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REVIEW

New insights into transcriptional reprogramming during cellular stress

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ABSTRACT

Cellular stress triggers reprogramming of transcription, which is required for the maintenance of homeostasis under adverse growth conditions. Stress-induced changes in transcription include induction of cyto-protective genes and repression of genes related to the regulation of the cell cycle, transcription and metabolism. Induction of transcription is mediated through the activation of stress-responsive transcription factors that facilitate the release of stalled RNA polymerase II and so allow for transcriptional elongation. Repression of transcription, in turn, involves components that retain RNA polymerase II in a paused state on gene promoters. Moreover, transcription during stress is regulated by a massive activation of enhancers and complex changes in chromatin organization. In this Review, we highlight the latest research regarding the molecular mechanisms of transcriptional reprogramming upon stress in the context of specific proteotoxic stress responses, including the heat-shock response, unfolded protein response, oxidative stress response and hypoxia response.

KEY WORDS: Chromatin, Enhancer, Post-translational modification, Stress response, Transcription

Introduction

Cells are constantly exposed to a multitude of stressors, including elevated temperatures, reactive oxygen species (ROS) and toxins. These adverse conditions disrupt cellular homeostasis by causing the accumulation of damaged DNA, proteins and lipids, and if the damaged macromolecules are not mitigated, cells will eventually die. Therefore, a critical function in maintaining homeostasis under stressful conditions is the reprogramming of transcription (Sies et al., 2017; Almanza et al., 2019; Joutsen and Sistonen, 2019). Depending on the type of stress, a distinct set of pro-survival genes are activated, while thousands of genes undergo simultaneous repression (Mahat et al., 2016; Dukler et al., 2017; Vihervaara et al., 2017). To activate stress-specific transcriptional programmes, cells utilize various stress-responsive transcription factors (TFs), such as heat-shock factor 1 (HSF1) and nuclear factor erythroid 2-related factor 2 (Nrf2; also known as NFE2L2), that regulate transcription during thermal and oxidative stress, respectively (Sies et al., 2017; Joutsen and Sistonen, 2019). Moreover, the transcriptional output is regulated by dynamic changes in histone modifications and chromatin organization, although these processes are still poorly understood in the context of stress (Niskanen et al., 2015; Mueller et al., 2017; Fujimoto et al., 2018; Lyu et al., 2018). Recent discoveries have also identified massive stress-induced transcription of enhancers, in addition to genes, which adds another layer of complexity to the regulation of transcription (Vihervaara et al., 2017; Lyu et al., 2018).

In this Review, we summarize the involvement of specific TFs in the regulation of four different stress responses: the heat-shock response (HSR), unfolded protein response (UPR), oxidative stress response and hypoxia response. We discuss the mechanisms of transcriptional regulation at the molecular level, including how transcription is initiated, repressed and terminated during stress. We also highlight the roles of chromatin architecture and enhancers in the stress-induced reprogramming of transcription.

Transcriptional programmes are specific to distinct types of stress

Cells need to upregulate distinct sets of cyto-protective genes to survive adverse conditions caused by, for example, protein aggregation, oxidation of macromolecules and lack of oxygen. Although stress-induced changes in transcription are regulated at multiple levels, a critical step of gene upregulation is the binding of stress-responsive TFs to the promoters of upregulated genes (Fig. 1). Here, we describe four key transcriptional responses to different types of stresses and the functional properties of TFs that mediate these responses.

Heat-shock response

The heat-shock response (HSR) is an evolutionarily well-conserved protective process that is triggered by proteoxic stress, a condition caused by increased protein misfolding and aggregation (Joutsen and Sistonen, 2019). The HSR was first reported in 1962 by Ferruccio Ritossa, who discovered specific chromosomal puffs in the salivary glands of *Drosophila busckii* upon exposure to elevated temperatures (Ritossa, 1962). These chromosomal puffs were later identified as sites of active transcription of genes encoding heat-shock proteins (HSPs). HSPs, in turn, function as molecular chaperones, thereby assisting in protein folding and clearance of protein aggregates that are formed upon proteotoxic stress, such as heat shock (Joutsen and Sistonen, 2019). Besides HSPs, heat shock induces transcription of several genes whose functions are not related to protein folding. Through experiments in mouse embryonic fibroblasts, many of these genes were shown to encode cytoskeletal proteins, such as actin-binding proteins (Mahat et al., 2016). The function of cytoskeleton during heat shock was demonstrated in *Caenorhabditis elegans*, where the maintenance of cytoskeletal integrity during heat shock is necessary for cellular transport and thermotolerance in worms (Baird et al., 2014). Importantly, heat shock causes downregulation of thousands of genes, whose functions include regulation of the cell cycle, transcription and metabolism (Mahat et al., 2016; Vihervaara et al., 2017).

In vertebrates, the HSR is transcriptionally regulated by a family of heat-shock factors (HSFs) comprising several members, namely,

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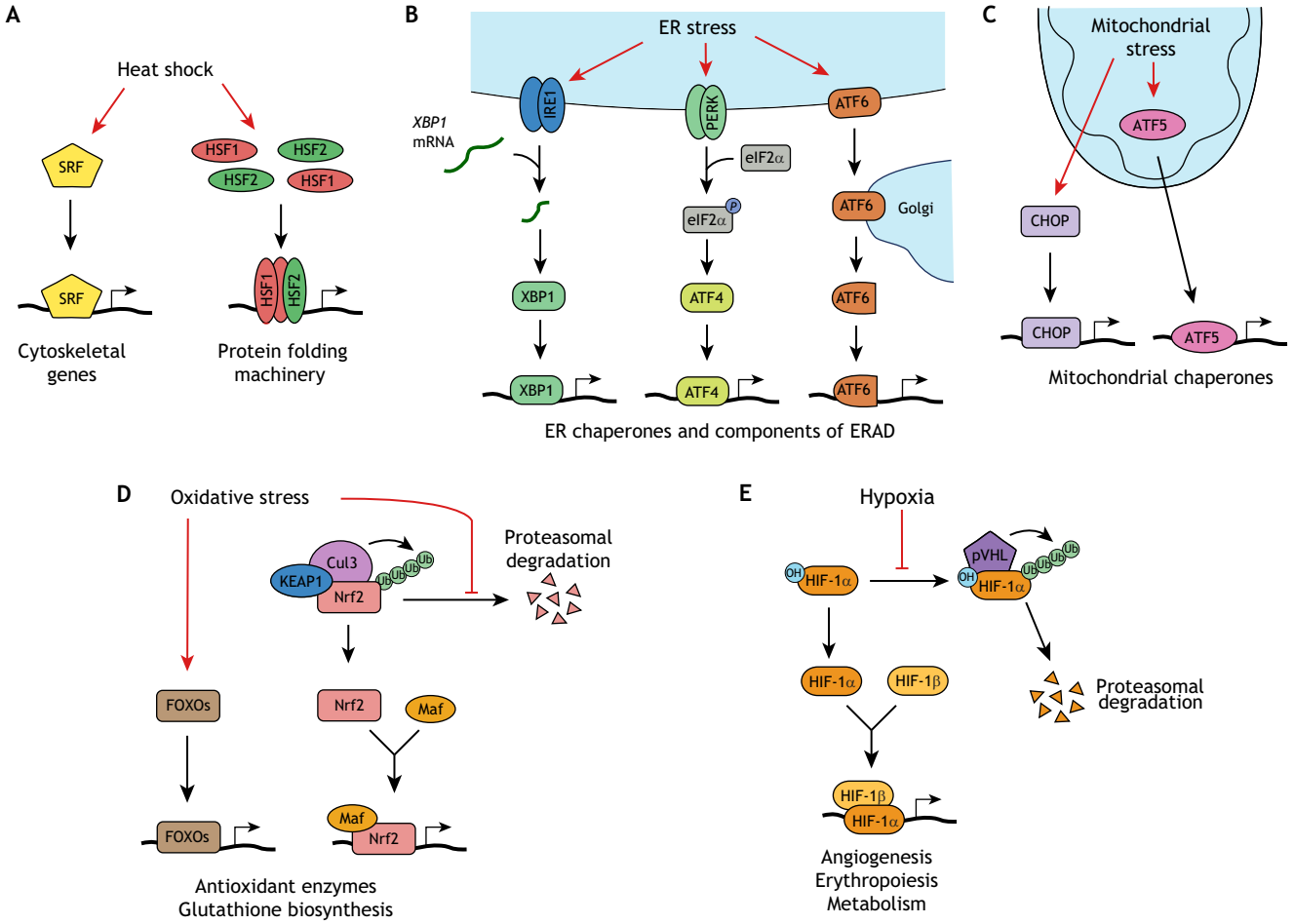

Fig. 1. Cells combat various types of proteotoxic stress by activating distinct stress-response pathways. (A) Heat shock causes the aggregation of proteins in the cytoplasm, which triggers the trimerization of HSF1 and HSF2. Trimeric HSF1 and HSF2 bind to DNA and initiate the transcription of genes related to the protein folding machinery. Heat shock also causes the binding of SRF to several heat-inducible cytoskeletal genes. (B) ER stress is caused by increased overload of proteins in ER, which activates the unfolded protein response (UPR) that consists of three branches mediated by IRE1, PERK and ATF6. Activation of these proteins leads to the accumulation of XBP1, ATF4 and proteolytically cleaved ATF6. Together, they initiate the transcription of ER chaperones and components of the ERAD machinery. (C) Mitochrondrial stress triggers the relocalization of ATF5 from mitochrondria to the nucleus and accumulation of CHOP, which together induce transcription of genes encoding mitochrondrial chaperones. (D) Oxidative stress dissociates Nrf2 from KEAP1 and Cul3. This prevents the ubiquitylation and subsequent proteasomal degradation of Nrf2, allowing the accumulation of Nrf2 in the nucleus. Nuclear Nrf2 dimerizes with small Maf proteins and activates transcription of genes required for increased cellular antioxidant capacity. Antioxidant capacity is enhanced also by oxidative stress-induced activation of the FOXO family of transcription factors. (E) Under normoxia, HIFs, including HIF-1α, HIF-2α and HIF-3α, are hydroxylated, which allows ubiquitylation of HIFs by pVHL and their subsequent proteasomal degradation. Hypoxia prevents the hydroxylation of HIFs, allowing them to escape proteasome-mediated degradation. This leads to the dimerization between one of the α subunits of HIF and HIF-1β, which together induce the transcription of genes that increase oxygen supply in cells. OH, hydroxyl group; P, phosphate; Ub, ubiquitin.

HSF1, HSF2, HSF3, HSF4, HSF5, HSFXs and HSFYs, whereas invertebrates express only a single HSF (Gomez-Pastor et al., 2018; Joutsen and Sistonen, 2019) (Fig. 1A). Among the mammalian HSFs, HSF1 is the master regulator of HSP expression, although HSF2 forms heterotrimers with HSF1 and modulates the expression of certain HSP genes, for example, *HSPA1A* (Östling et al., 2007; Jaeger et al., 2016). Upon stress, HSF1 trimerizes, undergoes multiple post-translational modifications (PTMs) and binds to the heat-shock elements (HSEs) on the promoters of its target genes, leading to transcriptional activation of these genes (Rabindran et al., 1993; Xu et al., 2012; Jaeger et al., 2014) (Fig. 1A). Nearly all heat-inducible HSP genes require HSF1 for their upregulation, but surprisingly, more than half of the all heat-inducible genes have been shown to be HSF1 independent (Mahat et al., 2016). Serum response factor (SRF) has been suggested to regulate some of these genes, since it is recruited to the promoters of several heat-induced genes whose upregulation is independent of HSF1 (Mahat et al., 2016) (Fig. 1A). Recently, the pluripotency factors octamer-binding transcription factor 4 (OCT4, also known as POU5F1), NANOG, and Kruppel-like factor 4 (KLF4) were reported to be involved in the loop formation between heat-activated enhancers and genes in human embryonic stem cells (hESCs) (Lyu et al., 2018). Binding of these TFs in enhancers was shown to correlate positively with the transcriptional level of the genes that are contacted by enhancers during heat shock, suggesting that these TFs likely mediate some of the heat-induced and HSF1-independent gene expression changes in stem cells (Lyu et al., 2018).

Unfolded protein response

The unfolded protein response (UPR) is activated when misfolded proteins accumulate inside the endoplasmic reticulum (ER) or mitochondria (Wang et al., 2018; Almanza et al., 2019). Since all

secreted and transmembrane proteins are folded within the ER, the maintenance of protein homeostasis in the ER is essential for normal physiology. Homeostasis within the ER is disturbed during cell growth and certain stages of cell differentiation, when the folding capacity of the ER is exceeded by high protein load, leading to ER stress. Furthermore, sustained ER stress is observed in several diseases, such as cystic fibrosis and neurogenerative diseases, due to misregulation of the UPR (Lindholm et al., 2017). Importantly, mitochondrial protein homeostasis is regulated by the mitochondrial UPR (UPR^{mt}), which is different from the corresponding stress response in the ER (UPR^{ER}) (Wang et al., 2018; Almanza et al., 2019) (Fig. 1B,C). The activation of these responses leads to a global inhibition of translation, which restricts protein influx into both organelles. Moreover, the UPR initiates an extensive reprogramming of transcription that increases the folding capacity in the ER and mitochondria through the upregulation of molecular chaperones and components involved in protein degradation (Wang et al., 2018; Almanza et al., 2019).

UPR^{ER} is regulated by three pathways, defined by their specific transmembrane proteins that monitor the folding status in the ER: inositol-requiring protein-1 (IRE1, also known as ERN1), protein kinase RNA-like ER kinase (PERK, also known as EIF2AK3) and activating transcription factor-6 (ATF6) (Almanza et al., 2019) (Fig. 1B). In response to ER stress, IRE1 forms active dimers and cleaves the mRNA of X-box binding protein-1 (XBP1), which is consequently translated to an active TF (Yoshida et al., 2001; Zhou et al., 2006). PERK, in turn, phosphorylates a critical component of the translation machinery, namely, eukaryotic translation initiation factor-2 α (eIF2α), under ER stress (Harding et al., 1999). This phosphorylation leads to a global inhibition of translation, excluding the translation of ATF4, which is increased by phosphorylation of eIF2α (Harding et al., 1999, 2000). Activation of the third sensor of the UPR^{ER}, ATF6, is initiated by the localization of ATF6 to the Golgi, where it is cleaved to produce a cytoplasmic portion of the protein that becomes a TF and moves to the nucleus (Ye et al., 2000; Shen et al., 2002). Together the three ER stress-activated TFs, XBP1, ATF6 and ATF4, activate the transcription of genes encoding ER chaperones, including binding immunoglobulin protein (BiP, also known as HSPA5), components of the ER-associated protein degradation (ERAD) pathway and proteins involved in the induction of apoptosis (Dombroski et al., 2010) (Fig. 1B). ERAD is a process during which misfolded proteins within the ER are ubiquitylated, thereby initiating their translocation to the cytoplasm, where they are recognized and degraded by proteasomes (Needham et al., 2019). Although several UPR^{ER}-induced genes are regulated by all three branches of the UPR^{ER}, certain genes are specifically activated by only one of the branches. For example, the genes encoding components of the SEC61 translocon complex of the ER membrane were shown to be specific targets of the IRE1–XBP1 branch (Adamson et al., 2016). Furthermore, some UPR^{ER}-induced genes are regulated by an additional group of ER stress-responsive TFs, such as JUN, TFEB, TFE3, NFAT and TCF/LEF, whose contributions to the genome-wide reprogramming of transcription during UPR^{ER} need further investigation (Jiang et al., 2016; Martina et al., 2016; Zhou et al., 2017).

Most of the research related to UPR has focused on the regulation of UPR^{ER}, and the mechanisms of UPR^{mt} have only recently been characterized. In *C. elegans*, the main regulator of UPR^{mt} is the transcription factor ATFS-1, whose mammalian ortholog ATF5 was found to play a similar role in the activation of UPR^{mt} (Wang et al., 2018). Under normal growth conditions, ATF5 localizes in mitochondria, but when mitochondrial protein homeostasis is disrupted, ATF5 is transported into the nucleus where it activates the transcription of mitochondrial chaperone genes (Fiorese et al., 2016) (Fig. 1C). Other central TFs that regulate UPR^{mt} synergistically include CCAAT/enhancer-binding protein β (C/EBPβ) and C/EBP homology protein (CHOP, also known as DDIT3) (Zhao et al., 2002).

Oxidative stress response

Oxidative stress is caused by ROS that disturb cellular redox homeostasis by oxidizing proteins, lipids and DNA. A majority of ROS are generated as a side product of mitochondrial electron transport, but ROS can be generated also by NADPH oxidases (NOXs) and during protein folding in the ER (Sies et al., 2017). Activation of the oxidative stress response is required to maintain redox homeostasis and it is largely regulated by Nrf2 in mammalian cells (Fig. 1D). Under normal growth conditions, Nrf2 is in a complex with Kelch-like ECH-associated protein 1 (KEAP1) and Cullin 3 (Cul3), an E3 ubiquitin ligase that ubiquitylates Nrf2, targeting it to proteasomal degradation. In response to oxidative stress, certain cysteine residues of KEAP1 become oxidized, which disrupts the interaction between KEAP1 and Cul3, allowing Nrf2 to escape proteasomal degradation and localize into the nucleus (Itoh et al., 1999; Cullinan et al., 2004; Kobayashi et al., 2004; Zhang et al., 2004; Suzuki and Yamamoto, 2017). Nuclear Nrf2, together with small Maf proteins, binds to the antioxidant response elements (AREs) in the promoters of Nrf2 target genes, which induces the upregulation of, for instance, antioxidant enzymes and enzymes involved in glutathione biosynthesis (Itoh et al., 1997; Lee et al., 2003; Malhotra et al., 2010) (Fig. 1D).

In addition to Nrf2, protection against oxidative stress requires members of the forkhead box O (FOXO) family of transcription factors, including FOXO1, FOXO3 and FOXO4 (Tothova et al., 2007). Activation of FOXOs is regulated by oxidative stress-induced PTMs, such as phosphorylation by c-Jun N-terminal kinase (JNK) and macrophage stimulating protein (MST1, also known as STK4), which causes nuclear accumulation of FOXOs (Essers et al., 2004; Jang et al., 2007). In the nucleus, activated FOXOs increase the transcription of several key antioxidant genes, such as catalase (*CAT*), glutathione peroxidase 1 (*GPX1*) and peroxiredoxin 3 (*PRDX3*) (Chiribau et al., 2008; Akasaki et al., 2014) (Fig. 1D). An additional complexity to the oxidative stress response is provided by an involvement of nuclear factor κB (NF-κB) and JUN in the regulation of certain oxidative stress-induced genes (Zhou et al., 2001; Chiu et al., 2010). Furthermore, HSF1, the master regulator of the HSR, is activated by oxidative stress, resulting in decreased ROS levels and upregulation of *HSPA1A* and *HSPB1* gene transcription (Ahn and Thiele, 2003; Choi et al., 2013). However, it is not yet known whether HSF1 regulates separate transcriptional programmes during oxidative stress and heat stress.

Hypoxia response

Hypoxia occurs when oxygen levels decrease in cells, leading to diminished energy production. To survive hypoxia, cells activate the transcription of genes that help to restore oxygen levels, while simultaneously, several genes related to energy production are downregulated. The hypoxia response is mainly controlled by hypoxia-inducible factors (HIFs), including a stably expressed HIF-1β subunit as well as HIF-1α, HIF-2α and HIF-3α subunits, whose amounts are regulated by oxygen levels (Majmundar et al., 2010) (Fig. 1E). HIF-1α is the most studied subunit, which is prolyl hydroxylated during normoxia; this allows an E3 ubiquitin ligase,

for instance, von Hippel–Lindau protein (pVHL), to bind to HIF-1α and mark it for proteasomal degradation (Huang et al., 2002; Kageyama et al., 2004). Upon hypoxia, the hydroxylation of HIF-1α is prevented, leading to its accumulation, dimerization with HIF-1β and binding to hypoxia response elements (HREs) in the HIF-1α target genes, subsequently inducing their transcription (Huang et al., 1996; Jiang et al., 1996; Mole et al., 2009) (Fig. 1E). Similar to what is found with HIF-1α, both HIF-2α and HIF-3α are regulated by pVHL-mediated degradation that is prevented during hypoxia, and so activate HIF-2α- and HIF-3α-dependent transcriptional programmes (Maxwell et al., 1999; Maynard et al., 2003; Mole et al., 2009; Zhang et al., 2014). Interestingly, a splice variant of HIF-3α is able to suppress HIF-1α- and HIF-2α-driven expression of a reporter gene during hypoxia, which is rescued by overexpression of HIF-1β, suggesting that HIF-3α represses HIF-1α and HIF-2α by competing for the available HIF-1β (Yamashita et al., 2008). However, the repression of HIF-1α and HIF-2α is not the only function of HIF-3α, since it has been shown to upregulate several hypoxia-inducible genes that partially overlap with those that are upregulated by HIF-1α (Zhang et al., 2014).

Mechanisms of transcriptional regulation during stress

The binding of stress-responsive TFs is required for transcriptional induction in response to stress, although several other mechanisms play important roles in this process. Moreover, thousands of genes are repressed by stress, which according to our current knowledge, occurs independently of the TFs that are required for the induction of transcription. In this section, we summarize the mechanisms of transcriptional induction, repression and termination (Fig. 2). We also discuss the roles of stress-activated enhancers and chromatin organization in these processes. Research on the molecular details of transcriptional regulation on a genome-wide scale has become possible in recent years due to profound advances in the state-of-the-art methods for nascent RNA analyses (Wissink et al., 2019).

Stress-induced changes in transcription

Activation of transcription

Stress-induced activation of transcription includes two key steps: the recruitment of RNA polymerase II (RNAPII) to transcription start sites (TSSs), prior to stress, and the release of paused RNAPII into transcriptional elongation during stress (Vihervaara et al., 2018) (Fig. 2A,B). Recruitment of RNAPII is preceded by opening of the chromatin structure in gene promoters, which can be mediated by several chromatin remodelers, as has been shown in different model organisms. In *Drosophila melanogaster*, the open chromatin state of heat-responsive promoters is largely regulated by GAGA-associated factor (GAF), which interacts with nucleosome remodeling factor (NURF) to allow nucleosome sliding (Xiao et al., 2001; Fuda et al., 2015; Duarte et al., 2016). In mammals, this process is regulated by two complexes, such as SWItch/sucrose non-fermentable (SWI/SNF) and facilitates chromatin transcription (FACT), both of which can be recruited to promoters by HSF1 (Sullivan et al., 2001; Fujimoto et al., 2012). After chromatin opening, the pre-initiation complex (PIC), containing both RNAPII and general TFs, forms upstream of the TSS. However, RNAPII transcribes only 20 to 50 nucleotides downsteam of the TSS, after which it is paused by negative elongation factor (NELF) and DRB sensitivity-inducing factor (DSIF) (Yamaguchi et al., 1999; Lee et al., 2008).

A critical part of transcriptional upregulation during stress is the release of paused RNAPII into elongation mode, which is triggered by the positive transcription elongation factor (P-TEFb) complex (Lis et al., 2000). In response to heat shock, P-TEFb binds to the promoters of heat-induced genes and phosphorylates NELF, DSIF and the C-terminal domain (CTD) of RNAPII. These phosphorylation events lead to the dissociation of NELF from the chromatin, while DSIF becomes a positive elongation factor that promotes the transcriptional elongation of RNAPII (Wada et al., 1997; Lis et al., 2000; Kim and Sharp, 2001; Fujinaga et al., 2004) (Fig. 2B). P-TEFb itself can be recruited to the promoters by HSF1 and RNA-binding motif protein 7 (RBM7) in response to heat shock and DNA damage, respectively (Lis et al., 2000; Bugai et al., 2019).

Interestingly, oxidative stress has been found to trigger the dissociation of NELF from the chromatin and movement of RNAPII along gene bodies in the presence of a P-TEFb inhibitor, suggesting that the mechanisms of the pause–release might vary depending on the type of stress (Nilson et al., 2017). In addition, oxidative stress causes oxidation of DNA, leading to the formation of 8-oxo-7,8-dihydroguanine (OG), which has been shown to increase transcriptional activity of vascular endothelial growth factor (VEGF) and endonuclease III-like protein 1 (*NTHL1*) by recruiting components of the base excision repair to their promoters (Fleming et al., 2017). Another study has shown that one of these components, 8-oxoguanine glycosylase 1 (OGG1), has a capability to enhance the binding of TFs and RNAPII to chromatin, explaining how OG stimulates transcription (Ba et al., 2014). Taken together, these studies indicate that the initiation of transcription by stress is a complex process; it is likely that additional stress-specific mechanisms are involved that need to be uncovered.

Repression of transcription

During stress, thousands of genes involved in the regulation of the cell cycle, transcription, translation and metabolism undergo repression. Repression caused by proteotoxic stress results from the inhibition of RNAPII pause–release, which leads to an increased accumulation of RNAPII in the TSS, while it is being cleared from gene bodies (Mahat et al., 2016; Dukler et al., 2017; Vihervaara et al., 2017) (Fig. 2C). Nonetheless, the detailed molecular mechanisms of stress-induced repression are still poorly understood and they appear to be largely independent of the TFs that are required for stress-mediated gene activation. Surprisingly, heat-induced repression has been shown to occur in the absence of HSF1 (Mahat et al., 2016). Similarly, only a subset of genes repressed by ER-stress-mediated PERK activation are dependent on ATF4, the main regulator of transcription downstream of PERK (Gonen et al., 2019). However, several genes have been shown to be downregulated in a HIF-1α-dependent manner during hypoxia, although these genes are not direct targets of HIF-1α, indicating an involvement of still unidentified factors in the repression (Mole et al., 2009).

A recent study has demonstrated that heat-induced repression is caused by an enhanced binding of NELF to the promoters of repressed genes, which leads to the clearance of RNAPII from their gene bodies (Aprile-Garcia et al., 2019). NELF binding, in turn, requires increased ubiquitylation of nascent proteins that are translated during heat shock and a subsequent binding of the stress-activated kinase p38α (also known as MAPK14) to the promoters of repressed genes (Fig. 2C). However, the mechanism by which the ubiquitylation of translated proteins results in increased binding of p38α and NELF to chromatin remains to be elucidated. Besides NELF, heat shock activates the transcription of the non-coding human Alu RNA and mouse B2 RNA that prevent the initiation of transcription on certain repressed genes by interfering with the binding of RNAPII to DNA (Allen et al.,

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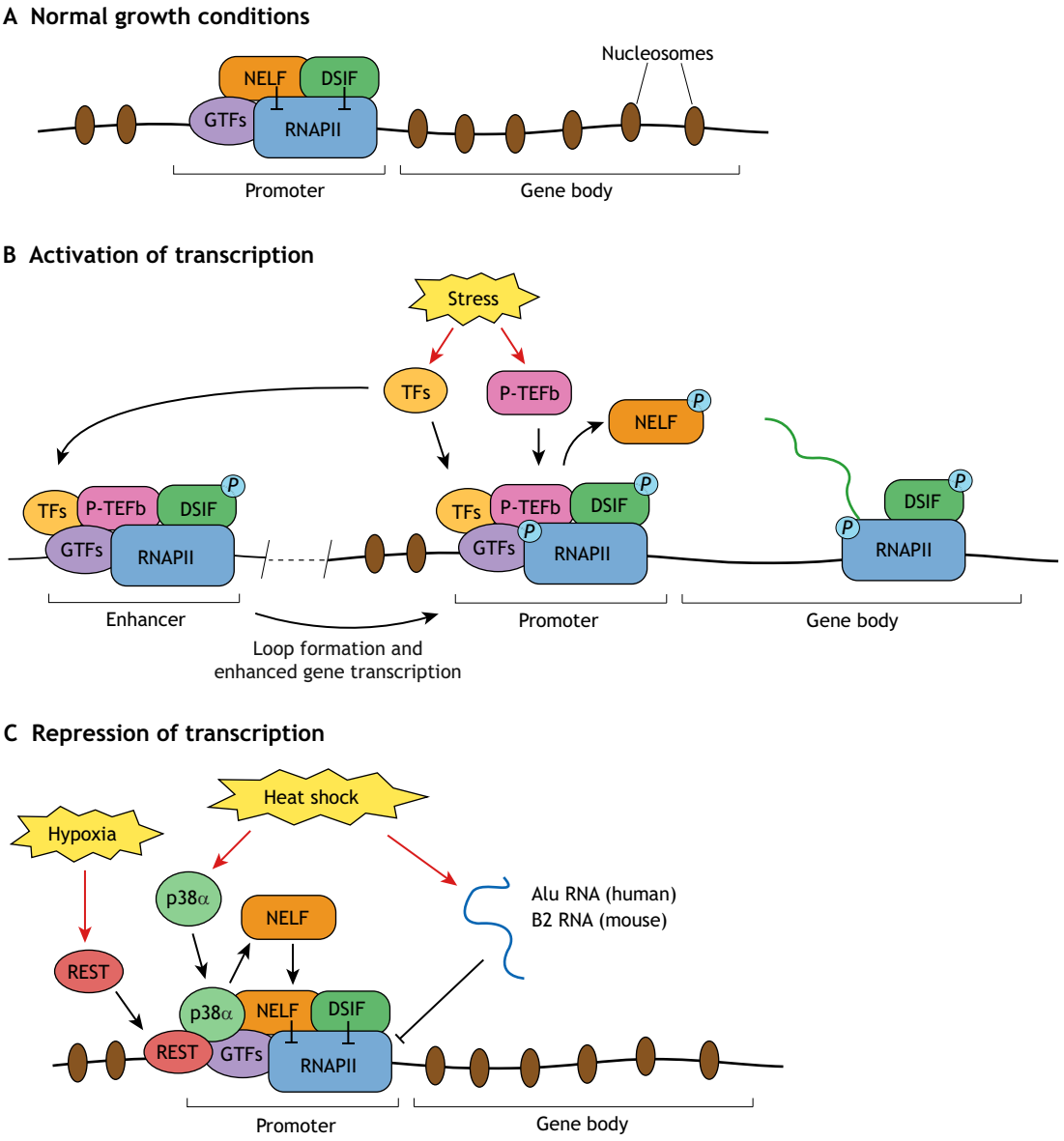

Fig. 2. Mechanisms of transcriptional activation and repression during stress. (A) Under normal growth conditions, promoters are occupied by general transcription factors (GTFs) and RNAPII, which is kept in a paused state by NELF and DSIF. (B) During the activation of stress-induced genes, various TFs bind to promoters and recruit the P-TEFb complex, which phosphorylates RNAPII, NELF and DSIF. This causes the dissociation of NELF and transcriptional elongation mediated by RNAPII. In addition, several TFs localize to enhancers in response to stress, which increases transcription of genes through loop formation. (C) During heat shock-induced repression, p38α binds to promoters and increases the recruitment of NELF, which reinforces RNAPII pausing. Furthermore, heat shock induces transcription of non-coding human Alu RNA and mouse B2 RNA that prevent the elongation mediated by RNAPII. In response to hypoxia, repressor element 1-silencing transcription factor (REST) becomes activated and causes the repression of several genes. P, phosphate.

2004; Mariner et al., 2008; Yakovchuk et al., 2009) (Fig. 2C). In response to hypoxia, repressor element 1-silencing transcription factor (REST) accumulates inside the nucleus and downregulates 20% of the genes that undergo repression (Cavadas et al., 2016) (Fig. 2C). Importantly, stress-induced repression is also regulated by complex changes in chromatin modifications and 3D structure of the genome, which will be discussed in the section 'Stress-induced remodeling of chromatin architecture' below.

Termination of transcription

Transcription is terminated when RNAPII encounters the polyadenylation signal (PAS) in the 3′ end of a gene, which causes the cleavage and release of the mRNA that is subsequently polyadenylated. After passing through the PAS, RNAPII can be either released from DNA or it can continue the synthesis of RNA, which eventually undergoes exonuclease-mediated degradation (Proudfoot, 2016). Interestingly, various types of stress, including heat shock, osmotic stress, oxidative stress and infection by herpes simplex virus 1 (HSV-1), disrupt the termination of transcription in several genes, resulting in readthrough transcription (Vilborg et al., 2015, 2017; Hennig et al., 2018). Readthrough transcription produces downstream of gene-containing transcripts (DoGs) that often span regions residing over 10 thousand base pairs (bp) downstream from the 3′ ends of genes (Vilborg et al., 2015, 2017). However, the function of DoGs is still a mystery, although it has been suggested that they are needed for the maintenance of a nuclear scaffold under stress conditions (Vilborg et al., 2015). DoGs remain associated with chromatin during osmotic stress

and have been found to prevent the nuclear shrinkage, which is caused by osmotic stress due to a loss of water from cells (Vilborg et al., 2015).

Although it is unclear how readthrough transcription is induced, genes that produce DoGs are in general devoid of canonical PASs (Vilborg et al., 2015, 2017; Hennig et al., 2018). It has also been suggested that Ca^{2+} signaling is required for readthrough transcription, since treatment of cells with the Ca^{2+} chelator BAPTA-AM prevents the induction of DoGs by osmotic stress (Vilborg et al., 2015). However, another study reported an overall decrease in gene transcription after BAPTA-AM treatment, questioning whether Ca^{2+} signaling specifically regulates readthrough transcription (Hennig et al., 2018).

Stress-induced enhancer activation

Enhancers are distal regulatory sequences in DNA that promote the transcription of nearby genes by contacting gene promoters through the formation of a loop. Enhancers are also transcribed themselves bi-directionally, producing enhancer RNAs (eRNAs), which have a functional role in contributing positively to gene transcription through a yet unknown mechanism (Chen et al., 2017). It has been reported in human K562 cells that heat shock induces the transcriptional upregulation of 5000 and downregulation of 1600 enhancers (Vihervaara et al., 2017). In contrast to genes, upregulated enhancers are mostly devoid of RNAPII prior to stress, but instead, they are bound by lineage-specific TFs, for example, GATA-binding protein 2 (GATA2) and T-cell acute lymphoid leukemia 1 (TAL1), which likely primes them for rapid activation (Vihervaara et al., 2017). Interestingly, another study in hESCs has shown that the pluripotency factors OCT4, NANOG and KLF4 are recruited to several enhancers during heat shock, resulting in a loop formation between the enhancers and promoters of upregulated genes (Lyu et al., 2018). It has also been reported that, in somatic cells, HSF1 increases the transcription of *FOXO3* in response to heat shock and oxidative stress through an intronic enhancer in the *FOXO3* gene body (Grossi et al., 2018). Similarly, Nrf2 is required for enhancer-mediated upregulation of heme oxygenase-1 (*HO-1*, also known as *HMOX1*) upon oxidative stress, while XBP1 upregulates the *INFB1* gene through an enhancer when macrophages are exposed to ER stress and bacterial lipopolysaccharide (Zeng et al., 2010; Maruyama et al., 2014). Taken together, there is increasing evidence for enhancers contributing to stress-induced gene transcription, and, importantly, the master regulators of different stress responses can bind to either enhancers or promoters to upregulate their target genes (Fig. 2B). However, several key questions remain unanswered; for example, what is the role of enhancers in driving unique transcriptional programmes in response to distinct types of stress, and what are the main regulators activating these enhancer-mediated changes in gene expression?

Stress-induced remodeling of chromatin architecture

Chromatin modifications

Different types of stress induce genome-wide changes in chromatin accessibility, which is required for transcriptional reprogramming (Shivaswamy and Iyer, 2008; Schick et al., 2015; Mueller et al., 2017). Heat shock has been shown to trigger the loss of nucleosomes from the promoters and gene bodies of activated genes, whereas increased nucleosome occupancy has been found in repressed genes (Shivaswamy and Iyer, 2008). Similarly, ER stress was reported to enhance chromatin accessibility in activated genes, although this occurred without changes in the nucleosome occupancy (Mueller et al., 2017). Regulation of chromatin accessibility involves extensive PTMs of histones, such as acetylation, methylation and phosphorylation, which are required to recruit chromatin remodelers to promoters (Swygert and Peterson, 2014). Acetylated histones H3 and H4 are commonly used as indicators for active transcription, and their levels increase in the promoters of upregulated genes and activated enhancers in response to various stress stimuli, whereas decreased acetylation of histones H3 and H4 can be often observed in repressed genes (Shivaswamy and Iyer, 2008; Schick et al., 2015; Mueller et al., 2017; Vihervaara et al., 2017) (Table 1). The effect of acetylated histones on transcription can be explained by their ability to recruit the SWI/SNF complex to promoters, which is needed for the removal of nucleosomes from gene bodies during the elongation of RNAPII (Hassan et al., 2001; Schwabish and Struhl, 2007).

In addition to acetylation, poly(ADP-ribosyl)lation (PARylation) of chromatin is also a stress-inducible PTM that has been shown to promote the transcription of HSP genes in response to heat shock (Table 1) (Murawska et al., 2011; Fujimoto et al., 2018). PARylation is catalyzed by poly(ADP-ribose) polymerase 1 (PARP1), which localizes to the *HSPA1A* promoter during heat shock and PARylates both the promoter and the gene body. This, in turn, is required for chromatin opening, thereby allowing HSF1 to bind to the promoter and to upregulate *HSPA1A* (Petesch and Lis, 2008; Fujimoto et al., 2018).

Another PTM that is strongly associated with chromatin is SUMOylation, the conjugation of small ubiquitin-like modifier proteins (SUMOs) to proteins (Table 1). SUMOylation of chromatin plays an important role in the establishment of cell identity and it is also massively increased in response to heat shock (Niskanen et al., 2015; Seifert et al., 2015; Cossec et al., 2018). Heat-induced SUMOylation is elevated extensively in the promoters of highly transcribed genes and enhancers, restricting the upregulation of

Table 1. Examples of stress-induced changes in chromatin modifications that regulate transcription

Modification	Change during stress	Effects on chromatin and transcription	References
Acetylation of histones	Increase in activated genes and enhancers; decrease in repressed genes	Increased chromatin accessibility; increased transcription	Shivaswamy and Iyer, 2008 Schick et al., 2015 Mueller et al., 2017 Vihervaara et al., 2017
Methylation of histones	Increased occupancy or decreased occupancy of genes	Increased/decreased transcription; maintenance of transcriptional memory to stress	Lämke et al., 2016 Fabrizio et al., 2019
PARylation	Increase in activated *HSP* genes	Increased chromatin accessibility; increased transcription	Petesch and Lis, 2008 Murawska et al., 2011 Fujimoto et al., 2018
SUMOylation	Increase in highly transcribed genes and enhancers; decrease in CTCF-binding sites	Restricted induction and enhanced repression of transcription	Niskanen et al., 2015 Seifert et al., 2015

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genes and promoting the repression of genes (Niskanen et al., 2015). Although the exact mechanism of SUMOylation-mediated regulation of transcription is not known, it is plausible that SUMOylation affects RNAPII pause–release, since subunits of two critical regulators of RNAPII pausing, P-TEFb and NELF, undergo increased SUMOylation in response to heat shock and proteasome inhibition (Hendriks et al., 2014). Interestingly, heat shock causes decreased SUMOylation in regions that contain the binding sites for CCCTC-binding factor (CTCF), an important regulator of chromatin 3D structure, implying a possible role for SUMOylation in this process (Niskanen et al., 2015). Nevertheless, several questions remain to be answered, including how stress-induced SUMOylation of chromatin is mechanistically regulated and how SUMOylation of individual chromatin-associated proteins affects transcription.

3D structure of chromatin

The 3D structure of chromosomes consists of several topologically associating domains (TADs), which are large-scale loops where enhancers and gene promoters are able to contact each other (Bonev and Cavalli, 2016). TADs are established by architectural proteins, such as CTCF and cohesin, residing within the boundaries of TADs. In human breast cancer cells, hyperosmotic stress was recently found to displace CTCF from chromatin, causing a global decrease in the number of TADs (Amat et al., 2019). Another study has shown that CTCF relocalizes to new sites upon heat shock and leads to formation of stress-induced TADs in hESCs (Lyu et al., 2018) (Fig. 3A). Enhancers and genes residing within the same stress-induced TAD are able to interact with each other, thereby activating these genes. Repression of genes, in turn, occurs when heat-induced reorganization of TADs disrupt the enhancer–promoter contacts that are established under normal growth conditions (Lyu et al., 2018). In contrast to these findings in hESCs, it has been shown in *D. melanogaster* cells that architectural proteins, such as CTCF and cohesin, relocalize from the TAD boundaries to the enhancers and promoters within TADs during heat shock (Li et al., 2015) (Fig. 3B). This relocalization results in a weakening of the TAD boundaries and an increased number of cohesin-mediated

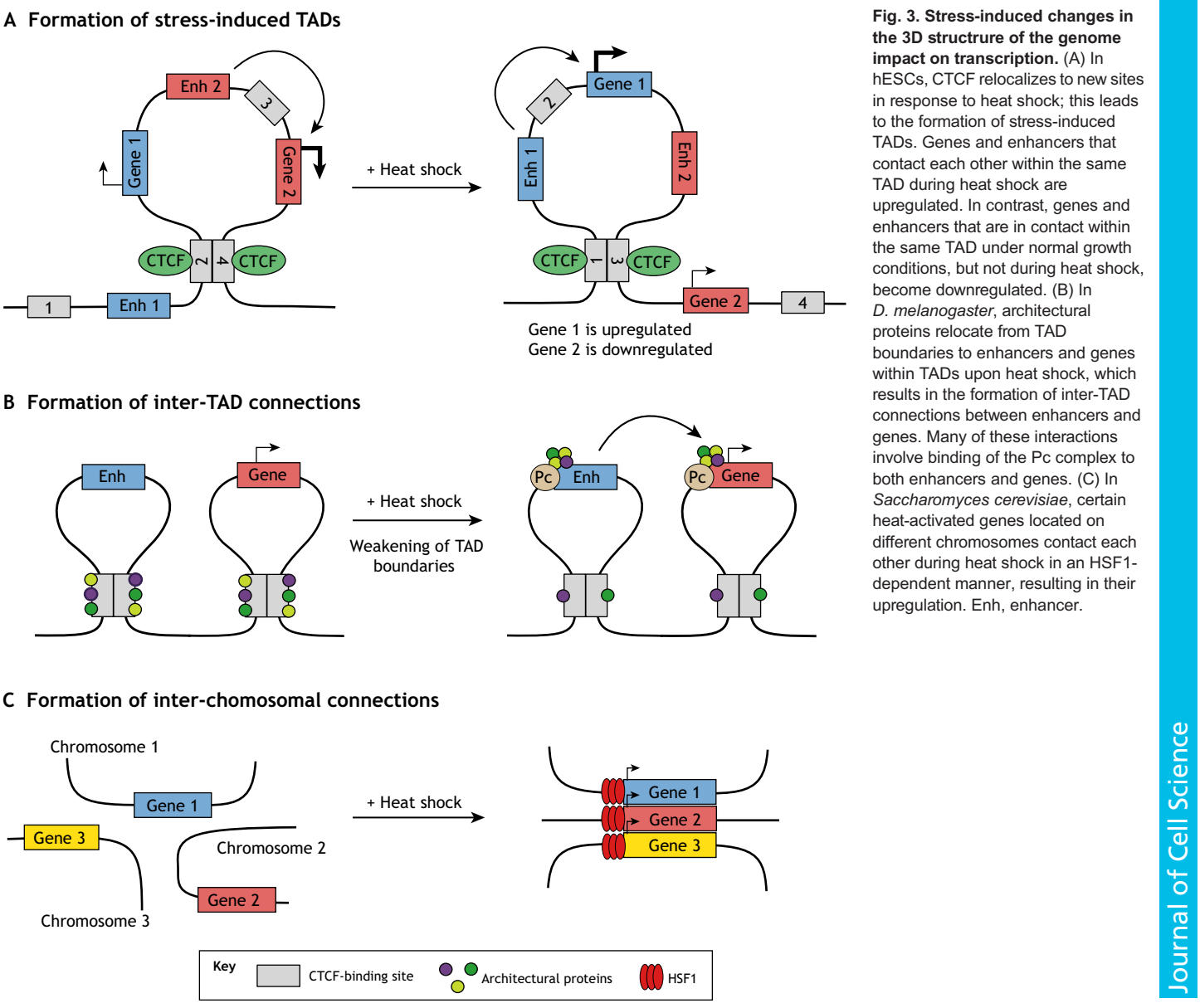

Fig. 3. Stress-induced changes in the 3D structrure of the genome impact on transcription. (A) In hESCs, CTCF relocalizes to new sites in response to heat shock; this leads to the formation of stress-induced TADs. Genes and enhancers that contact each other within the same TAD during heat shock are upregulated. In contrast, genes and enhancers that are in contact within the same TAD under normal growth conditions, but not during heat shock, become downregulated. (B) In *D. melanogaster*, architectural proteins relocate from TAD boundaries to enhancers and genes within TADs upon heat shock, which results in the formation of inter-TAD connections between enhancers and genes. Many of these interactions involve binding of the Pc complex to both enhancers and genes. (C) In *Saccharomyces cerevisiae*, certain heat-activated genes located on different chromosomes contact each other during heat shock in an HSF1-dependent manner, resulting in their upregulation. Enh, enhancer.

inter-TAD interactions. Interestingly, many of these interactions involve the Polycomb (Pc) complex, which forms Pc bodies in the nucleolus and is required for the heat-induced repression of certain genes (Li et al., 2015).

In addition to intra-chromosomal interactions, HSP genes located on different chromosomes have been shown to be able to interact with each other in yeast exposed to heat shock (Chowdhary et al., 2017) (Fig. 3C). These inter-chromosomal interactions require HSF1, revealing a new role for HSF1 in the regulation of the 3D structure of the genome, which is independent of its functions as a TF (Chowdhary et al., 2019) (Fig. 3C). Although the functional impact of these inter-chromosomal contacts is unclear, they are likely to be needed for coalescence of the heat-responsive genes into transcriptionally active foci to drive their synchronous induction. Whether similar interactions occur in response to other types of stress and which proteins mediate those interactions, remain to be investigated.

Concluding remarks and future perspectives

Transcriptional reprogramming upon stress involves both an induction of pro-survival genes and a repression of several genes related to transcription, translation and cell cycle. These changes are mediated through RNAPII pause–release, which is increased in upregulated genes and decreased in downregulated genes (Vihervaara et al., 2018). Although the induction of transcription requires binding of stress-responsive TFs to the promoters, recent studies have uncovered entirely new mechanisms in the regulation of transcription, including the role of enhancers and chromatin organization. Several enhancers are transcriptionally upregulated during stress, and importantly, TFs can bind to both promoters and enhancers to regulate stress-induced gene transcription (Maruyama et al., 2014; Vihervaara et al., 2017; Grossi et al., 2018; Lyu et al., 2018). However, the impact of enhancers on genome-wide and stress-specific transcriptional programmes remains unknown. It is also evident that chromatin organization undergoes large-scale changes in response to stress, including alterations in both intra- and inter-chromosomal interactions (Li et al., 2015; Chowdhary et al., 2017; Lyu et al., 2018; Amat et al., 2019). These processes are still poorly understood, and future studies are needed to reveal how chromosomal interactions are established and how they influence transcription under stress. These questions are closely related to ongoing research on phase separation, which is defined as a coalescence of macromolecules into membraneless structures (Alberti, 2017). Phase separation of chromatin-bound proteins generates long-distance interactions between different regions of the genome, which leads to the formation of chromatin subcompartments (Hnisz et al., 2017; Strom et al., 2017; Erdel and Rippe, 2018). Many of these subcompartments, such as heterochromatin foci and enhancer clusters, are involved in transcription and therefore, they likely contribute to stress-induced changes in transcription (Hnisz et al., 2017; Strom et al., 2017).

Heat shock has been frequently used to study stress-induced transcription and while these studies have been fundamental for understanding transcription in a great detail, our knowledge of the mechanisms of transcriptional regulation during other types of stress is still scarce. More emphasis should be also placed on determining whether individual cells respond differently to stress than do cell populations, which is now possible due to recent advances in single-cell techniques. Furthermore, transcriptional regulation should be examined under acute and chronic stress conditions, since cells are exposed to continuous stress in a number of diseases. For example, hyperactivation of stress-responsive TFs is commonly found in cancer (Ryan et al., 2000; Dai et al., 2007; Shibata et al., 2008). In addition, the transcriptomes are regulated differently between cancer and healthy cells, which can be observed as an altered use of enhancers and changes in the chromatin architecture (Bradner et al., 2017). Thus, it will be important to investigate various aspects of the transcriptional regulation in diseased and healthy cells to uncover how stress-induced transcription is modified in human diseases.

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Competing interests

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