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Mechanisms for the epigenetic inheritance of stress response in single cells

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Abstract

Cells have evolved to dynamically respond to different types of environmental and physiological stress conditions. The information about a previous stress stimulus experience by a mother cell can be passed to its descendants, allowing them to better adapt to and survive in new environments. In recent years, live-cell imaging combined with cell-lineage tracking approaches has elucidated many important principles that guide stress inheritance at the single-cell and population level. In this review, we summarize different strategies cells can employ to pass the 'memory' of previous stress responses to their descendants. Among these strategies, we focus on a recent discovery of how specific features of Msn2 nucleo-cytoplasmic shuttling dynamics could be inherited across cell lineages. We also discuss how stress response can be transmitted to progenies through changes in chromatin and through partitioning of anti-stress factors and/or damaged macromolecules between mother and daughter cells during cell division. Finally, we highlight how emergent technologies will help address open questions in the field.

Keywords

Stress response; Msn2; epigenetic inheritance; single cells; yeast; mammalian cells

INTRODUCTION

All cellular life faces constant challenges of internal and external stress. Unicellular organisms such as bacteria and yeast must sense and adapt to environmental fluctuations in nutrient, temperature and osmotic pressure to ensure survival[1]. Exposure to toxins and high doses of radiation can cause damages to DNA, lipid and protein molecules. Cells within an

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embryo respond to mechanical stretch and compression during normal embryonic development. In response to oncogene activation, cellular defense mechanisms can lead to senescence or apoptosis of precancerous cells[2]. At the systems level, the immune system comprised of diverse cell types is a highly evolved stress response mechanism that can identify a wide variety of pathogens as well as cancerous cells and defend the organism against them.

A descendant cell's inheritance of its ancestors' previous stress responses in a 'memory'-like fashion can be expected to serve as a mechanism to enhance cell survival. It is generally believed that such an inheritance allows the descendant cell to more rapidly adapt to a new environment[3], or acquire immunity against a previously encountered pathogen. Inheritance of stress response can occur through both genetic and epigenetic means. For example, antibiotic treatments are known to increase genomic mutation rates in many species of bacteria, and these mutations can be passed on to descendant cells to drive drug-resistance[4]. Moreover, some bacteria acquire viral resistance by integrating short fragments of viral nucleic acids into CRISPR repeats[5], which can be stably inherited. Contrary to genetic mutations, changes facilitated by non-genetic factors are often dynamic and reversible. Epigenetic mechanisms operating at a fast timescale can be particularly advantageous for cells growing in fluctuating environments[6], because they can allow cells to rapidly switch between different gene expression or growth states in response to the dynamic changes in the external stress conditions.

In this review, we discuss different epigenetic mechanisms that cells can employ to pass their stress response histories to their descendants. We focus on the recent discoveries of the heritable features of transcription factor dynamics in response to stress. We then highlight how the emergent technologies will help address open questions in the field.

STRATEGIES for the EPIGENETIC INHERITANCE of STRESS RESPONSE

1. Inheritance of transcription factor dynamics

Cells have evolved complex signaling networks to sense and respond to different stress signals by activating specific downstream genes[7]. Transcription factors (TFs) are key components of the signaling cascades orchestrating a cell's response to stress[8]. Curiously, many TFs exhibit dynamic behaviors in response to stress[9,10]. A recent genome-wide screen identified ~8% of the yeast TFs stochastically shuttle in and out of the nucleus under various conditions[9]. Single-cell studies in recent years have revealed that transcription factors can transmit quantitative information corresponding to distinct environmental conditions[11,12]. This information can in principle be encoded in the nuclear localization frequency, amplitude, and duration of the specific transcription factors[11,12].

Msn2 is a major transcription factor in yeast *S. cerevisiae*. It regulates the expression of ~200 genes in response to a variety of stressors, including glucose starvation, oxidative stress, heat shock, and osmotic stress[13,14]. Using high-resolution time-lapse microscopy on single yeast cells, previous studies have found that Msn2 dynamically shuttles between cytoplasm and the nucleus[11,12,15,16]. In the case of stress caused by glucose limitation, the Msn2 nuclear localization was revealed to occur every 1.5–2 min on average[11,16] (Fig. 1).

The dynamics of Msn2 nuclear localization is controlled by the phosphorylation state of this protein. Under normal growth conditions, cAMP-dependent protein kinase A (PKA) phosphorylates the nuclear localization sequence on Msn2 and keeps it in the cytoplasm. PKA activity is downregulated upon glucose limitation, leading to dephosphorylation of Msn2 and its transport into the nucleus[13] (Fig. 1). Additionally, protein phosphatase 1 (PP1) can also directly dephosphorylate Msn2, leading to its nuclear localization[17]. Thus, each Msn2 nuclear localization event corresponds to the simultaneous dephosphorylation of a large fraction of the ~125 copies of Msn2 molecules per cell[18]. Increasing the intensity of glucose limitation stress increases the frequency[12,16] and amplitude[16] of Msn2 nuclear localization, but does not affect its duration[12,16].

To understand if the key features of the Msn2 localization dynamics are heritable, Chatterjee & Acar (2018) used a microfluidic chip to track Msn2 nuclear localization dynamics in lineages or 'families' of yeast cells during long-term (15–18hrs) glucose limitation[16]. They found that the frequency of Msn2 nuclear localization was inherited in progenies of mother cells, whereas the amplitude and duration did not show such inheritance. At high stress levels (0.1% glucose), mother, daughter and granddaughter cells often exhibited synchronous Msn2 localization events. What can account for the inheritance of this seemingly stochastic dynamics of Msn2 between the mother cell and its descendants? One hypothesis is that the activity of either the upstream kinase PKA or the PP1 phosphatase could be passed on from mother to its descendants, leading to synchronized Msn2 phosphorylation states, and in turn, similar nuclear localization patterns across generations. Indeed, an elegant study published by Hao & O'Shea[12] (2012) showed that applying a PKA inhibitor (1-NM-PP1) to yeast cells carrying mutations in all three catalytic subunits of PKA (Tpk1, Tpk2, Tpk3) is sufficient to precisely control the amplitude, frequency and duration of the Msn2 nuclear localization.

In another example, the tumor suppressor protein p53 and its negative regulator Mdm2 were shown to display heritable nuclear localization dynamics in response to DNA damage[19]. Geva-Zatorsky *et al.* (2006) tracked p53 and Mdm2 protein levels in individual breast cancer cells taken from an isogeneic clone following γ-irradiation damage[19]. Upon irradiation, protein levels of p53 and Mdm2 continuously oscillated in a large population of cells with a period of ~5.5hrs for at least three days. This oscillatory behavior was attributed to the presence of a negative feedback loop between p53 and Mdm2[20]. After cell division, Mdm2 protein levels in sister cell-pairs continued to oscillate in the same phase, until the signal became unsynchronized after ~11hrs, suggesting that the information was transmitted from the mother cells to their progenies.

Similar to p53, nuclear factor κB (NFkB) also exhibits oscillatory behavior due to a negative feedback loop between NFkB and its inhibitor IκB[21]. NFκB is the primary TF of the innate immune system[22]; it also plays a role in cells' response to mechanical stress[23]. Upon stimulation with TNF-α, NFκB was shown to display sustained nucleo-cytoplasmic oscillations with a period of ~100min for over 20hrs, after which the oscillations slowly dampened[21]. Interestingly, the period of the oscillations was highly similar (albeit slightly out of phase) in sister cell-pairs after cell division[24]. To find out how long this similarity could last, the authors derived multiple clonal lines from single cells and tracked them over

30 generations. Their results showed that the oscillation period distribution for each clone resembled each other. What caused the inheritance of NFkB oscillation is still unknown; the authors proposed that it may have been caused by epigenetic mechanisms acting through specific proteins or chromatin modifications[24].

Despite these examples, not all transcription factors' dynamics are heritable. In response to extracellular calcium, another transcription factor, Crz1, translocates into the nucleus in a rapid burst (synchronized among cells) followed by short (~2min), stochastic bursts[11]. Increased calcium concentration results in an increased frequency of Crz1 nuclear localization but does not affect its nuclear localization duration[11]. Unlike Msn2, however, the overall nuclear localization dynamics of Crz1 appear to operate in an asynchronous manner between related cell pairs as the burst dynamics in daughter cells do not appear to be correlated with those in the mother cells[11], suggesting that Crz1 nuclear localization dynamics is not heritable.

2. Stress-induced changes in chromatin

Beyond altering nuclear localization dynamics of specific transcription factors, stress signaling can also cause changes in chromatin structure or modifications in DNA and histone marks[3] (Fig 2). Several types of stressors have been shown to trigger global re-organization of chromatin structure. For example, prolonged heat stress induces decondensation of the ribosomal DNA (rDNA) region and activation of silenced repetitive elements in *Arabidopsis thaliana*[25]. Bacterial and viroid infections can cause decondensation of heterochromatin in some plants[26,27]. Interestingly, both glucose starvation (Xue & Acar, in revision) and rapamycin treatment[28] in budding yeast induce condensation, rather than decondensation, of the rDNA chromatin. Global condensation of chromatin is also reported in HeLa cells in response to serum starvation[29]. The exact biological function of these stress-induced changes in chromatin structure is not well understood. Additionally, it still remains to be determined whether these changes can be stably inherited over multiple cell generations.

Numerous stress-signaling kinases, including AKT[30,31], JAK2[32] and AMPK[33], have been shown to directly or indirectly modify histone marks. In response to metabolic stress or UV damage, the mammalian AMPK kinase directly binds to promoters and open reading frames of target genes and phosphorylates histone H2B[33]. Oncogenic stress (e.g., due to overexpression of an oncogene) in human cells induces the expression of a histone H3K27 demethylase JMJD3, which in turn removes repressive H3K27me3 marks on tumor suppressor genes $p16^{INK4A}$ and $p14^{ARF}$ to help initiate cellular senescence[34]. To date, over 20 phosphorylation sites on histones regulated by upstream signaling kinases have been reported[2]. Another specific stress response, the DNA damage response (DDR), is intimately linked to chromatin modifications[35]. DNA damage can trigger phosphorylation or dephosphorylation of different histones (e.g. H2A, H2B and H3) and chromatin modifiers, with different histone phosphorylation states facilitating distinct cellular decisions, such as cell cycle arrest, DNA repair, chromatin condensation, or apoptosis[36].

MicroRNAs (miRNAs), short RNAs of ~22 nucleotides, have recently been found to play a key role in regulating diverse stress responses in mammals, insects and plants[37]. Many

miRNAs are strategically positioned as part of negative or positive feedback loops established by known transcription factors mediating stress responses. For example, miR-9, miR-155, and miR-146 have been found to be expressed as part of the NFkB-dependent signaling cascade in response to inflammation; they in turn repress the targets of pro-inflammatory pathway to help reset the inflammatory response[37].

Epigenetic modifications can be either dynamically changing or relatively stable[38]. It has been proposed that, although some epigenetic changes are transient and can be reversed by chromatin modifiers, others may leave a lasting 'epigenetic memory' on chromatin, causing cells to be 'locked' in specific gene expression states[2]. Despite the appeal of this idea, experimental evidence (especially at the single cell level) in support of this hypothesis is still lacking.

3. Facilitating epigenetic inheritance via cell division and fusion

Cell division is a simple yet powerful mechanism that can allow mother cells to pass different anti-stress factors on to daughter cells (Fig. 3). In theory, this mechanism can equip daughter cells with anti-stress factors as soon as they are born into the harsh environment, hence improving their survival rate. Anti-stress factors may include transcription factors, activated protein kinases, mRNAs that encode proteins conferring stress resistance, and miRNAs. Additionally, storage carbohydrates (especially trehalose) produced in response to glucose starvation protect cells in poor nutrient conditions and contribute to chronological lifespan extension in yeast[39]. Some of these anti-stress factors are long-lived. For example, miRNAs can be relatively stable with a half-life of ~12 days *in vivo*[37], implying that their activity can be passed on to descendant cells over multiple cell divisions.

In addition to passing on anti-stress factors, cell division can control partitioning of damaged macromolecules and restrict them to a certain population of cells. This asymmetric damage segregation has been observed in bacteria[40], yeast[41,42], and stem cells[43,44], and is thought to produce newborn cells that are 'damage-protected' at the cost of more damaged, 'aged' mother cells. For instance, carbonylated proteins, as a result of irreversible oxidative damage, are found to accumulate in mother cells of the budding yeast during cytokinesis[41]. In *E. coli*, damaged proteins tend to form aggregates that localize to the old pole from the previous cell division[45]. Recent single-cell lineage studies have shown that the degree of asymmetry in the damage partitioning process in *E. coli* was heritable, such that cells with more damage showed higher levels of asymmetric segregation of damaged proteins[46]. Continuous re-distribution of damaged proteins in individual cells was shown to be evolutionarily advantageous as it can enhance bacterial growth on a population level[46].

Intriguingly, cell division can also serve as a 'timer' that causes mother cells and their progenies to synchronously switch between distinct phenotypic states even after cell division. Using time-lapse microscopy, Kaufmann *et al.* (2007) studied the phenotypic switching behavior in lineages of yeast cells containing an engineered version of the galactose utilization (GAL) network[47]. In the yeast strain[48] they used, the endogenous negative feedback loop mediated by the Gal80 promoter had been abolished and the Gal80 expression was driven by the TET promoter. It had already been shown how Gal80 (repressor of Gal4 activity) expression and galactose concentration affected the stochastic

switching frequency between the OFF and ON states of the bimodal GAL network[48]. The authors observed that some mother and daughter cells switched to the ON state synchronously, and this correlation in switching times lasted for several cell generations. How could this switching behavior be heritable? Quantitative modeling showed that the synchrony in phenotypic switching was predominantly dependent on Gal80. Although GAL network is not a stress-response network, stress-response networks with similar topologies would be expected to utilize the same mechanism to make related cells respond to stress in synchrony.

As a process operating in the opposite direction to cell division, cell-to-cell fusion (particularly in the context of fertilization) can be an important mechanism for trans-generational inheritance of stress responses[49] (Fig. 3C). Recent studies in mice have shown that several types of miRNAs are produced in sperm cells in response to chronic stress; these miRNAs are passed on to the oocyte during fertilization and can suppress gene expression in the embryo[50,51].

CONCLUSIONS and FUTURE PERSPECTIVES

In conclusion, cells can utilize multi-layered epigenetic regulatory mechanisms to pass on a ‘memory’ of previous stress responses to the next generation. These mechanisms include controlling the dynamics of the nuclear localization of transcription factors, changing chromatin structure and biochemistry, and partitioning anti-stress factors and/or damaged molecules between mother and daughter cells.

In the past decade, live-cell imaging technologies together with cell-lineage tracking approaches have uncovered many fundamental principles that guide stress-response inheritance at the single-cell and population level. Despite significant advances made, several important questions still remain unaddressed. For example, what upstream events cause the synchronous nucleo-cytoplasmic shuttling dynamics of certain transcription factors between mother and daughter cells? How are the activities of the kinases involved in stress signaling inherited across cell lineages? Which stress-induced epigenetic modifications are stably passed on to daughter cells and which are erased? What is the physiological relevance of these stable and transient modifications? What are the biological functions of the stress-induced global structural changes in chromatin? How are different anti-stress factors partitioned during the cell division and how do the different partitioning schemes impact stress response in progenies?

Some of these questions are ready to be addressed using recently developed biosensors. Live-cell biosensors for monitoring cAMP levels and PKA activity are now available for *S. cerevisiae*[52] and mammalian cells[53,54]. It would be very informative to examine PKA activities in single cells and determine whether the PKA activities are similar in mother cells and their descendants. Live-cell reporters of histone H3[55] and H4[56] lysine acetylation have also been developed. More recently, a fluorescence complementation sensor has been used for real-time visualization of DNA methylation and H3K9me3 marks at major satellite repeats[57]. It will be exciting to apply these reporters to the tracking of the long-term inheritance of these epigenetic marks in live cells. For detection of low-abundance miRNAs

in live cells, a reporter has been developed based on programmable molecular hairpins that can self-assemble to produce FRET signal[58]. Finally, the combination of single-cell RNA-seq technology with cell-lineage tracking methods[59] can be very powerful to examine stress-induced global transcriptomic changes that occur in single cells and to track how these changes are inherited across cell lineages. Applying all these new tools to track the long-term inheritance of epigenetic changes in live cells will be instrumental in answering the questions posed earlier. We anticipate that these technological innovations will drive the discovery of new principles, expanding our understanding of the mechanisms underlying stress-response inheritance.

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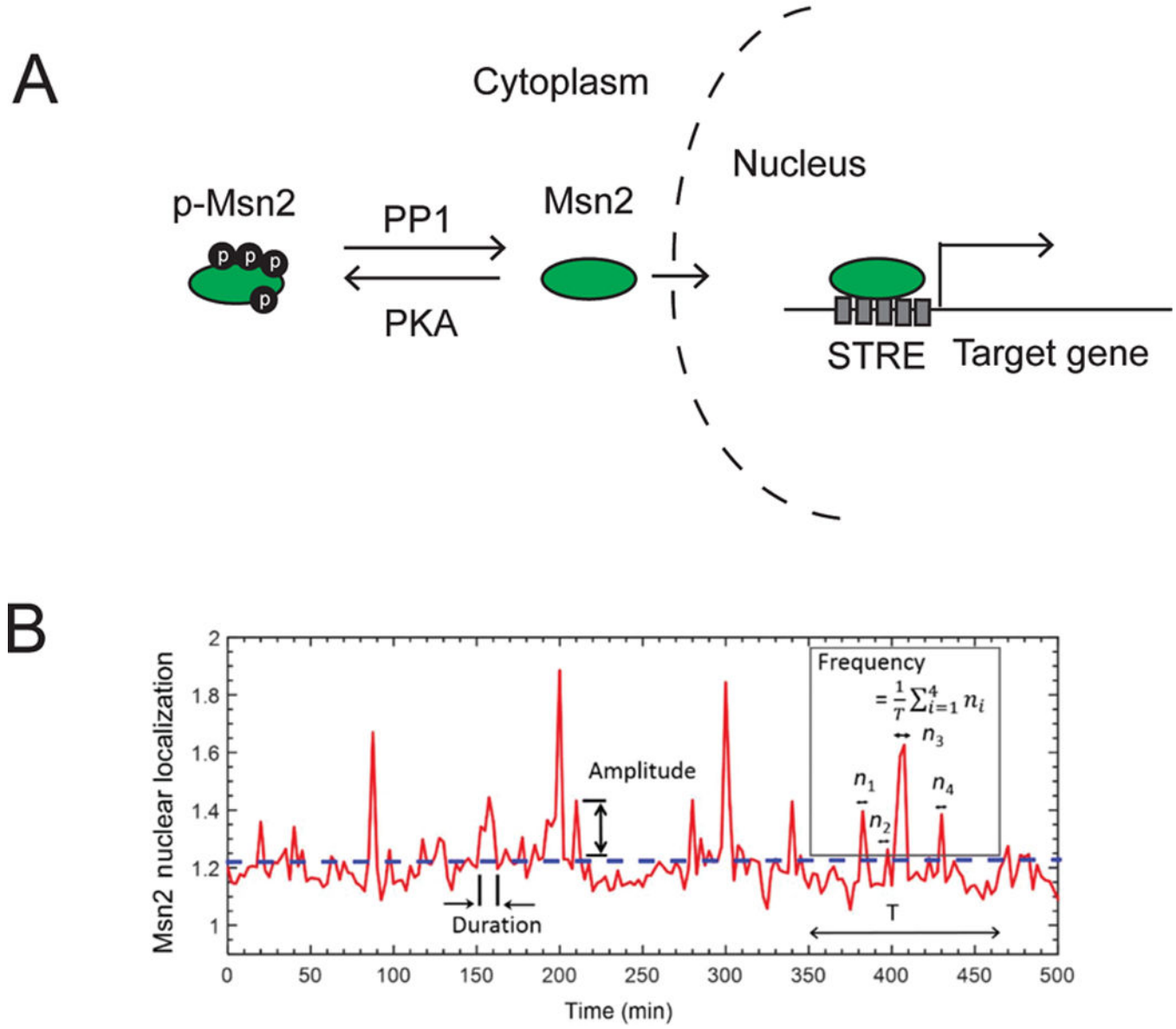

Figure 1. Stress induces dynamic changes in Msn2 nuclear localization.

A. In response to various stress stimuli, Msn2 proteins become dephosphorylated and translocate into the nucleus to activate downstream gene expression. PP1: Protein phosphatase 1, PKA: cAMP-dependent protein kinase A, STRE: stress response element. **B.** Msn2 nuclear localization trajectory of a cell, showing how amplitude, frequency, and duration of Msn2 nuclear localization are quantified. The dashed horizontal line denotes the threshold level above which there would be an Msn2 nuclear localization event. n_i denotes the number of above-the-threshold localization events. T denotes the length of time interval used for the calculation of frequency. Figure panel was taken from [16].

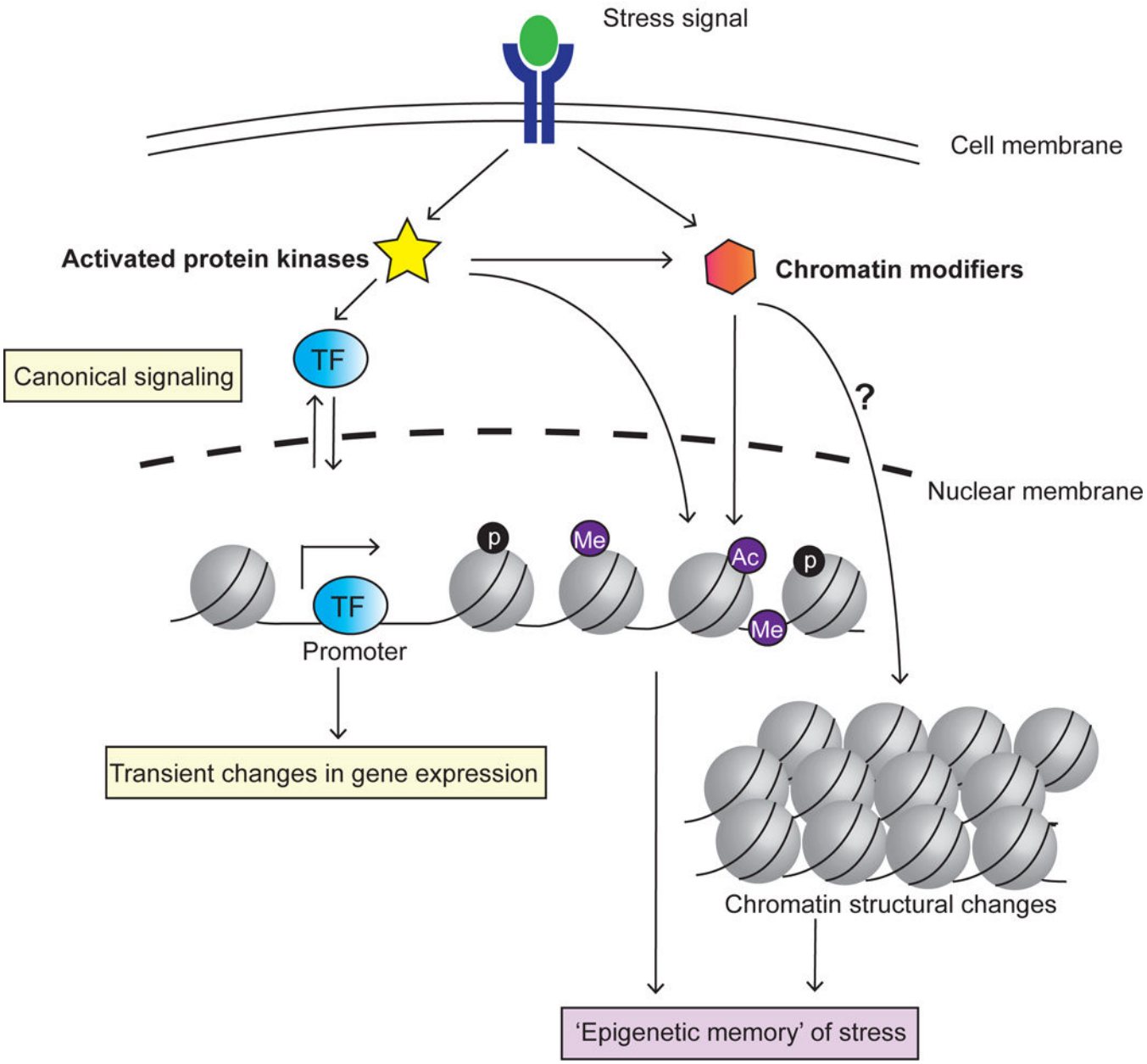

Figure 2. Stress can cause heritable changes in chromatin structure and biochemistry.

Activated protein kinases can directly or indirectly change epigenetic marks on DNA and histones. Stress response can also change the 3D structure of chromatin. If sufficiently stable, these epigenetic changes can be heritable by daughter cells, corresponding to passing an 'epigenetic memory' of mother's specific transcriptional states. p: phosphorylation; Me: Methylation; Ac: Acetylation.

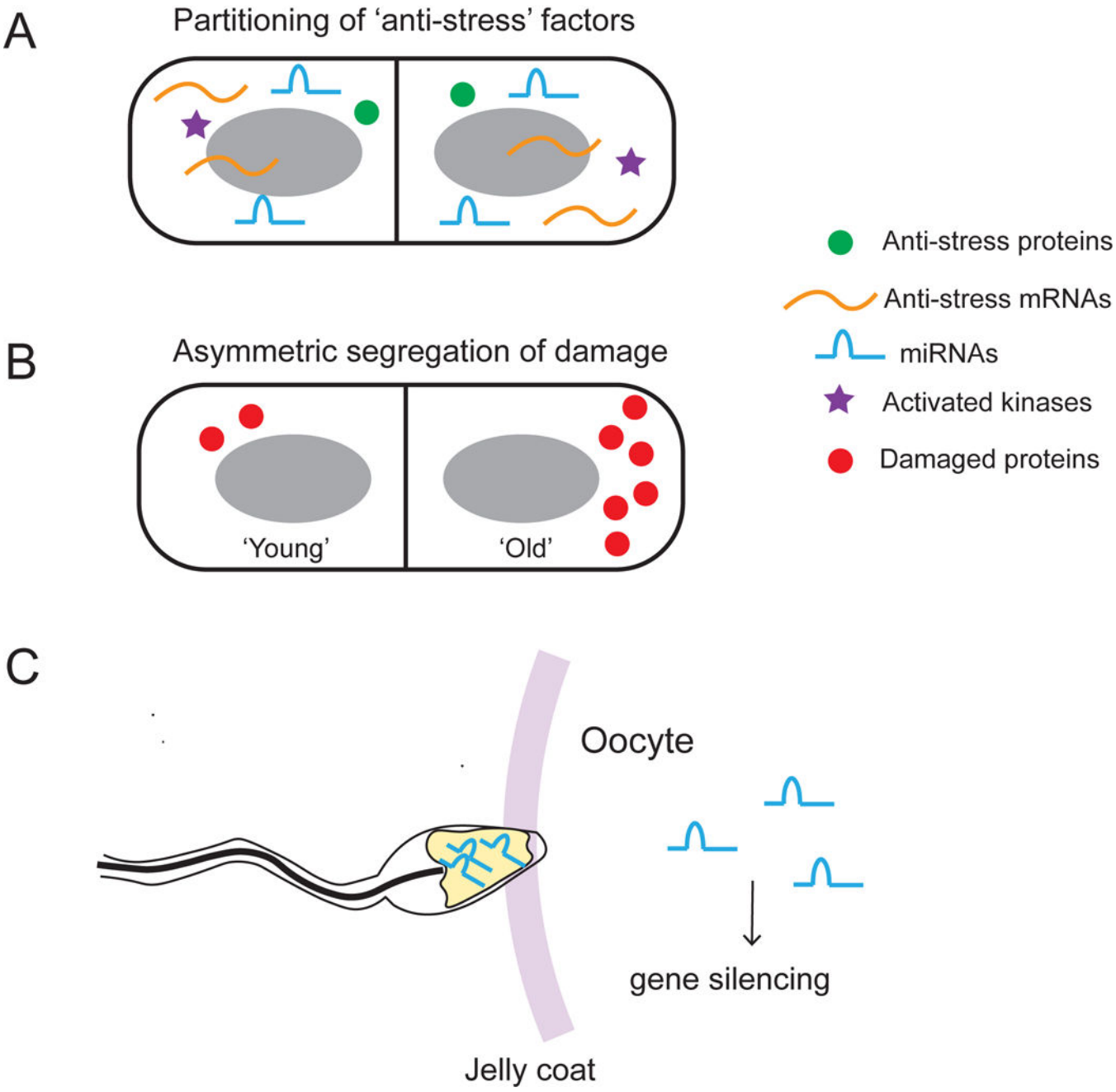

Figure 3. Cell division and cell-to-cell fusion propagate stress response to descendants.
A. Anti-stress proteins, mRNAs and miRNAs are passed on to daughter cells during cell division. **B.** Asymmetrical segregation of damaged molecules generates a 'damage-protected' daughter cell at the expense of the mother cell's being burdened with more damage. **C.** Sperm carrying miRNAs produced as a result of stress-induction transmits the stress signal to an oocyte during fertilization.