occurs in an open reading frame, it typically activates the gene (Greenberg and Bourc'his, 2019; Jones, 2012; Moore et al., 2013). De novo DNA methylation is facilitated by the DNA methyltransferase enzymes DNMT3a and DNMT3b, which can be targeted to specific genes through the guidance of piwi-interacting RNA (Flores et al., 2013; Okano et al., 1999). Stress is well documented to induce de novo DNA methylation, leading to differentially methylated regions (DMRs). Due to their influence on gene expression, DMRs can impact morphology, physiology, behavior, and development (Angers et al., 2010).

Stress-induced DMRs have been reported across taxa, from plants to insects to humans (Ou et al., 2012; Shi et al., 2011; Martin and Fry, 2018). Through this epigenetic mechanism, the environment generates new phenotypes in individuals that, for better or worse, affect their fitness (Table 3). Many putatively adaptive responses have been observed. For example, the spiny chromis damselfish (*Acanthochromis polyacanthus*) was recently shown to accumulate 193 DMRs after exposure to increased temperature (Ryu et al., 2018). Those DMRs correlated with increased aerobic scope, which enhanced tolerance to heat stress (Ryu et al., 2018). Similarly, purple sea urchins (*Strongylocentrotus purpuratus*) that experienced upwelling conditions during

gametogenesis induced DMRs in their progeny that were associated with increased body size (Strader et al., 2019; Wong et al., 2019). However, stress can sometimes also lead to transgenerational transmission of traits that reduce fitness. Ionizing radiation in zebrafish (*Danio rerio*), for example, was shown to induce 5658 DMRs; 19 of these were passed through one generation, and 5 were passed through two generations (Kamstra et al., 2018). In this case, the DMRs were localized to genes involved in cancer and apoptosis, which could help explain the developmental defects observed in the progeny inheriting these epigenetic marks (Kamstra et al., 2018).

Whether adaptive or maladaptive, phenotypes generated through stress-induced DMRs can be inherited within individuals and across generations. Within individuals, patterns of DNA methylation are often stably maintained through mitosis by the DNMT1 enzyme (Smith and Meissner, 2013). DNMT1 itself, however, has a relatively high error rate of about 5% (Bird, 2002). As a result, additional variation in DNA methylation patterns can emerge through time within an individual's cell population, which affects organismal phenotype. The mechanism of transgenerational inheritance of DNA methylation is not yet fully understood. A natural limitation to this process is that widespread reprogramming of DNA methylation takes place during gametogenesis and shortly after fertilization, but some genetic loci are protected during these events (Angers et al., 2010; Engmann and Mansuy, 2020). Even so, it has been observed on many occasions that stress-induced DMRs can be transferred through multiple generations, including in the examples mentioned above.

As an epigenetic mark, DNA methylation rapidly elicits phenotypic variation that can equip some individuals and their progeny to better cope with stress they experience. Importantly, DNA methylation functions beyond an epigenetic mark as well, in a much more permanent manner. Namely, it increases rates of mutation by frequently causing cytosine to thymine transitions (Zhou et al., 2020; Yang et al., 2021; Holliday and Grigg, 1993). This pattern is so apparent that species with widespread DNA methylation exhibit global depletion of CpG dinucleotides, because this is where DNA methylation most often occurs (Gruenbaum et al., 1982). In humans, 60-80% of all CpG sites are methylated (Smith and Meissner, 2013). With such extensive DNA methylation, the human genome only has 20% of the expected amount of CpG dinucleotides, presumably because many cytosines in these sequences have been mutated into thymines (Bird, 1980). In contrast, fruit flies (*Drosophila melanogaster*), which display a

very low level of DNA methylation, still have >90% of the expected amount of CpG sites (Capuano et al., 2014; Lyko, 2001; Bird, 1980). Because DNA methylation is targeted, C→T mutation can be targeted as well. Therefore, when stress induces DMRs, resulting phenotypic advantages can potentially be fixed in a lineage by nonrandom mutation to specific genetic loci (Angers et al., 2010).

Stress impacts genome structure through chromoanagenesis

Of all the physiological mechanisms of stress-induced evolution, changes to genome structure are the most dramatic. In a process called chromoanagenesis (also known as genome chaos), severe stress causes cells to rapidly shatter the genome and rearrange its contents (Heng and Heng, 2020). Structural genomic variants are the outcome of this process, and they can include any combination of copy number variants, chromosomal fusions, fissions, translocations, inversions, and reshuffling (Mérot et al., 2020; Heng, 2009). These structural changes strongly affect organismal fitness by changing gene regulatory networks, altering gene dosage, functionally deleting genes, or even creating new genes from previously non-coding DNA (Mérot et al., 2020; Pellestor and Gatinois, 2020; Ye et al., 2018). Most often, the effects of chromoanagenesis are deleterious. On the rare occasion, however, the generated phenotypic diversity is lifesaving (Figure 2).

Stress-induced changes in genome structure are well studied in the context of human disease. It has been discovered within the past 20 years that structural genomic variants are a universal feature of cancer, and they are frequently associated with additional diseases such as Alzheimer's (Heng, 2009; Horne et al., 2014). Using disease study systems, three categories of chromoanagenesis have been identified: chromothripsis, chromoanasynthesis, and chromoplexy (Koltsova et al., 2019). Chromothripsis refers to a single event where one chromosome is shattered and randomly stitched back together. The process is triggered by a high load of DNA double-strand breaks, which result under the pressure of numerous environmental stresses (Koltsova et al., 2019). Additional forces including telomere attrition, abortive apoptosis, and mitotic errors also prompt chromothripsis (Pellestor and Gatinois, 2020). Chromoanasynthesis is a process that specifically leads to the generation of copy number variants, and it is triggered by DNA replication and repair errors (Koltsova et al., 2019). Finally, chromoplexy describes the

reshuffling of several chromosomes over the course of multiple events, and it is often caused by replication stress, mitotic errors, and premature chromosome compaction (Shen, 2013).

Beyond causing disease states of somatic cells, chromoanagenesis proceeds within the germline and within embryos during early development (Pellestor and Gatinois, 2020). In this context, chromoanagenesis can be adaptive and lead to rapid speciation in asexually reproducing organisms and even in heterogametic species, as long as both parents experience compatible genome changes for sexual reproduction (Heng, 2009). Every type of structural genomic variant has been implicated in driving speciation (Campbell et al., 2018; Feulner and De-Kayne, 2017). Accordingly, both the morphology and number of chromosomes vary widely across taxa (Ferguson-Smith and Trifonov, 2007). For example, the number of chromosome pairs in eukaryotes ranges from one to 720 (Schubert and Vu, 2016; Khandelwal, 1990). In light of evolutionary history, chromoanagenesis could be a large contributor to this structural genomic variation because periods of major evolutionary change tend to occur during periods of severe stress. For example, the "Big Five" mass extinctions and their subsequent events of adaptive radiation corresponded to large changes in temperature, sea-level, volcanic and tectonic activity, and meteor impacts (Condamine et al., 2013). During such periods, eurytopic species are favored over stenotopic species while the opposite is the case during long, stable geological periods (Kültz, 2003). Corresponding patterns of evolutionary history have been interpreted by the theory of punctuated equilibrium (Gould, 1982).

Structural genomic variants can be adaptive under various contexts (Table 4). When challenged by the widely used herbicide glyphosate, palmer amaranth (*Amaranthus palmeri*) developed a copy number variant that enabled resistance to the herbicide (Gaines et al., 2010). Similarly, the codling moth (*Cydia pomonella*) developed a sex-linked resistance to insecticides through a chromosome fusion (Nguyen et al., 2013). Chromosome inversions have been adaptive in the context of behavior, mating strategies, and morphology (Wellenreuther and Bernatchez, 2018). For example, inversions produced cryptic color phenotypes in stick insects (*Timema cristinae*) and facilitated appropriate migratory behaviors in rainbow trout (*Oncorhynchus mykiss*) (Lindtke et al., 2017; Wellenreuther and Bernatchez, 2018).

Whether the process occurs in somatic cells or gametes, chromoanagenesis elicits major phenotypic changes by altering genome structure in individuals facing severe stress. Most of the time, the outcomes are deleterious – either a disease emerges, or individuals generate gametes

that are incompatible with potential mates, rendering the individuals sterile. On the lucky occasion, structural genomic variants enable successful survival and reproduction, and they do so within one generation.

Stress affects the activity of transposable elements

Transposable elements (TEs) have long been considered an engine of evolutionary change fueled by stress (McClintock, 1984), and they make up a large portion of eukaryotic genomes. In mammals, about 40% of the genome is comprised of TEs, and in plants, that value can be as high as 85% (Chénais et al., 2012). TEs are sequences of DNA, sometimes called "jumping genes," that can readily move throughout the genome. The process of their transposition can proceed through "copy and paste" or "cut and paste" strategies. In the copy and paste strategy, class I TEs are transcribed into an RNA intermediate then reverse transcribed back into DNA at a new location. In the cut and paste strategy, many class II TEs have their DNA sequence broken out of its position, then relocated (Wicker et al., 2007). Oftentimes, all the information needed for transposition is encoded within the TE. If this is the case, then they are called autonomous TEs, and depending on their family, they encode enzymes such as reverse transcriptase, proteinase, RNase, integrase, and transposase. Nonautonomous TEs have also evolved, and they lack some of the necessary components for transposition. As a result, they rely on autonomous TEs for their mobilization (Wicker et al., 2007).

When activated, TEs can quickly produce distinctive phenotypes by impacting gene expression, gene products, and genome structure. The expression of genes can be affected when newly incorporated TEs provide *cis*-regulatory elements (CREs), change the context of existing CREs, or alter the local epigenetic landscape (Chénais et al., 2012; Lanciano and Mirouze, 2018). Similarly, transposition can alter gene products when inserted TEs cause alternative transcription start sites, alternative splicing, or premature termination. New exons and introns can even be created in the process (Lanciano and Mirouze, 2018). For transposition to occur, DNA double-strand breaks (DSBs) are needed to cut out and insert TEs. This form of DNA damage increases rates of mutation, specifically at the sites of deletion and insertion (Biémont and Vieira, 2006). Furthermore, transposition-induced DSBs can produce structural genomic variants by feeding into the chromothripsis pathway, which leads to chromosome inversions and chromosome reshuffling (Figure 2) (Pellestor and Gatinois, 2020). TEs generate additional

structural genomic variants as a consequence of the high sequence similarity between TEs of the same family, in particular at their flanking sequences such as inverted terminal repeats (ITRs). This similarity enables non-allelic homologous recombination, which can cause chromosome inversions, duplications, translocations, and deletions (Kent et al., 2017).

Numerous stresses can alter TE activity, including cold and heat stresses, UV irradiation, salinity stress, and pollution (Miousse et al., 2015; Rey et al., 2016). However, the pattern of alteration is context dependent. In response to stress, TEs may be activated, repressed, activated then repressed, or repressed then activated (Horváth et al., 2017). Furthermore, when TEs are activated, it can be at the transcriptional level, the transpositional level, or both (Horváth et al., 2017). Epigenetic regulation is one major force that mediates this change (Biémont and Vieira, 2006). TEs are repressed under the control of DNA methylation and histone PTMs (Zemach et al., 2010). When stress alters these epigenetic marks, TEs can be released from repression and freed to transcribe their contents and/or mobilize to other parts of the genome (Pappalardo et al., 2021). Another stress-sensitive mechanism of TE activation involves the heat shock protein 90 family (HSP90). While HSP90 silences TEs under optimal environmental conditions, moderate stress can limit this function when HSP90 is instead needed to protect protein conformation (Ryan et al., 2016). Notably, the limitation of available HSP90 also increases phenotypic diversity by releasing cryptic genetic variation (CGV) from suppression (Paaby and Rockman, 2014). Therefore, HSP90 has been considered a key evolutionary capacitor (Rutherford and Lindquist, 1998).

Stress-induced changes in TEs have been observed across eukaryotic taxa (Table 5), and on many occasions, they have proven to be adaptive. For example, insecticide exposure has altered TE activity in insects. In the fruit fly (*Drosophila melanogaster*), this led to the overexpression of an insecticide detoxifying gene (Chung et al., 2007). In the common house mosquito (*Culex pipiens*), this led to the alternative splicing of a toxin receptor gene (Darboux et al., 2007). In both instances, the TEs induced by insecticides resulted in insecticide resistance. Similarly, climate has been shown to induce potentially adaptive TEs in the Asian tiger mosquito (*Aedes albopictus*). The frequency of TE insertions varies between a native population in a tropical environment and an invasive population in a temperate environment. In the invasive population, TEs of multiple families are inserted at higher frequencies, and they are positioned

within the proximity of genes that likely facilitate overwintering (Goubert et al., 2017). Altered regulation of these genes could increase the fitness of mosquitoes living in colder climates.

Through the alteration of TE activity, stress generates rapid phenotypic variation. The variation can be significant because TE activation has the power to affect gene expression, gene products, and genome structure. When these changes happen in the germline, they can be passed from parent to offspring indefinitely. This standard form of transmission is referred to as "vertical transfer." However, "horizontal transfer" of TEs can happen as well, where TEs jump between species. In the evolutionary history of vertebrates, for example, at least 975 events of horizontal transfer of TEs have occurred (Zhang et al., 2020).

Life experience and physiology shape evolution

Contrary to the principles of the Modern Synthesis of evolutionary theory, stress that an individual encounters throughout its lifetime is now known to induce heritable phenotypic variation (Burggren, 2014; Jablonka and Lamb, 2020; Noble, 2013; Skinner, 2015). This concept of stress-induced evolution (SIE) has been accepted for decades in regard to prokaryotes (Radman, 1975; Bjedov et al., 2003; Foster, 2007; Rosenberg et al., 2012). In prokaryotes, stress significantly increases rates of mutation, largely through the activation of the SOS system and RpoS stress response (Radman, 1975; Foster, 2007). Although these systems do not exist in eukaryotes, more recent studies have demonstrated that eukaryotes employ several powerful mechanisms to increase phenotypic variation in response to stress. Beyond the increased rates of mutation via DNA damage and lowered DNA repair fidelity that occur outside of the prokaryotic SOS and RpoS systems, variation is achieved through histone PTMs, DNA methylation, chromoanagenesis, and transposable element activity.

In multicellular eukaryotes, the mechanisms of SIE can proceed in both the soma and the germline. Somatic cell evolution has been studied intensively in the context of disease (Anway et al., 2006; Heng, 2009; Rajesh Kumar et al., 2002), proving that the outcome of these mechanisms can be maladaptive. Considering that many multicellular organisms consist of millions, billions, or even trillions of cells, e.g., 37 trillion cells in humans (Bianconi et al., 2013), the large population of cells provides a sufficient pool of beneficial alterations that selection can act on. A classic example of adaptive somatic cell evolution is the production of antibodies in vertebrates. After organisms are exposed to new antigens, the variable regions of

immunoglobulin genes in B cells become hypermutated (Diaz and Flajnik, 1998; Wysocki et al., 1986). This mechanism ultimately increases the affinity of antibodies to circulating antigens, thereby strengthening the immune system. While these changes to somatic cells easily impact the fitness of individuals by affecting their ability to survive and reproduce, stress arguably has the strongest influence over organismal evolution when alterations happen within the germline. Each of the physiological mechanisms of SIE can proceed within the germline, although this happens less frequently than in somatic cells because germ cell chromatin is transcriptionally silent and better protected from damage (Bao and Yan, 2012; Engmann and Mansuy, 2020; Heng, 2009; Milholland et al., 2017). Nonetheless, critical windows of development exist where stress is more likely to induce stably transmitted epigenetic marks in the germline (Skinner, 2011). Embryonic gonadal sex determination is the first critical window, and gametogenesis is the second (Hanson and Skinner, 2016).

Despite the popularity of the idea that the soma and the germline are completely isolated, i.e., the Weismann Barrier (Weismann, 1890), this barrier can be bypassed through microvesicles. Microvesicles, in the form of either shedding vesicles or exosomes, are released from all cell types (Camussi et al., 2010; Doyle and Wang, 2019). Once released, they can remain in the extracellular matrix within the proximity of the cell of origin, or they can travel through biological fluids to reach distant target cells (Camussi et al., 2010). These microvesicles contain components of the origin cell, including RNA and proteins. By delivering both of these components, microvesicles have the power to epigenetically reprogram target cells (Engmann and Mansuy, 2020; Sharma, 2014). This important transfer of information can take place between two somatic cells, or between somatic and germ cells. A recent study clearly demonstrated this phenomenon in mice xenografted with human tumor cells. RNA from the xenografted cells traveled through the bloodstream in exosomes until being finally received by spermatozoa (Cossetti et al., 2014). Therefore, germ cells do not necessarily need to be directly altered by stress; it is possible for information from affected somatic cells to reach and modify the germline. Impressively, Charles Darwin essentially predicted the existence of microvesicles. He described them as “gemmules” in 1868, before they could have possibly been detected (Noble, 2021).

Through all the physiological mechanisms discussed in this brief essay, eukaryotic organisms can establish heritable phenotypic variation in response to stress. Notably, DNA base

mutation is not the only driver of this variation. Rapid phenotypic diversity can be achieved by histone PTMs, DNA methylation, chromoanagenesis, and transposable element activity. The induced variation can be adaptive, maladaptive, or neutral in specific contexts. In any case, it is produced at a time when homeostasis cannot be maintained, and the system is forced to explore novelty.

Conclusions and future perspectives

This essay summarizes five physiological mechanisms of stress-induced evolution (SIE), which serve to generate novelty in populations experiencing altered environmental conditions. Due to their widespread presence across the phylogenetic web of life, these mechanisms have likely been favored during evolution by conferring significant selective advantages that outweigh potential disadvantages, such as the increased susceptibility to pathologies. A better understanding of the profound implications of these mechanisms for cells, organisms, and populations represents an exciting frontier in biology. Many open questions that should be of great interest to comparative physiologists remain, including the following. Is there a correlation between the prevalence of SIE mechanisms, incidence of proliferative disease, and average lifespan across different species? How does the magnitude of stress impact the proportion of favorable to unfavorable phenotypes produced through SIE mechanisms in a population? To what extent has SIE driven punctuated equilibrium throughout evolutionary history? How does SIE impact ecosystem succession during geological periods of rapid environmental change? SIE represents an exciting new paradigm in comparative evolutionary physiology that challenges long-standing dogmas and stimulates the creative intellect of current and future physiologists. In this brief essay, we share our enthusiasm for this fascinating area of biology to inspire future research on SIE by a broader scientific community.

Competing interests

No competing interests declared

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References

494 Abe, Y., Fujiwara, Y., Takahashi, H., Matsumura, Y., Sawada, T., Jiang, S., Nakaki, R., Uchida, A., Nagao,
495 N., Naito, M., et al. (2018). Histone demethylase JMJD1A coordinates acute and chronic
496 adaptation to cold stress via thermogenic phospho-switch. *Nat. Commun.* 9, 1566.

497 Alabert, C. and Groth, A. (2012). Chromatin replication and epigenome maintenance. *Nat. Rev. Mol. Cell*
498 *Biol.* 13, 153–167.

499 Angers, B., Castonguay, E. and Massicotte, R. (2010). Environmentally induced phenotypes and DNA
500 methylation: how to deal with unpredictable conditions until the next generation and after. *Mol.*
501 *Ecol.* 19, 1283–1295.

502 Aniagu, S. O., Day, N., Chipman, J. K., Taylor, E. W., Butler, P. J. and Winter, M. J. (2006). Does exhaustive
503 exercise result in oxidative stress and associated DNA damage in the Chub (Leuciscus cephalus)?
504 *Environ. Mol. Mutagen.* 47, 616–623.

505 Anway, M. D., Cupp, A. S., Uzumcu, M. and Skinner, M. K. (2005). Epigenetic Transgenerational Actions
506 of Endocrine Disruptors and Male Fertility. *Science* 308, 1466–1469.

507 Anway, M. D., Leathers, C. and Skinner, M. K. (2006). Endocrine Disruptor Vinclozolin Induced Epigenetic
508 Transgenerational Adult-Onset Disease. *Endocrinology* 147, 5515–5523.

509 Bagdonas, E. and Zukas, K. (2004). Repair of UVC induced DNA lesions in erythrocytes from Carassius
510 auratus gibelio. *Sveik. Moksl.* 22–24.

511 Banerjee, G., Gupta, N., Tiwari, J. and Raman, G. (2005). Ultraviolet-induced transformation of
512 keratinocytes: possible involvement of long interspersed element-1 reverse transcriptase.
513 *Photodermatol. Photoimmunol. Photomed.* 21, 32–39.

514 Bao, J. and Bedford, M. T. (2016). Epigenetic regulation of the histone-to-protamine transition during
515 spermiogenesis. *Reprod. Camb. Engl.* 151, R55–R70.

516 Bao, J. and Yan, W. (2012). Male Germline Control of Transposable Elements. *Biol. Reprod.* 86,.

517 Barth, J. M. I., Berg, P. R., Jonsson, P. R., Bonanomi, S., Corell, H., Hemmer-Hansen, J., Jakobsen, K. S.,
518 Johannesson, K., Jorde, P. E., Knutsen, H., et al. (2017). Genome architecture enables local
519 adaptation of Atlantic cod despite high connectivity. *Mol. Ecol.* 26, 4452–4466.

520 Barzilai, A. and Yamamoto, K.-I. (2004). DNA damage responses to oxidative stress. *DNA Repair* 3, 1109–
521 1115.

522 Bianconi, E., Piovesan, A., Facchin, F., Beraudi, A., Casadei, R., Frabetti, F., Vitale, L., Pelleri, M. C.,
523 Tassani, S., Piva, F., et al. (2013). An estimation of the number of cells in the human body. *Ann.*
524 *Hum. Biol.* 40, 463–471.

525 Biémont, C. and Vieira, C. (2006). Junk DNA as an evolutionary force. *Nature* 443, 521–524.

526 Bird, A. P. (1980). DNA methylation and the frequency of CpG in animal DNA. *Nucleic Acids Res.* 8, 1499–
527 1504.

Bird, A. (2002). DNA methylation patterns and epigenetic memory. *Genes Dev.* 16, 6–21.

Bjedov, I., Tenaillon, O., Gérard, B., Souza, V., Denamur, E., Radman, M., Taddei, F. and Matic, I. (2003). Stress-Induced Mutagenesis in Bacteria. *Science* 300, 1404–1409.

Bošković, A. and Rando, O. J. (2018). Transgenerational Epigenetic Inheritance. *Annu. Rev. Genet.* 52, 21–41.

Boyko, A., Blevins, T., Yao, Y., Golubov, A., Bilichak, A., Ilnytskyy, Y., Hollander, J., Jr, F. M. and Kovalchuk, I. (2010a). Transgenerational Adaptation of Arabidopsis to Stress Requires DNA Methylation and the Function of Dicer-Like Proteins. *PLOS ONE* 5, e9514.

Boyko, A., Golubov, A., Bilichak, A. and Kovalchuk, I. (2010b). Chlorine Ions but not Sodium Ions Alter Genome Stability of Arabidopsis thaliana. *Plant Cell Physiol.* 51, 1066–1078.

Brown, C. J., Todd, K. M. and Rosenzweig, R. F. (1998). Multiple duplications of yeast hexose transport genes in response to selection in a glucose-limited environment. *Mol. Biol. Evol.* 15, 931–942.

Burggren, W. W. (2014). Epigenetics as a source of variation in comparative animal physiology - or - Lamarck is lookin' pretty good these days. *J. Exp. Biol.* 217, 682–689.

Burggren, W. (2016). Epigenetic Inheritance and Its Role in Evolutionary Biology: Re-Evaluation and New Perspectives. *Biology* 5, 24.

Call, E., Jones, R., DeMonja, K., Burton, J. N., Jellum, S., Bernkopf, A. and Oberg, C. (2017). "The elastic limit": Introducing a novel concept in communicating excessive shear and tissue deformation. *World Counc. Enteros. Ther. J.* 37, 16–20.

Campbell, C. R., Poelstra, J. W. and Yoder, A. D. (2018). What is Speciation Genomics? The roles of ecology, gene flow, and genomic architecture in the formation of species. *Biol. J. Linn. Soc.* 124, 561–583.

Camussi, G., Deregibus, M.-C., Bruno, S., Grange, C., Fonsato, V. and Tetta, C. (2010). Exosome/microvesicle-mediated epigenetic reprogramming of cells. *Am. J. Cancer Res.* 1, 98–110.

Cantone, L., Nordio, F., Hou, L., Apostoli, P., Bonzini, M., Tarantini, L., Angelici, L., Bollati, V., Zanobetti, A., Schwartz, J., et al. (2011). Inhalable metal-rich air particles and histone H3K4 dimethylation and H3K9 acetylation in a cross-sectional study of steel workers. *Environ. Health Perspect.* 119, 964–969.

Capuano, F., Mülleder, M., Kok, R., Blom, H. J. and Ralser, M. (2014). Cytosine DNA Methylation Is Found in Drosophila melanogaster but Absent in Saccharomyces cerevisiae, Schizosaccharomyces pombe, and Other Yeast Species. *Anal. Chem.* 86, 3697–3702.

Cathcart, R., Schwiers, E., Saul, R. L. and Ames, B. N. (1984). Thymine glycol and thymidine glycol in human and rat urine: a possible assay for oxidative DNA damage. *Proc. Natl. Acad. Sci.* 81, 5633–5637.

563 Cavrak, V. V., Lettner, N., Jamge, S., Kosarewicz, A., Bayer, L. M. and Scheid, O. M. (2014). How a
564 Retrotransposon Exploits the Plant's Heat Stress Response for Its Activation. *PLOS Genet.* 10,
565 e1004115.

566 Chadha, S. and Sharma, M. (2014). Transposable Elements as Stress Adaptive Capacitors Induce
567 Genomic Instability in Fungal Pathogen Magnaporthe oryzae. *PLOS ONE* 9, e94415.

568 Chakarov, S., Petkova, R., Russev, G. C. and Zhelev, N. (2014). DNA damage and mutation. Types of DNA
569 damage. *BioDiscovery* 11, e8957.

570 Champroux, A., Cocquet, J., Henry-Berger, J., Drevet, J. R. and Kocer, A. (2018). A Decade of Exploring
571 the Mammalian Sperm Epigenome: Paternal Epigenetic and Transgenerational Inheritance.
572 *Front. Cell Dev. Biol.* 6, 50.

573 Chang, H. H. Y., Pannunzio, N. R., Adachi, N. and Lieber, M. R. (2017). Non-homologous DNA end joining
574 and alternative pathways to double-strand break repair. *Nat. Rev. Mol. Cell Biol.* 18, 495–506.

575 Chatterjee, N. and Walker, G. C. (2017). Mechanisms of DNA damage, repair, and mutagenesis. *Environ.*
576 *Mol. Mutagen.* 58, 235–263.

577 Chen, J. J., Mitchell, D. L. and Britt, A. B. (1994). A Light-Dependent Pathway for the Elimination of UV-
578 Induced Pyrimidine (6-4) Pyrimidinone Photoproducts in Arabidopsis. *Plant Cell* 6, 1311–1317.

579 Chen, L.-T., Luo, M., Wang, Y.-Y. and Wu, K. (2010). Involvement of Arabidopsis histone deacetylase
580 HDA6 in ABA and salt stress response. *J. Exp. Bot.* 61, 3345–3353.

581 Chénais, B., Caruso, A., Hiard, S. and Casse, N. (2012). The impact of transposable elements on
582 eukaryotic genomes: From genome size increase to genetic adaptation to stressful
583 environments. *Gene* 509, 7–15.

584 Cheng, C.-H., Guo, Z.-X., Luo, S.-W. and Wang, A.-L. (2018). Effects of high temperature on biochemical
585 parameters, oxidative stress, DNA damage and apoptosis of pufferfish (Takifugu obscurus).
586 *Ecotoxicol. Environ. Saf.* 150, 190–198.

587 Cheng, L., Trenberth, K. E., Gruber, N., Abraham, J. P., Fasullo, J. T., Li, G., Mann, M. E., Zhao, X. and Zhu,
588 J. (2020). Improved Estimates of Changes in Upper Ocean Salinity and the Hydrological Cycle. *J.*
589 *Clim.* 33, 10357–10381.

590 Choy, C. K. M., Benzie, I. F. F. and Cho, P. (2005). UV-Mediated DNA Strand Breaks in Corneal Epithelial
591 Cells Assessed Using the Comet Assay Procedure. *Photochem. Photobiol.* 81, 493–497.

592 Chung, H., Bogwitz, M. R., McCart, C., Andrianopoulos, A., ffrench-Constant, R. H., Batterham, P. and
593 Daborn, P. J. (2007). Cis-Regulatory Elements in the Accord Retrotransposon Result in Tissue-
594 Specific Expression of the Drosophila melanogaster Insecticide Resistance Gene Cyp6g1.
595 *Genetics* 175, 1071–1077.

596 Clingen, P. H., Arlett, C. F., Roza, L., Mori, T., Nikaido, O. and Green, M. H. L. (1995). Induction of
597 Cyclobutane Pyrimidine Dimers, Pyrimidine(6-4)pyrimidone Photoproducts, and Dewar Valence
598 Isomers by Natural Sunlight in Normal Human Mononuclear Cells. *Cancer Res.* 55, 2245–2248.

599 Condamine, F. L., Rolland, J. and Morlon, H. (2013). Macroevolutionary perspectives to environmental
600 change. *Ecol. Lett.* 16, 72–85.

601 Cook, D. E., Lee, T. G., Guo, X., Melito, S., Wang, K., Bayless, A. M., Wang, J., Hughes, T. J., Willis, D. K.,
602 Clemente, T. E., et al. (2012). Copy Number Variation of Multiple Genes at Rhg1 Mediates
603 Nematode Resistance in Soybean. *Science* 338, 1206–1209.

604 Cossetti, C., Lugini, L., Astrologo, L., Saggio, I., Fais, S. and Spadafora, C. (2014). Soma-to-Germline
605 Transmission of RNA in Mice Xenografted with Human Tumour Cells: Possible Transport by
606 Exosomes. *PLOS ONE* 9, e101629.

607 da Silva, F. A., Guimarães, E. M. C., Carvalho, N. D. M., Ferreira, A. M. V., Schneider, C. H., Carvalho-Zilse,
608 G. A., Feldberg, E. and Gross, M. C. (2020). Transposable DNA Elements in Amazonian Fish: From
609 Genome Enlargement to Genetic Adaptation to Stressful Environments. *Cytogenet. Genome Res.*
610 160, 148–155.

611 D'Alessandro, G., Frizzi, G. and Mariani, M. (1957). Effect of DDT selection pressure on the frequency of
612 chromosomal structures in Anopheles atroparvus. *Bull. World Health Organ.* 16, 859–864.

613 Darboux, I., Charles, J.-F., Pauchet, Y., Warot, S. and Pauron, D. (2007). Transposon-mediated resistance
614 to Bacillus sphaericus in a field-evolved population of Culex pipiens (Diptera: Culicidae). *Cell.*
615 *Microbiol.* 9, 2022–2029.

616 Diaz, M. and Flajnik, M. E. (1998). Evolution of somatic hypermutation and gene conversion in adaptive
617 immunity. *Immunol. Rev.* 162, 13–24.

618 Diaz-Mendez, I., Alhama, J., Pueyo, C. and Lopez-Barea, J. (1997). Fish 8-oxo-dG levels as biomarker of
619 oxidative damages by environmental pollutants. *Mutat. Res. Fundam. Mol. Mech. Mutagen.*
620 379, S168.

621 Doyle, L. M. and Wang, M. Z. (2019). Overview of Extracellular Vesicles, Their Origin, Composition,
622 Purpose, and Methods for Exosome Isolation and Analysis. *Cells* 8, 727.

623 Duncan, B. K. and Miller, J. H. (1980). Mutagenic deamination of cytosine residues in DNA. *Nature* 287,
624 560–561.

625 Engmann, O. and Mansuy, I. M. (2020). Chapter 18 - Stress and its effects across generations. In *Stress*
626 *Resilience* (ed. Chen, A.), pp. 269–290. Academic Press.

627 Fan, J., Krautkramer, K. A., Feldman, J. L. and Denu, J. M. (2015). Metabolic Regulation of Histone Post-
628 Translational Modifications. *ACS Chem. Biol.* 10, 95–108.

629 Feng, Q., Yang, C., Lin, X., Wang, J., Ou, X., Zhang, C., Chen, Y. and Liu, B. (2012). Salt and alkaline stress
630 induced transgenerational alteration in DNA methylation of rice ('Oryza sativa'). *Aust. J. Crop Sci.*
631 6, 877–883.

632 Ferguson-Smith, M. A. and Trifonov, V. (2007). Mammalian karyotype evolution. *Nat. Rev. Genet.* 8,
633 950–962.

Feulner, P. G. D. and De-Kayne, R. (2017). Genome evolution, structural rearrangements and speciation. *J. Evol. Biol.* 30, 1488–1490.

Flores, K. B., Wolschin, F. and Amdam, G. V. (2013). The Role of Methylation of DNA in Environmental Adaptation. *Integr. Comp. Biol.* 53, 359–372.

Foster, P. L. (2007). Stress-Induced Mutagenesis in Bacteria. *Crit. Rev. Biochem. Mol. Biol.* 42, 373–397.

Fryxell, K. J. and Zuckerkandl, E. (2000). Cytosine Deamination Plays a Primary Role in the Evolution of Mammalian Isochores. *Mol. Biol. Evol.* 17, 1371–1383.

Gaines, T. A., Zhang, W., Wang, D., Bukun, B., Chisholm, S. T., Shaner, D. L., Nissen, S. J., Patzoldt, W. L., Tranel, P. J., Culpepper, A. S., et al. (2010). Gene amplification confers glyphosate resistance in Amaranthus palmeri. *Proc. Natl. Acad. Sci.* 107, 1029–1034.

Galhardo, R. S., Hastings, P. J. and Rosenberg, S. M. (2007). Mutation as a Stress Response and the Regulation of Evolvability. *Crit. Rev. Biochem. Mol. Biol.* 42, 399–435.

García-Giménez, J.-L., Garcés, C., Romá-Mateo, C. and Pallardó, F. V. (2021). Oxidative stress-mediated alterations in histone post-translational modifications. *Free Radic. Biol. Med.* 170, 6–18.

Garinis, G. A., Mitchell, J. R., Moorhouse, M. J., Hanada, K., de Waard, H., Vandeputte, D., Jans, J., Brand, K., Smid, M., van der Spek, P. J., et al. (2005). Transcriptome analysis reveals cyclobutane pyrimidine dimers as a major source of UV-induced DNA breaks. *EMBO J.* 24, 3952–3962.

Geiser, C., Mandáková, T., Arrigo, N., Lysak, M. A. and Parisod, C. (2016). Repeated Whole-Genome Duplication, Karyotype Reshuffling, and Biased Retention of Stress-Responding Genes in Buckler Mustard. *Plant Cell* 28, 17–27.

Gerlach, V. L., Aravind, L., Gotway, G., Schultz, R. A., Koonin, E. V. and Friedberg, E. C. (1999). Human and mouse homologs of Escherichia coli DinB (DNA polymerase IV), members of the UmuC/DinB superfamily. *Proc. Natl. Acad. Sci. U. S. A.* 96, 11922–11927.

Goubert, C., Henri, H., Minard, G., Moro, C. V., Mavingui, P., Vieira, C. and Boulesteix, M. (2017). High-throughput sequencing of transposable element insertions suggests adaptive evolution of the invasive Asian tiger mosquito towards temperate environments. *Mol. Ecol.* 26, 3968–3981.

Gould, S. J. (1982). The meaning of punctuated equilibrium and its role in validating a hierarchical approach to macroevolution. In *Perspectives in Evolution* (ed. Milkman, R.), pp. 83–104. Sunderland, MA: Sinauer Associates Inc.

Greenberg, M. V. C. and Bourc'his, D. (2019). The diverse roles of DNA methylation in mammalian development and disease. *Nat. Rev. Mol. Cell Biol.* 20, 590–607.

Grollman, A. P. and Moriya, M. (1993). Mutagenesis by 8-oxoguanine: an enemy within. *Trends Genet.* 9, 246–249.

Gruenbaum, Y., Cedar, H. and Razin, A. (1982). Substrate and sequence specificity of a eukaryotic DNA methylase. *Nature* 295, 620–622.

669 Hanson, M. A. and Skinner, M. K. (2016). Developmental origins of epigenetic transgenerational
670 inheritance. *Environ. Epigenetics* 2, dvw002.

671 Hashida, S., Kitamura, K., Mikami, T. and Kishima, Y. (2003). Temperature Shift Coordinately Changes the
672 Activity and the Methylation State of Transposon Tam3 in Antirrhinum majus. *Plant Physiol.* 132,
673 1207–1216.

674 Heckwolf, M. J., Meyer, B. S., Häsler, R., Höppner, M. P., Eizaguirre, C. and Reusch, T. B. H. (2020). Two
675 different epigenetic information channels in wild three-spined sticklebacks are involved in
676 salinity adaptation. *Sci. Adv.* 6, eaaz1138.

677 Heng, H. H. Q. (2009). The genome-centric concept: resynthesis of evolutionary theory. *BioEssays* 31,
678 512–525.

679 Heng, J. and Heng, H. H. (2020). Genome chaos: Creating new genomic information essential for cancer
680 macroevolution. *Semin. Cancer Biol.*

681 Hoegh-Guldberg, O., Mumby, P. J., Hooten, A. J., Steneck, R. S., Greenfield, P., Gomez, E., Harvell, C. D.,
682 Sale, P. F., Edwards, A. J., Caldeira, K., et al. (2007). Coral Reefs Under Rapid Climate Change and
683 Ocean Acidification. *Science* 318, 1737–1742.

684 Holliday, R. and Grigg, G. W. (1993). DNA methylation and mutation. *Mutat. Res. Mol. Mech. Mutagen.*
685 285, 61–67.

686 Honda, S., Hjelmeland, L. M. and Handa, J. T. (2001). Oxidative Stress–Induced Single-Strand Breaks in
687 Chromosomal Telomeres of Human Retinal Pigment Epithelial Cells In Vitro. *Invest. Ophthalmol.*
688 *Vis. Sci.* 42, 2139–2144.

689 Horne, S. D., Chowdhury, S. K. and Heng, H. H. (2014). Stress, genomic adaptation, and the evolutionary
690 trade-off. *Front Genet* 5, 92.

691 Horváth, V., Merenciano, M. and González, J. (2017). Revisiting the Relationship between Transposable
692 Elements and the Eukaryotic Stress Response. *Trends Genet.* 33, 832–841.

693 Hsu, K.-F., Wilkins, S. E., Hopkinson, R. J., Sekirnik, R., Flashman, E., Kawamura, A., McCullagh, J. S. O.,
694 Walport, L. J. and Schofield, C. J. (2021). Hypoxia and hypoxia mimetics differentially modulate
695 histone post-translational modifications. *Epigenetics* 16, 14–27.

696 Hummel, B., Hansen, E. C., Yoveva, A., Aprile-Garcia, F., Hussong, R. and Sawarkar, R. (2017). The
697 evolutionary capacitor HSP90 buffers the regulatory effects of mammalian endogenous
698 retroviruses. *Nat. Struct. Mol. Biol.* 24, 234–242.

699 Jablonka, E. and Lamb, M. J. (2020). Inheritance Systems and the Extended Evolutionary Synthesis. *Elem.*
700 *Philos. Biol.*

701 Jeremias, G., Barbosa, J., Marques, S. M., De Schamphelaere, K. A. C., Van Nieuwerburgh, F., Deforce, D.,
702 Goncalves, F. J. M., Pereira, J. L. and Asselman, J. (2018). Transgenerational Inheritance of DNA
703 Hypomethylation in Daphnia magna in Response to Salinity Stress. *Environ. Sci. Technol.* 52,
704 10114–10123.

Jones, P. A. (2012). Functions of DNA methylation: islands, start sites, gene bodies and beyond. *Nat. Rev. Genet.* 13, 484–492.

Kamstra, J. H., Hurem, S., Martin, L. M., Lindeman, L. C., Legler, J., Oughton, D., Salbu, B., Brede, D. A., Lyche, J. L. and Aleström, P. (2018). Ionizing radiation induces transgenerational effects of DNA methylation in zebrafish. *Sci. Rep.* 8, 15373.

Kantidze, O. L., Velichko, A. K., Luzhin, A. V. and Razin, S. V. (2016). Heat stress-induced DNA damage. *Acta Naturae Англоязычная Версия* 8, 75–78.

Karger, D. N., Schmatz, D. R., Dettling, G. and Zimmermann, N. E. (2020). High-resolution monthly precipitation and temperature time series from 2006 to 2100. *Sci. Data* 7, 248.

Kent, T. V., Uzunović, J. and Wright, S. I. (2017). Coevolution between transposable elements and recombination. *Philos. Trans. R. Soc. B Biol. Sci.* 372, 20160458.

Khandelwal, S. (1990). Chromosome evolution in the genus Ophioglossum L. *Bot. J. Linn. Soc.* 102, 205–217.

Kim, J.-M., To, T. K., Ishida, J., Morosawa, T., Kawashima, M., Matsui, A., Toyoda, T., Kimura, H., Shinozaki, K. and Seki, M. (2008). Alterations of Lysine Modifications on the Histone H3 N-Tail under Drought Stress Conditions in Arabidopsis thaliana. *Plant Cell Physiol.* 49, 1580–1588.

Klosin, A., Casas, E., Hidalgo-Carcedo, C., Vavouri, T. and Lehner, B. (2017). Transgenerational transmission of environmental information in C. elegans. *Science* 356, 320–323.

Koltsova, A. S., Pendina, A. A., Efimova, O. A., Chiryaeva, O. G., Kuznetzova, T. V. and Baranov, V. S. (2019). On the Complexity of Mechanisms and Consequences of Chromothripsis: An Update. *Front. Genet.* 10, 393.

Kouzarides, T. (2007). Chromatin Modifications and Their Function. *Cell* 128, 693–705.

Kültz, D. (2003). Evolution of the cellular stress proteome: from monophyletic origin to ubiquitous function. *J Exp Biol* 206, 3119–24.

Kültz, D. (2005). Molecular and evolutionary basis of the cellular stress response. *Annu Rev Physiol* 67, 225–57.

Kültz, D. (2020a). Defining biological stress and stress responses based on principles of physics. *J. Exp. Zool. Part Ecol. Integr. Physiol.* 333, 350–358.

Kültz, D. (2020b). Evolution of cellular stress response mechanisms. *J. Exp. Zool. Part Ecol. Integr. Physiol.* 333, 359–378.

Kültz, D. and Chakravarty, D. (2001). Hyperosmolality in the form of elevated NaCl but not urea causes DNA damage in murine kidney cells. *Proc. Natl. Acad. Sci.* 98, 1999–2004.

Kwon, C. S., Lee, D., Choi, G. and Chung, W.-I. (2009). Histone occupancy-dependent and -independent removal of H3K27 trimethylation at cold-responsive genes in Arabidopsis. *Plant J.* 60, 112–121.

739 Lämke, J., Brzezinka, K., Altmann, S. and Bäurle, I. (2016). A hit-and-run heat shock factor governs
740 sustained histone methylation and transcriptional stress memory. *EMBO J.* 35, 162–175.

741 Lanciano, S. and Mirouze, M. (2018). Transposable elements: all mobile, all different, some stress
742 responsive, some adaptive? *Curr. Opin. Genet. Dev.* 49, 106–114.

743 Lankinen, M. H., Vilpo, L. M. and Vilpo, J. A. (1996). UV- and γ-irradiation-induced DNA single-strand
744 breaks and their repair in human blood granulocytes and lymphocytes. *Mutat. Res. Mol. Mech.*
745 *Mutagen.* 352, 31–38.

746 Lerman, D. N., Michalak, P., Helin, A. B., Bettencourt, B. R. and Feder, M. E. (2003). Modification of Heat-
747 Shock Gene Expression in Drosophila melanogaster Populations via Transposable Elements. *Mol.*
748 *Biol. Evol.* 20, 135–144.

749 Liepelt, A., Karbe, L. and Westendorf, J. (1995). Induction of DNA strand breaks in rainbow trout
750 Oncorhynchus mykiss under hypoxic and hyperoxic conditions. *Aquat. Toxicol.* 33, 177–181.

751 Lindtke, D., Lucek, K., Soria-Carrasco, V., Villoutreix, R., Farkas, T. E., Riesch, R., Dennis, S. R., Gompert, Z.
752 and Nosil, P. (2017). Long-term balancing selection on chromosomal variants associated with
753 crypsis in a stick insect. *Mol. Ecol.* 26, 6189–6205.

754 Liu, T., Li, Y., Duan, W., Huang, F. and Hou, X. (2017). Cold acclimation alters DNA methylation patterns
755 and confers tolerance to heat and increases growth rate in Brassica rapa. *J. Exp. Bot.* 68, 1213–
756 1224.

757 Luger, K., Mäder, A. W., Richmond, R. K., Sargent, D. F. and Richmond, T. J. (1997). Crystal structure of
758 the nucleosome core particle at 2.8 Å resolution. *Nature* 389, 251–260.

759 Lyko, F. (2001). DNA methylation learns to fly. *Trends Genet.* 17, 169–172.

760 Makova, K. D. and Hardison, R. C. (2015). The effects of chromatin organization on variation in mutation
761 rates in the genome. *Nat. Rev. Genet.* 16, 213–223.

762 Manikkam, M., Haque, M. M., Guerrero-Bosagna, C., Nilsson, E. E. and Skinner, M. K. (2014). Pesticide
763 Methoxychlor Promotes the Epigenetic Transgenerational Inheritance of Adult-Onset Disease
764 through the Female Germline. *PLOS ONE* 9, e102091.

765 Martin, E. M. and Fry, R. C. (2018). Environmental Influences on the Epigenome: Exposure- Associated
766 DNA Methylation in Human Populations. *Annu. Rev. Public Health* 39, 309–333.

767 Masuda, Y., Hanaoka, F. and Masutani, C. (2016). Translesion DNA Synthesis and Damage Tolerance
768 Pathways. In *DNA Replication, Recombination, and Repair: Molecular Mechanisms and*
769 *Pathology* (ed. Hanaoka, F.) and Sugasawa, K.), pp. 249–304. Tokyo: Springer Japan.

770 Matsui, M., Nishigori, C., Imamura, S., Miyachi, Y., Toyokuni, S., Takada, J., Akaboshi, M. and Ishikawa,
771 M. (1999). The Role of Oxidative DNA Damage in Human Arsenic Carcinogenesis: Detection of 8-
772 Hydroxy-2□-Deoxyguanosine in Arsenic-Related Bowen's Disease. *J. Invest. Dermatol.* 113, 26–
773 31.

McClintock, B. (1984). The significance of responses of the genome to challenge. *Science* 226, 792–801.

Mérot, C., Oomen, R. A., Tigano, A. and Wellenreuther, M. (2020). A Roadmap for Understanding the Evolutionary Significance of Structural Genomic Variation. *Trends Ecol. Evol.* 35, 561–572.

Metzger, D. C. H. and Schulte, P. M. (2017). Persistent and plastic effects of temperature on DNA methylation across the genome of threespine stickleback (Gasterosteus aculeatus). *Proc. R. Soc. B Biol. Sci.* 284, 20171667.

Mihaylova, V. T., Bindra, R. S., Yuan, J., Campisi, D., Narayanan, L., Jensen, R., Giordano, F., Johnson, R. S., Rockwell, S. and Glazer, P. M. (2003). Decreased Expression of the DNA Mismatch Repair Gene Mlh1 under Hypoxic Stress in Mammalian Cells. *Mol. Cell. Biol.* 23, 3265–3273.

Milholland, B., Dong, X., Zhang, L., Hao, X., Suh, Y. and Vijg, J. (2017). Differences between germline and somatic mutation rates in humans and mice. *Nat. Commun.* 8, 15183.

Miousse, I. R., Chalbot, M.-C. G., Lumen, A., Ferguson, A., Kavouras, I. G. and Koturbash, I. (2015). Response of transposable elements to environmental stressors. *Mutat. Res. Mutat. Res.* 765, 19–39.

Mitchell, D. L., Nguyen, T. D. and Cleaver, J. E. (1990). Nonrandom induction of pyrimidine-pyrimidone (6-4) photoproducts in ultraviolet-irradiated human chromatin. *J. Biol. Chem.* 265, 5353–5356.

Møller, P., Loft, S., Lundby, C. and Olsen, N. V. (2001). Acute hypoxia and hypoxic exercise induce DNA strand breaks and oxidative DNA damage in humans. *FASEB J.* 15, 1181–1186.

Moore, L. D., Le, T. and Fan, G. (2013). DNA Methylation and Its Basic Function. *Neuropsychopharmacology* 38, 23–38.

Moriya, M. (1993). Single-stranded shuttle phagemid for mutagenesis studies in mammalian cells: 8-oxoguanine in DNA induces targeted G.C-->T.A transversions in simian kidney cells. *Proc. Natl. Acad. Sci.* 90, 1122–1126.

Mørkve Knudsen, T., Rezwan, F. I., Jiang, Y., Karmaus, W., Svanes, C. and Holloway, J. W. (2018). Transgenerational and intergenerational epigenetic inheritance in allergic diseases. *J. Allergy Clin. Immunol.* 142, 765–772.

Naito, K., Zhang, F., Tsukiyama, T., Saito, H., Hancock, C. N., Richardson, A. O., Okumoto, Y., Tanisaka, T. and Wessler, S. R. (2009). Unexpected consequences of a sudden and massive transposon amplification on rice gene expression. *Nature* 461, 1130–1134.

Nguyen, P., Sýkorová, M., Šíchová, J., Kůta, V., Dalíková, M., Čapková Frydrychová, R., Neven, L. G., Sahara, K. and Marec, F. (2013). Neo-sex chromosomes and adaptive potential in tortricid pests. *Proc. Natl. Acad. Sci.* 110, 6931–6936.

Nilsson, E. E., Sadler-Riggleman, I. and Skinner, M. K. (2018). Environmentally induced epigenetic transgenerational inheritance of disease. *Environ. Epigenetics* 4, dvy016.

Noble, D. (2013). Physiology is rocking the foundations of evolutionary biology. *Exp. Physiol.* 98, 1235–1243.

Noble, D. (2021). The Illusions of the Modern Synthesis. *Biosemiotics* 14, 5–24.

Norouzitallab, P., Baruah, K., Vandegehuchte, M., Stappen, G. V., Catania, F., Bussche, J. V., Vanhaecke, L., Sorgeloos, P. and Bossier, P. (2014). Environmental heat stress induces epigenetic transgenerational inheritance of robustness in parthenogenetic Artemia model. *FASEB J.* 28, 3552–3563.

Norton, V. G., Imai, B. S., Yau, P. and Bradbury, E. M. (1989). Histone acetylation reduces nucleosome core particle linking number change. *Cell* 57, 449–457.

Nowak, M. D., Birkeland, S., Mandáková, T., Choudhury, R. R., Guo, X., Gustafsson, A. L. S., Gizaw, A., Schrøder-Nielsen, A., Fracassetti, M., Brysting, A. K., et al. (2021). The genome of Draba nivalis shows signatures of adaptation to the extreme environmental stresses of the Arctic. *Mol. Ecol. Resour.* 21, 661–676.

Okano, M., Bell, D. W., Haber, D. A. and Li, E. (1999). DNA Methyltransferases Dnmt3a and Dnmt3b Are Essential for De Novo Methylation and Mammalian Development. *Cell* 99, 247–257.

Ou, X., Zhang, Y., Xu, C., Lin, X., Zang, Q., Zhuang, T., Jiang, L., Wettstein, D. von and Liu, B. (2012). Transgenerational Inheritance of Modified DNA Methylation Patterns and Enhanced Tolerance Induced by Heavy Metal Stress in Rice (Oryza sativa L.). *PLOS ONE* 7, e41143.

Paaby, A. B. and Rockman, M. V. (2014). Cryptic genetic variation, evolution's hidden substrate. *Nat. Rev. Genet.* 15, 247–258.

Pappalardo, A. M., Ferrito, V., Biscotti, M. A., Canapa, A. and Capriglione, T. (2021). Transposable Elements and Stress in Vertebrates: An Overview. *Int. J. Mol. Sci.* 22, 1970.

Pellestor, F. and Gatinois, V. (2020). Chromoanagenesis: a piece of the macroevolution scenario. *Mol. Cytogenet.* 13, 3.

Perez, M. F. and Lehner, B. (2019). Intergenerational and transgenerational epigenetic inheritance in animals. *Nat. Cell Biol.* 21, 143–151.

Perry, G. H., Dominy, N. J., Claw, K. G., Lee, A. S., Fiegler, H., Redon, R., Werner, J., Villanea, F. A., Mountain, J. L., Misra, R., et al. (2007). Diet and the evolution of human amylase gene copy number variation. *Nat. Genet.* 39, 1256–1260.

Pilzecker, B. and Jacobs, H. (2019). Mutating for Good: DNA Damage Responses During Somatic Hypermutation. *Front. Immunol.* 10, 438.

Pilzecker, B., Buoninfante, O. A. and Jacobs, H. (2019). DNA damage tolerance in stem cells, ageing, mutagenesis, disease and cancer therapy. *Nucleic Acids Res.* 47, 7163–7181.

Radman, M. (1975). SOS Repair Hypothesis: Phenomenology of an Inducible DNA Repair Which is Accompanied by Mutagenesis. In *Molecular Mechanisms for Repair of DNA: Part A* (ed. Hanawalt, P. C.) and Setlow, R. B.), pp. 355–367. Boston, MA: Springer US.

Rajesh Kumar, T., Doreswamy, K., Shrilatha, B., and Muralidhara (2002). Oxidative stress associated DNA damage in testis of mice: induction of abnormal sperms and effects on fertility. *Mutat. Res. Toxicol. Environ. Mutagen.* 513, 103–111.

Rego, C., Balanyà, J., Fragata, I., Matos, M., Rezende, E. L. and Santos, M. (2010). Clinal Patterns of Chromosomal Inversion Polymorphisms in Drosophila Subobscura Are Partly Associated with Thermal Preferences and Heat Stress Resistance. *Evolution* 64, 385–397.

Rey, O., Danchin, E., Mirouze, M., Loot, C. and Blanchet, S. (2016). Adaptation to Global Change: A Transposable Element–Epigenetics Perspective. *Trends Ecol. Evol.* 31, 514–526.

Rocca, K. A., Gray, E. M., Costantini, C. and Besansky, N. J. (2009). 2La chromosomal inversion enhances thermal tolerance of Anopheles gambiae larvae. *Malar. J.* 8, 147.

Rosenberg, S. M., Shee, C., Frisch, R. L. and Hastings, P. J. (2012). Stress-induced mutation via DNA breaks in Escherichia coli: A molecular mechanism with implications for evolution and medicine. *BioEssays* 34, 885–892.

Rutherford, S. L. and Lindquist, S. (1998). Hsp90 as a capacitor for morphological evolution. *Nature* 396, 336–342.

Ryan, C. P., Brownlie, J. C. and Whyard, S. (2016). Hsp90 and Physiological Stress Are Linked to Autonomous Transposon Mobility and Heritable Genetic Change in Nematodes. *Genome Biol. Evol.* 8, 3794–3805.

Ryu, T., Veilleux, H. D., Donelson, J. M., Munday, P. L. and Ravasi, T. (2018). The epigenetic landscape of transgenerational acclimation to ocean warming. *Nat. Clim. Change* 8, 504–509.

Sallmyr, A., Fan, J. and Rassool, F. V. (2008). Genomic instability in myeloid malignancies: Increased reactive oxygen species (ROS), DNA double strand breaks (DSBs) and error-prone repair. *Cancer Lett.* 270, 1–9.

Samson, M., Jow, M. M., Wong, C. C. L., Fitzpatrick, C., Aslanian, A., Saucedo, I., Estrada, R., Ito, T., Park, S. R., Iii, J. R. Y., et al. (2014). The Specification and Global Reprogramming of Histone Epigenetic Marks during Gamete Formation and Early Embryo Development in C. elegans. *PLOS Genet.* 10, e1004588.

Saperas, N., Chiva, M., Pfeiffer, D. C., Kasinsky, H. E. and Ausió, J. (1997). Sperm Nuclear Basic Proteins (SNBPs) of Agnathans and Chondrichthyans: Variability and Evolution of Sperm Proteins in Fish. *J. Mol. Evol.* 44, 422–431.

Schubert, I. and Vu, G. T. H. (2016). Genome Stability and Evolution: Attempting a Holistic View. *Trends Plant Sci.* 21, 749–757.

Seong, K.-H., Li, D., Shimizu, H., Nakamura, R. and Ishii, S. (2011). Inheritance of Stress-Induced, ATF-2-Dependent Epigenetic Change. *Cell* 145, 1049–1061.

Sharma, A. (2014). Bioinformatic analysis revealing association of exosomal mRNAs and proteins in epigenetic inheritance. *J. Theor. Biol.* 357, 143–149.

Shen, M. M. (2013). Chromoplexy: A New Category of Complex Rearrangements in the Cancer Genome. *Cancer Cell* 23, 567–569.

Shi, Y. Y., Huang, Z. Y., Zeng, Z. J., Wang, Z. L., Wu, X. B. and Yan, W. Y. (2011). Diet and Cell Size Both Affect Queen-Worker Differentiation through DNA Methylation in Honey Bees (Apis mellifera, Apidae). *PLOS ONE* 6, e18808.

Skinner, M. K. (2011). Environmental epigenetic transgenerational inheritance and somatic epigenetic mitotic stability. *Epigenetics* 6, 838–842.

Skinner, M. K. (2015). Environmental Epigenetics and a Unified Theory of the Molecular Aspects of Evolution: A Neo-Lamarckian Concept that Facilitates Neo-Darwinian Evolution. *Genome Biol. Evol.* 7, 1296–1302.

Skinner, M. K., Manikkam, M., Tracey, R., Guerrero-Bosagna, C., Haque, M. and Nilsson, E. E. (2013). Ancestral dichlorodiphenyltrichloroethane (DDT) exposure promotes epigenetic transgenerational inheritance of obesity. *BMC Med.* 11, 228.

Smith, Z. D. and Meissner, A. (2013). DNA methylation: roles in mammalian development. *Nat. Rev. Genet.* 14, 204–220.

Song, Y., Jia, Z., Hou, Y., Ma, X., Li, L., Jin, X. and An, L. (2020). Roles of DNA Methylation in Cold Priming in Tartary Buckwheat. *Front. Plant Sci.* 11, 2022.

Soon, L. L. L., Ausio, J., Breed, W. G., Power, J. H. T. and Muller, S. (1997). Isolation of histones and related chromatin structures from spermatozoa nuclei of a dasyurid marsupial, Sminthopsis crassicaudata. *J. Exp. Zool.* 278, 322–332.

Strader, M. E., Wong, J. M., Kozal, L. C., Leach, T. S. and Hofmann, G. E. (2019). Parental environments alter DNA methylation in offspring of the purple sea urchin, Strongylocentrotus purpuratus. *J. Exp. Mar. Biol. Ecol.* 517, 54–64.

Sun, W., Dong, H., Becker, A. S., Dapito, D. H., Modica, S., Grandl, G., Opitz, L., Efthymiou, V., Straub, L. G., Sarker, G., et al. (2018). Cold-induced epigenetic programming of the sperm enhances brown adipose tissue activity in the offspring. *Nat. Med.* 24, 1372–1383.

Sutton, T., Baumann, U., Hayes, J., Collins, N. C., Shi, B.-J., Schnurbusch, T., Hay, A., Mayo, G., Pallotta, M., Tester, M., et al. (2007). Boron-Toxicity Tolerance in Barley Arising from Efflux Transporter Amplification. *Science* 318, 1446–1449.

Tanou, G., Molassiotis, A. and Diamantidis, G. (2009). Induction of reactive oxygen species and necrotic death-like destruction in strawberry leaves by salinity. *Environ. Exp. Bot.* 65, 270–281.

Tian, L., Cheng, Y.-Q., Shan, Z.-W., Li, J., Wang, C.-C., Han, X.-D., Sun, J. and Ma, E. (2012). Approaching the ideal elastic limit of metallic glasses. *Nat. Commun.* 3, 609.

Van Meter, M., Kashyap, M., Rezazadeh, S., Geneva, A. J., Morello, T. D., Seluanov, A. and Gorbunova, V. (2014). SIRT6 represses LINE1 retrotransposons by ribosylating KAP1 but this repression fails with stress and age. *Nat. Commun.* 5, 5011.

Vandegehuchte, M. B., De Coninck, D., Vandenbrouck, T., De Coen, W. M. and Janssen, C. R. (2010). Gene transcription profiles, global DNA methylation and potential transgenerational epigenetic effects related to Zn exposure history in Daphnia magna. *Environ. Pollut.* 158, 3323–3329.

Walker, C. and Burggren, W. (2020). Remodeling the epigenome and (epi)cytoskeleton: a new paradigm for co-regulation by methylation. *J. Exp. Biol.* 223, jeb220632.

Wang, W.-N., Zhou, J., Wang, P., Tian, T.-T., Zheng, Y., Liu, Y., Mai, W. and Wang, A.-L. (2009). Oxidative stress, DNA damage and antioxidant enzyme gene expression in the Pacific white shrimp, Litopenaeus vannamei when exposed to acute pH stress. *Comp. Biochem. Physiol. Part C Toxicol. Pharmacol.* 150, 428–435.

Weismann, A. (1890). Prof. Weismann's Theory of Heredity. *Nature* 41, 317–323.

Wellenreuther, M. and Bernatchez, L. (2018). Eco-Evolutionary Genomics of Chromosomal Inversions. *Trends Ecol. Evol.* 33, 427–440.

Wicker, T., Sabot, F., Hua-Van, A., Bennetzen, J. L., Capy, P., Chalhoub, B., Flavell, A., Leroy, P., Morgante, M., Panaud, O., et al. (2007). A unified classification system for eukaryotic transposable elements. *Nat. Rev. Genet.* 8, 973–982.

Wimmer, M. E., Vassoler, F. M., White, S. L., Schmidt, H. D., Sidoli, S., Han, Y., Garcia, B. A. and Pierce, R. C. (2019). Impaired cocaine-induced behavioral plasticity in the male offspring of cocaine-experienced sires. *Eur. J. Neurosci.* 49, 1115–1126.

Wong, J. M., Kozal, L. C., Leach, T. S., Hoshijima, U. and Hofmann, G. E. (2019). Transgenerational effects in an ecological context: Conditioning of adult sea urchins to upwelling conditions alters maternal provisioning and progeny phenotype. *J. Exp. Mar. Biol. Ecol.* 517, 65–77.

Woodhouse, R. M. and Ashe, A. (2020). How do histone modifications contribute to transgenerational epigenetic inheritance in C. elegans? *Biochem. Soc. Trans.* 48, 1019–1034.

Wysocki, L., Manser, T. and Gefter, M. L. (1986). Somatic evolution of variable region structures during an immune response. *Proc. Natl. Acad. Sci.* 83, 1847–1851.

Xue, C., Liu, S., Chen, C., Zhu, J., Yang, X., Zhou, Y., Guo, R., Liu, X. and Gong, Z. (2018). Global Proteome Analysis Links Lysine Acetylation to Diverse Functions in Oryza Sativa. *Proteomics* 18, 1700036.

Yamanaka, K., Takabayashi, F., Mizoi, M., An, Y., Hasegawa, A. and Okada, S. (2001). Oral Exposure of Dimethylarsinic Acid, a Main Metabolite of Inorganic Arsenics, in Mice Leads to an Increase in 8-Oxo-2□-deoxyguanosine Level, Specifically in the Target Organs for Arsenic Carcinogenesis. *Biochem. Biophys. Res. Commun.* 287, 66–70.

Yang, J., Horton, J. R., Akdemir, K. C., Li, J., Huang, Y., Kumar, J., Blumenthal, R. M., Zhang, X. and Cheng, X. (2021). Preferential CEBP binding to T:G mismatches and increased C-to-T human somatic mutations. *Nucleic Acids Res.* 49, 5084–5094.

Yasuda, K., Ito, M., Sugita, T., Tsukiyama, T., Saito, H., Naito, K., Teraishi, M., Tanisaka, T. and Okumoto, Y. (2013). Utilization of transposable element mPing as a novel genetic tool for modification of the stress response in rice. *Mol. Breed.* 32, 505–516.

Ye, C. J., Liu, G. and Heng, H. H. (2018). Experimental Induction of Genome Chaos. In *Chromothripsis: Methods and Protocols* (ed. Pellestor, F.), pp. 337–352. Totowa: Humana Press Inc.

Yoon, J.-H., Bhatia, G., Prakash, S. and Prakash, L. (2010). Error-free replicative bypass of thymine glycol by the combined action of DNA polymerases κ and ζ in human cells. *Proc. Natl. Acad. Sci.* 107, 14116–14121.

Yuan, L., Liu, X., Luo, M., Yang, S. and Wu, K. (2013). Involvement of Histone Modifications in Plant Abiotic Stress Responses. *J. Integr. Plant Biol.* 55, 892–901.

Zemach, A., McDaniel, I. E., Silva, P. and Zilberman, D. (2010). Genome-Wide Evolutionary Analysis of Eukaryotic DNA Methylation. *Science* 328, 916–919.

Zhang, H.-H., Peccoud, J., Xu, M.-R.-X., Zhang, X.-G. and Gilbert, C. (2020). Horizontal transfer and evolution of transposable elements in vertebrates. *Nat. Commun.* 11, 1362.

Zhao, Y. and Garcia, B. A. (2015). Comprehensive Catalog of Currently Documented Histone Modifications. *Cold Spring Harb. Perspect. Biol.* 7, a025064.

Zheng, X., Chen, L., Li, M., Lou, Q., Xia, H., Wang, P., Li, T., Liu, H. and Luo, L. (2013). Transgenerational Variations in DNA Methylation Induced by Drought Stress in Two Rice Varieties with Distinguished Difference to Drought Resistance. *PLOS ONE* 8, e80253.

Zheng, H.-T., Zhuang, Z.-X., Chen, C.-J., Liao, H.-Y., Chen, H.-L., Hsueh, H.-C., Chen, C.-F., Chen, S.-E. and Huang, S.-Y. (2021). Effects of acute heat stress on protein expression and histone modification in the adrenal gland of male layer-type country chickens. *Sci. Rep.* 11, 6499.

Zhou, Y., He, F., Pu, W., Gu, X., Wang, J. and Su, Z. (2020). The Impact of DNA Methylation Dynamics on the Mutation Rate During Human Germline Development. *G3 GenesGenomesGenetics* 10, 3337–3346.

Figure Legends:

Figure 1. The modes of epigenetic inheritance of histone PTMs. Stress induces changes in the relative abundance of histone PTMs in somatic cells (represented by white stars) and/or germ cells (represented by black stars). When an epigenetic mark persists through time within the F_0 individual, it is intragenerationally inherited. If the mark is passed through one generation due to direct gamete exposure, it is intergenerationally inherited. In the case of transgenerational inheritance, the mark can be passed through multiple generations, and progeny inheriting the mark never need to experience the stress.

Figure 2. Stress-induced effects on genome structure. First, stress causes strain on cellular systems. These perturbations lead to chromoanagenesis in the form of chromothripsis, chromoplexy, or chromoanasynthesis. Each subset of chromoanagenesis produces a set of structural genomic variants. These structural genomic variants can be maladaptive or adaptive. It should be noted that not all activators of chromoanagenesis are included in this diagram.

Tables

Table 1. Examples of stress-induced DNA damage.

Stress	DNA Damage	Species	Reference
Oxidative stress	Strand breaks	Human (*Homo sapiens*)	(Honda et al., 2001)
		Mouse (*Mus musculus*)	(Rajesh Kumar et al., 2002)
		Chub (*Leuciscus cephalus*)	(Aniagu et al., 2006)
	Thymine glycol	Rat (*Rattus norvegicus*)	(Cathcart et al., 1984)
		Human (*Homo sapiens*)	(Yoon et al., 2010)
	8-oxo-deoxyguanosine	Gilt-head bream (*Sparus aurata*)	(Diaz-Mendez et al., 1997)
		Mouse (*Mus musculus*)	(Yamanaka et al., 2001)
		Human (*Homo sapiens*)	(Matsui et al., 1999)
Hypoxia	Single-strand breaks	Rainbow trout (*Oncorhynchus mykiss*)	(Liepelt et al., 1995)
		Human (*Homo sapiens*)	(Møller et al., 2001)
Salinity stress	Double-strand breaks	Mouse (*Mus musculus*)	(Kültz and Chakravarty, 2001)
		Thale cress (*Arabidopsis thaliana*)	(Boyko et al., 2010b)
	Single-strand breaks	Strawberry (*Fragaria x ananassa*)	(Tanou et al., 2009)
Extreme pH	Strand breaks	Pacific white shrimp (*Litopenaeus vannamei*)	(Wang et al., 2009)
	AP sites	Human (*Homo sapiens*)	(Chatterjee and Walker, 2017)
Heat stress	Strand breaks	Pufferfish (*Takifugu obscurus*)	(Cheng et al., 2018)
	AP sites	Human (*Homo sapiens*)	(Chatterjee and Walker, 2017)
	Deaminated cytosine	Mammals (multiple species)	(Fryxell and Zuckerkandl, 2000)
UV irradiation	Strand breaks	Human (*Homo sapiens*)	(Lankinen et al., 1996)
		Pig (*Sus sp.*)	(Choy et al., 2005)
	Cyclobutane pyrimidine dimers	Human (*Homo sapiens*)	(Clingen et al., 1995)
		Mouse (*Mus musculus*)	(Garinis et al., 2005)
		Rockcress (*Arabidopsis sp.*)	(Chen et al., 1994)
	Pyrimidine-pyrimidone photoproducts	Human (*Homo sapiens*)	(Mitchell et al., 1990)
		Prussian carp (*Carassius auratus gibelio*)	(Bagdonas and Zukas, 2004)
		Rockcress (*Arabidopsis sp.*)	(Chen et al., 1994)

Table 2. Examples of stress-induced change in histone PTMs.

Stress	Change in Histone PTMs	Species	Associated Phenotype (if reported)	Reference
Heat stress	Increase in H3K27me3	Chicken (*Gallus gallus domesticus*)	Increased glucocorticoid production	(Zheng et al., 2021)
	Increase in H3K4me2/3	Thale cress (*Arabidopsis thaliana*)	Transcriptional memory of heat stress	(Lämke et al., 2016)
	Decrease in H3K9me2/3**	Fruit fly (*Drosophila melanogaster*)	Not reported	(Seong et al., 2011)
	Decrease in H3K9me3**	Nematode worm (*Caenorhabditis elegans*)	Altered gene expression**	(Klosin et al., 2017)
	Acetylation of histones H3 and H4**	Brine shrimp (*Artemia*)	Enhanced tolerance to lethal heat stress; resistance to *Vibrio campbellii***	(Norouzitallab et al., 2014)
Cold stress	Decrease in H3K9me2	Mouse (*Mus musculus*)	Long-term tolerance to cold stress	(Abe et al., 2018)
	Decrease in H3K27me3	Thale cress (*Arabidopsis thaliana*)	Activation of cold stress genes	(Kwon et al., 2009)
	Increase in H3K27ac and H3K36ac	Rice (*Oryza sativa*)	Not reported	(Xue et al., 2018)
Salinity stress	Decrease in H3K9me2/3**	Fruit fly (*Drosophila melanogaster*)	Not reported	(Seong et al., 2011)
	Increase in H3K4me3 and H3K9K14ac; decrease in H3K9me2	Thale cress (*Arabidopsis thaliana*)	Activation of salinity-induced genes	(Chen et al., 2010)
Drought stress	Increase in H3K4me3 and H3K9ac	Thale cress (*Arabidopsis thaliana*)	Activation of drought-induced genes	(Kim et al., 2008)
Toxin exposure	Decrease in H3K4me2, H3K18ac, H3K27me2, and H3K20me2; increase in H3K14ac*	Rat (*Rattus norvegicus*)	Desensitization to toxin (cocaine)*	(Wimmer et al., 2019)
	Increase in H3K4me2 and H3K9ac	Human (*Homo sapiens*)	Increased risk of lung cancer	(Cantone et al., 2011)

*Effect observed in next generation

**Effect observed through multiple generations

Table 3. Examples of stress-induced change in DNA methylation.

Stress	Species	Associated Phenotype (if reported)	Reference
Heat stress	Spiny chromis damselfish (*Acanthochromis polyacanthus*)	Increased aerobic scope*	(Ryu et al., 2018)
	Brine shrimp (*Artemia*)	Enhanced tolerance to lethal heat stress; resistance to *Vibrio campbellii***	(Norouzitallab et al., 2014)
Cold stress	Mouse (*Mus musculus*)	Increased tolerance to cold stress; reduced risk of obesity*	(Sun et al., 2018)
	Tartary buckwheat (*Fagopyrum tataricum*)	Altered expression of genes involved in cold memory	(Song et al., 2020)
	Turnip (*Brassica rapa*)	Increased growth rate and heat tolerance	(Liu et al., 2017)
	Three-spined stickleback (*Gasterosteus aculeatus*)	Not reported	(Metzger and Schulte, 2017)
Salinity stress	Rice (*Oryza sativa*)	Tolerance to salinity stress*	(Feng et al., 2012)
	Thale cress (*Arabidopsis thaliana*)	Tolerance to salinity stress*	(Boyko et al., 2010a)
	Water flea (*Daphnia magna*)	Altered expression of genes involved in the cellular stress response**	(Jeremias et al., 2018)
	Three-spined stickleback (*Gasterosteus aculeatus*)	Not reported	(Heckwolf et al., 2020)
Upwelling	Purple sea urchin (*Strongylocentrotus purpuratus*)	Increased body size*	(Strader et al., 2019; Wong et al., 2019)
Drought stress	Rice (*Oryza sativa*)	Altered gene expression**	(Zheng et al., 2013)
Pesticides	Rat (*Rattus norvegicus*)	Risk of obesity**	(Skinner et al., 2013)
		Reduced male fertility**	(Anway et al., 2005)
		Adult-onset disease**	(Anway et al., 2006) (Manikkam et al., 2014)
Ionizing radiation	Zebrafish (*Danio rerio*)	Developmental defects**	(Kamstra et al., 2018)
Toxin exposure	Water flea (*Daphnia magna*)	Altered gene expression*	(Vandegehuchte et al., 2010)

*Effect observed in next generation

**Effect observed through multiple generations

Table 4. Examples of stress-induced change in genome structure.

Stress	Change in Genome Structure	Species	Associated Phenotype	Reference
Altered climate	Chromosome inversion	Mosquito (*Anopheles gambiae*)	Increased thermotolerance in larvae	(Rocca et al., 2009)
		Fruit fly (*Drosophila subobscura*)	Altered optimal temperature	(Rego et al., 2010)
	Chromosome reshuffling	Buckler mustard (*Biscutella laevigata*)	Heightened tolerance to abiotic stresses	(Geiser et al., 2016)
		Yellow arctic whitlow grass (*Draba nivalis*)	Increased tolerance to cold, drought, and oxidative stresses	(Nowak et al., 2021)
Altered nutrient availability	Copy number variant	Human (*Homo sapiens*)	Increased abundance of salivary amylase protein	(Perry et al., 2007)
		Baker's yeast (*Saccharomyces cerevisiae*)	Increased efficiency of glucose metabolism	(Brown et al., 1998)
Hyposaline stress	Chromosome inversion	Atlantic cod (*Gadus morhua*)	Reduced recombination in genes necessary to tolerate low salinity	(Barth et al., 2017)
Pathogens	Copy number variant	Soybean (*Glycine max*)	Pathogen resistance	(Cook et al., 2012)
Toxin exposure	Chromosome inversion	Mosquito (*Anopheles atroparvus*)	DDT resistance	(D'Alessandro et al., 1957)
	Copy number variant	Barley (*Hordeum vulgare*)	Boron-toxicity tolerance	(Sutton et al., 2007)
		Palmer amaranth (*Amaranthus palmeri*)	Herbicide resistance	(Gaines et al., 2010)

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1050 **Table 5. Examples of stress-induced change in transposable elements.**

Stress	Species	Change in Transposable Elements	Associated Phenotype (if reported)	Reference
Heat stress	Thale cress (*Arabidopsis thaliana*)	Activation of *ONSEN* retrotransposon	Not reported	(Cavrak et al., 2014)
	Fruit fly (*Drosophila melanogaster*)	*P element* transposition disrupting heat shock protein gene *hsp70Ba*	Altered thermotolerance	(Lerman et al., 2003)
	Rice blast fungus (*Magnaporthe oryzae*)	Activation of *Pyret*, *MAGGY*, *Pot2*, *MINE*, *Mg-SINE*, *Grasshopper*, and *MGLR3*	Genomic instability	(Chadha and Sharma, 2014)
	Nematode worms (*Caenorhabditis elegans* and *Caenorhabditis briggsae*)	Activation of *CemaT1* and *Tc1*	Genomic instability	(Ryan et al., 2016)
	Mouse (*Mus musculus*)	Activation of *MERV-L* and *IAPEz*	Altered gene expression	(Hummel et al., 2017)
Cold stress	Asian tiger mosquito (*Aedes albopictus*)	Altered insertion frequency of *Lian1*, *RTE4*, *RTE5*, *L2B*, and *IL1*	Localization of TEs to genes potentially involved in overwintering	(Goubert et al., 2017)
	Rice (*Oryza sativa*)	Activation of *mPing*	Altered gene expression	(Naito et al., 2009)
	Common snapdragon (*Antirrhinum majus*)	Activation of *Tam3*	Not reported	(Hashida et al., 2003)
UV irradiation	Human (*Homo sapiens*)	Activation of *L1*	Malignant transformation of keratinocytes	(Banerjee et al., 2005)
Pollution	Amazon cichlid (*Cichlasoma amazonarum*)	Differential insertion patterns of *Rex 1*, *Rex 3*, and *Rex 6*	Not reported	(da Silva et al., 2020)
Oxidative stress	Mouse (*Mus musculus*)	Activation of *L1*	Not reported	(Van Meter et al., 2014)
	Nematode worms (*Caenorhabditis elegans* and *Caenorhabditis briggsae*)	Activation of *CemaT1* and *Tc1*	Genomic instability	(Ryan et al., 2016)
Pesticides	Fruit fly (*Drosophila melanogaster*)	Activation of *Accord* retrotransposon	Insecticide resistance via overexpression of insecticide detoxifying gene	(Chung et al., 2007)
	Common house mosquito (*Culex pipiens*)	Insertion of TE-like DNA into coding region of *cmp1*	Insecticide resistance via alternative splicing of toxin receptor	(Darboux et al., 2007)
Salinity stress	Rice (*Oryza sativa*)	Activation of *mPing*	Higher salinity stress tolerance via	(Naito et al., 2009; Yasuda

			overexpression of ZFP252	et al., 2013)

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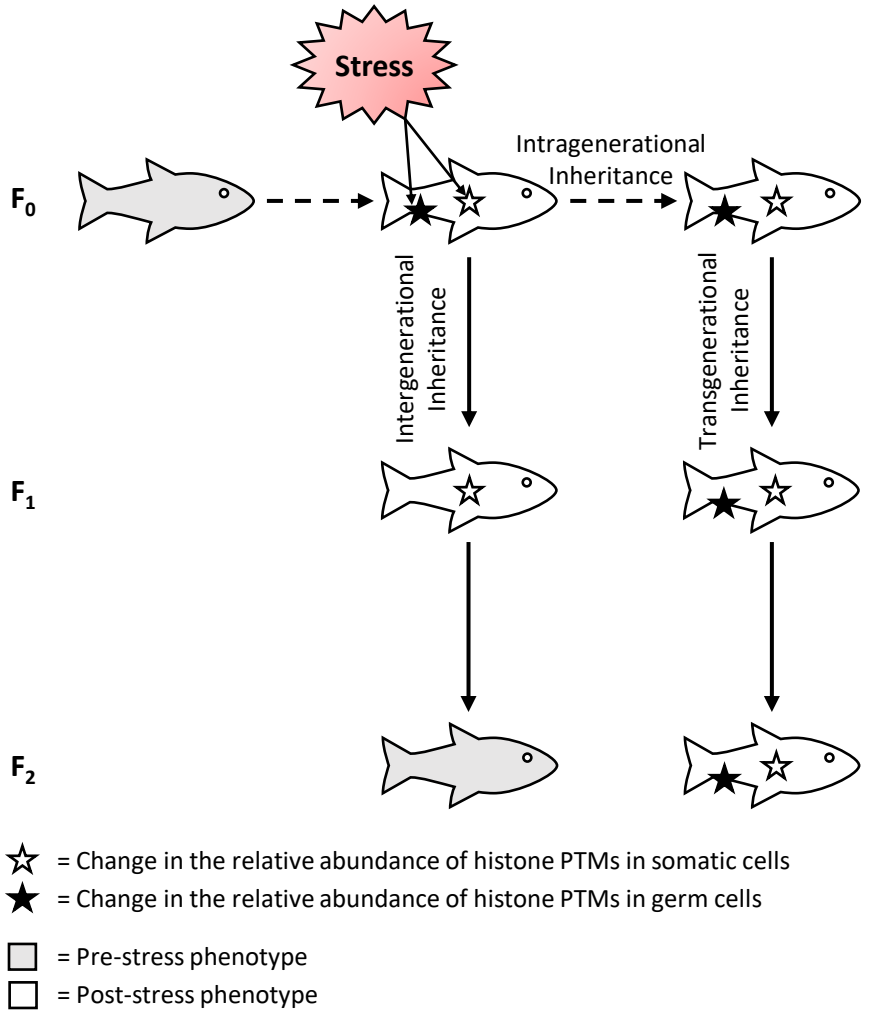
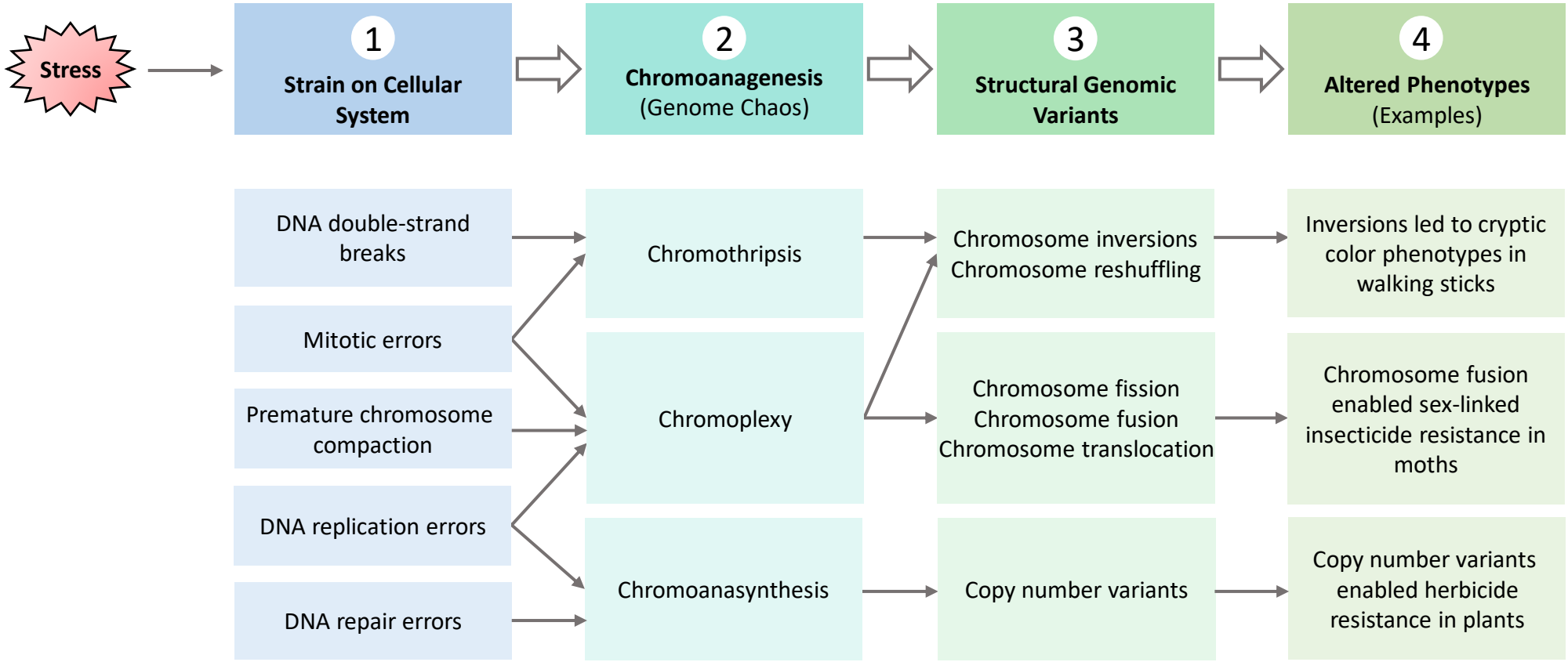

Stress
Intragenerational
Inheritance
F0
Intergenerational
Inheritance
Transgenerational
Inheritance
F1
F2
= Change in the relative abundance of histone PTMs in somatic cells
= Change in the relative abundance of histone PTMs in germ cells
= Pre-stress phenotype
= Post-stress phenotype


Stress
1
Strain on Cellular System
2
Chromoanagenesis (Genome Chaos)
3
Structural Genomic Variants
4
Altered Phenotypes (Examples)
DNA double-strand breaks
Mitotic errors
Premature chromosome compaction
DNA replication errors
DNA repair errors
Chromothripsis
Chromoplexy
Chromoanasynthesis
Chromosome inversions
Chromosome reshuffling
Chromosome fission
Chromosome fusion
Chromosome translocation
Copy number variants
Inversions led to cryptic color phenotypes in walking sticks
Chromosome fusion enabled sex-linked insecticide resistance in moths
Copy number variants enabled herbicide resistance in plants