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DNA damage responses and stress resistance: Concepts from bacterial SOS to metazoan immunity

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Abstract

The critical need for species preservation has driven the evolution of mechanisms that integrate stress signals from both exogenous and endogenous sources. Past research has been largely focused on cell-autonomous stress responses; however, recently their systemic outcomes within an organism and their implications at the ecological and species levels have emerged. Maintenance of species depends on the high fidelity transmission of the genome over infinite generations; thus, many pathways exist to monitor and restore the integrity of the genome and to coordinate DNA repair with other cellular processes, such as cell division and growth. The specifics of these DNA damage responses (DDR) vary vastly but some general themes are conserved from ancient organisms, such as bacteria and archaea, to humans. Despite decades of research, however, DDRs still have many layers of complexity and some surprises left to be discovered. One of the most interesting current research topics is the link between DNA damage and stress resistance: the outcomes of DDRs can protect the organism from other secondary challenges. At this time, these types of responses are best characterized in bacteria and the simple metazoan model, *Caenorhabditis elegans*, but it is becoming clear that similar processes also exist in higher organisms.

The bacterial SOS response: Nature's most primitive DDR

Molecular basis of the SOS response

Evelyn Witkin and Miroslav Radman first described the inducible SOS response to damaged DNA in the mid-1970s through their work on mutagenesis in *Escherichia coli* (Radman, 1975; Witkin, 1976). While there are variations on the theme, SOS response pathways have been found in diverse bacterial species, including some important human pathogens, e.g. *Vibrio cholerae* and *Pseudomonas aeruginosa* (Baharoglu and Mazel, 2014). Although the biological functions are extremely complex, the logic of the SOS response is straightforward. In the absence of DNA damage, the LexA repressor remains bound to a large collection of genes, the SOS regulon. Upon DNA damage, the RecA recombinase

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(Rad51 in archaea and eukaryotes) binds to newly formed single-strand DNA to form a RecA-DNA filament. This nucleoprotein filament stimulates the autoproteolytic cleavage of LexA, leading to its removal from gene promoters and the expression of the SOS regulon. The outcomes of the SOS response are complex and in some ways paradoxical. The obvious effect of SOS activation is the tightly coordinated induction of DNA repair genes and DNA repair and cell division. Quite remarkably, the timing of gene expression in *E. coli* reflects the level of desperation to cope with the DNA damage (discussed in (Michel, 2005)). The first genes to be induced are the classical components of the nucleotide excision repair pathway, a high fidelity mechanism that can rapidly repair a broad spectrum of lesions. Genes involved in homologous recombination (HR), including RecA, are induced more slowly to enhance the capacity for HR-dependent DNA repair and at around the same time the cell division inhibitor *sfiA* is induced. Inhibition of cell division to allow time for DNA repair is a highly conserved component of DDRs. After 40 minutes of ongoing SOS induction, cells express the mutagenic error-prone DNA polymerase Pol V (*umuC* and *umuD*), a last-ditch effort to bypass DNA lesions to allow completion of DNA replication, although at the expense of increased mutation rates (Tippin et al., 2004). Thus, this process whose goal is to maintain genome stability will, when chronically activated, shift in favor of introducing genetic fluidity for the sake of species preservation (Figure 1).

Advantageous outcomes of SOS induction

Ongoing work on the SOS response has revealed that it can affect important outcomes outside of DNA repair that, while clearly protecting individual cells, can also provide advantages on the population level; thus, it could be argued that it represents a more general stress response that is stimulated by DNA damage (in fact, the SOS response can be induced independent of DNA damage, for example, during the uptake of foreign DNA, see (Baharoglu and Mazel, 2014)). Such a phenomenon has been demonstrated by studies on the interactions between bacteria and therapeutically used fluorquinolone (FQ) antibiotics, in particular ciprofloxacin. While the increased mutagenesis associated with chronic SOS induction is known to contribute to the genetic acquisition of antibiotic resistance (Erill et al., 2007; Kelley, 2006), the SOS response can also contribute to both antibiotic tolerance and fitness in competitive environments. The generation of phenotypic variants within a clonal population can have profound effects on whether the population survives exposure to exogenous stress or succumbs and is lost. This principle has been demonstrated by the identification of “persister” cells within isogenic *E. coli* populations that have increased antibiotic tolerance. FQ antibiotics target DNA gyrase and topoisomerase IV (topo IV) (Drlica and Zhao, 1997; Zhao et al., 1997). After poisoning by the drug, gyrase and topo IV induce DNA double-strand breaks via endonuclease activity, thus inducing the SOS response. At high doses of ciprofloxacin, expression of the SOS-regulated *tisAB/istR* locus decreases intracellular ATP level, probably inducing tolerance by inducing stasis (Dörr et al., 2009; 2010; Gurnev et al., 2012). Such persister cells can then wait until the antibiotic assault is foiled and then resume growth to propagate the population. Thus, it is clear that antibiotic-induced DNA damage, through triggering the SOS response, can impart a survival advantage to the bacteria independent of the DNA repair activities associated with the SOS response.

SOS induction following antibiotic-induced DNA damage can also provide a competitive advantage to cells chronically exposed to sub-lethal doses of ciprofloxacin. In *Pseudomonas aeruginosa*, it has been recently demonstrated that SOS induction upon exposure to the antibiotic confers a competitive advantage to cells (Torres-Barceló et al., 2015). In this work, a wild type strain was mixed with a strain defective for SOS induction and the rate of survival was measured after co-culturing. At the sub-lethal dose, the wild type strain was sufficiently fitter to eliminate the SOS-defective strain from the culture. Ciprofloxacin exposure led to a detectable increase in the mutation rate, as expected in situations with robust DNA damage. While bacteria cultured for many generations in sub-lethal drug showed higher levels of drug resistance, there was no evidence that these changes required activation of the SOS response. In this context, the SOS response offers an acute competitive advantage that is independent of the increase in genome instability (Figure 1). The authors suggest that the mutagenic outcomes of SOS induction are side effect, and not the selectable phenotype of this stress response pathway.

From these examples in the bacterial domain of life, it is evident that a DNA damage response can offer advantages that support the maintenance of the species under challenging conditions, such as resistance to chronic antibiotic exposure or increased fitness in competitive environments. The obvious question then is whether or not a similar paradigm exists in metazoans: can DNA damage provide protection against secondary stresses to help ensure the ongoing survival of the species?

DDR and stress tolerance: insights from the worm

Eukaryotic cells employ DNA damage checkpoints that in the most ancestral forms halt cell cycle progression to allow removal of the damage before resumption of replication or cell division (Bartek and Lukas, 2007). This aspect of the DDR has been highly conserved even in humans. Dysfunctional checkpoints can hamper the repair process and fuel genome instability. In humans, such dysfunction is most prominently linked to DNA damage-driven cancer development. With the advent of multicellularity the selective pressure altered the function of the DDR. The maintenance of heritable genomes became the task of germ cells. Increasingly specialized somatic cells supported survival and maximized the chances for the germline to produce the next generation. The realization of the distinct tasks of germ and somatic cell types was first recognized by the zoologist August Weismann and most pointedly incorporated by Tom Kirkwood into perhaps the most comprehensive theory of aging, the “disposable soma theory of aging,” which posits that the organism’s resources need to be balanced between the maintenance of somatic tissues and the activity of germ cells in order to maximize fitness and upon successful reproduction, the soma becomes disposable (Kirkwood and Cremer, 1982).

The DDR in the germline

The distinctive tasks of the DDR in germ cells and somatic tissues are particularly well illustrated in the nematode *Caenorhabditis elegans*. Germ cells mitotically divide and, once pushed out of the germ stem cell niche, transit into meiosis to initially form sperm until the animals switch their germline gender during the final stage of larval development and then

during adulthood produce oocytes that arrest in diakinesis until they are fertilized in the spermatheca of the hermaphrodite (Kimble and Crittenden, 2005). Upon genotoxic insult, for example following ionizing or UV radiation, the conserved DNA damage checkpoint arrests the proliferation of mitotic germ cells to allow the DNA repair machinery to remove the lesions before resumption of the cell cycle (Ahmed and Hodgkin, 2000; Gartner et al., 2000). The cell cycle arrest function is essential for withstanding the genotoxic consequences as checkpoint defects lead to the production of dead embryos that result from ongoing meiotic proliferation of compromised germ cells (Gartner et al., 2000). The same checkpoint pathways trigger apoptotic cell death in meiotic pachytene cells. The *C. elegans* p53 homolog CEP-1 induces the expression of the BH3-only domain proteins EGL-1 and CED-13, which inhibit the Bcl2 homolog CED-9 to release the Apaf1 equivalent CED-4 that in turn activates the caspase CED-3 to take apart the genomically compromised cell whose remnants are consequently swept up by engulfing cells (Derry et al., 2001; Hofmann et al., 2002; Schumacher et al., 2001; 2005b). The apoptotic fate is specifically confined to the late pachytene stage, when normally meiotic recombination should be concluded. Therefore, the availability of CEP-1, which prior to the late stage of pachytene, is translationally repressed by GLD-1, allows the culling of aberrantly recombining meiotic cells (Schumacher et al., 2005a). Germ cells that pass the quality checks during mitosis and meiotic pachytene are awarded with large amounts of cytoplasm during diakinesis. At this stage, the mother provides the major investments into the following generation in the form of cytoplasm and RNAs. During embryogenesis, the DDR coordinates timing of cell division (Brauchle et al., 2003) but no apoptotic culling of somatic cells occurs as somatic cells in *C. elegans* are irreplaceable. Moreover, DNA damage tolerance mechanisms such as translesion synthesis support embryonic DNA replication (Roerink et al., 2012). Persistent DNA damage resulting for instance by checkpoint defects in the germ cells, can lead to mitotic catastrophe rather than an orderly DDR in the embryos (Gartner et al., 2000).

The DDR in somatic tissue

In contrast to the germ cells, somatic tissues are far more tolerant towards DNA damage, particularly double strand breaks. For instance, somatic tissues can continue to support a normal lifespan even upon treatment with IR doses as high as 1000 Gy (Johnson and Hartman, 1988). Also, the usage of DNA repair shifts from highly accurate homologous recombination, which is employed by germ cells, to error-prone non-homologous end joining (NHEJ) (Vermezovic et al., 2012). Conceptually in line with Kirkwood's disposable soma theory of aging, genome maintenance in somatic tissues needs to be less stringent, as essentially only a few days of adult survival are required to pass the germ cells onwards. The somatic requirements on genome maintenance have become most strikingly apparent in nucleotide excision repair (NER) mutants. NER is required for the removal of helix-distorting lesions such as those typically induced by UV radiation (Stergiou et al., 2007). Global-genome (GG-) NER is required in germ cells and during early embryogenesis to remove such damage throughout the entire genome (transcribed and non-transcribed regions) to prevent stalling of DNA replication forks (Lans et al., 2010). In contrast, transcription-coupled (TC-) NER is predominantly required in transcriptionally active somatic cell types to prevent disturbances to the transcriptional machinery (Mueller et al., 2014).

Systemic aspects of the DDR

Interestingly, the DDR in *C. elegans* is not confined to the damaged cells themselves. Also a consequence of the requirements of cell non-autonomous coordination in metazoans, at least some genomically compromised cell types exert signals to the entire organism. A particularly exciting example of such coordination is the recently uncovered “germline DNA damage-induced stress resistance” (GDISR) (Ermolaeva et al., 2013). GDISR has initially been observed in GG-NER mutant animals that are unable to remove UV-induced DNA lesions in germ cells. Unexpectedly, the somatic tissues of these animals were highly resistant to heat and oxidative stress when pre-treated with UV. The somatic stress resistance was also established upon IR or hydroxyurea (HU) exposure. Interestingly, endogenous meiotic DSBs in pachytene cells were sufficient to elevate the stress resistance throughout the somatic tissues. It was hypothesized that GDISR could extend the reproductive lifespan of the animal when it requires additional time to restore genome integrity in damaged germ cells (Ermolaeva and Schumacher, 2014a). Indeed, it was observed that offspring reduction that was reduced following UV radiation could resume following repair at times past the normal reproductive zenith of the worm (Ermolaeva et al., 2013). This behavior is thus reminiscent of the species-preserving function of the SOS response in bacteria discussed above (Figure 1).

The instructive nature of the germ line towards somatic maintenance has been documented across species in many instances. *C. elegans* has probably provided the simplest and most mechanistically instructive example for such interactions. A classic experiment was performed in Cynthia Kenyon’s lab in the 1990s. The germ line can be completely ablated by laser surgery that removes the primordial germ cells (PGCs) at the youngest larval stage. Such worms develop normal somatic tissues but completely lack all germ cells. These animals proved to be highly stress resistant and long-lived (Hsin and Kenyon, 1999). The decisive experiment followed when not only the PGCs, but also the two surrounding somatic gonad precursors (SGPs), were eliminated resulting in an evenly sterile animal that now also lacked the somatic tissue that encapsulates the germ line. Such animals lost the longevity indicating that it is not the distribution of resources from offspring generation to somatic maintenance but rather signaling mechanisms through which the germ line limits somatic maintenance and longevity. The molecular nature of such signaling mechanisms has remained largely obscure. More insight has been gained into the executing somatic mechanisms. Intestinal KRI-1 (Berman and Kenyon, 2006), the transcription elongation factor TCER-1 (Ghazi et al., 2009), and the transcription factors DAF-16 (Lin et al., 2001), DAF-12 (Yamawaki et al., 2010), PHA-4 (Lapierre et al., 2011), NHR-49 (Ratnappan et al., 2014), NHR-80 (Goudeau et al., 2011), HLH-30 (Lapierre et al., 2013), and SKN-1 (Wei and Kenyon, 2016) are operating in intestinal cells to elevate stress resistance and longevity in either PGC-ablated animals or in –for practical reasons more widely employed– animals that fail to maintain germ cell proliferation due to a mutation in the Notch receptor *glp-1*. The somatic stress response circuits involve additional cell types as for instance the neuronal microRNA *mir-71* (Boulas and Horvitz, 2012) and synthesis of the steroid hormone dafachronic acid (DA) in somatic tissues are involved in the lifespan extension upon germline ablation (Gerisch et al., 2007; Thondamal et al., 2014). However, the germline-

derived signaling circuits governing the activation of somatic response factors to germline (in)activity are yet to be identified.

The DDR in tissue maintenance

Interestingly, the effect of the germ line on somatic longevity has been documented in various species ranging from nematodes and fruit flies to mammals. Even a study following the records of eunuchs at the Korean court over several hundred years have determined an average of 19 years longer lifespan than typically observed in socially comparable aristocratic contemporaries (Min et al., 2012). However, the mechanisms of such interactions have remained largely obscure. It is likely that they involve intricate hormonal circuits that communicate between somatic tissues and the germ cells.

In case of genomically compromised germ cells in *C. elegans*, a systematic investigation of DDR and longevity assurance signaling factors has implicated ERK1/2 MAPK signaling mediated by MPK-1 in triggering GDISR (Ermolaeva et al., 2013). MPK-1 signaling has been implicated in the regulation of various physiological processes ranging from oocyte maturation to vulva development (Church et al., 1995; Lackner et al., 1994). MAPK signaling, most prominently through the p38 MAPK PMK-1, but also through MPK-1, also regulates the expression of immune genes when responding to various infections of *C. elegans* (Kim et al., 2002; Nicholas and Hodgkin, 2004; Troemel et al., 2006). MPK-1 is also activated following DNA damage in pachytene cells and is required for inducing apoptotic cell death (Rutkowski et al., 2011). MPK-1, in contrast to CEP-1 or the apoptotic machinery, however, is also required for establishing somatic stress resistance during GDISR (Ermolaeva et al., 2013). The common transcription program that is triggered by the various genotoxic insults that leads to GDISR contain commonly induced innate immune genes. Indeed, GDISR not only results in stress resistance, but also in a strong defense against bacterial infections in the intestine. The innate immune effector genes are comprised of three classes of genes, C-type lectins, antimicrobial peptides, and CUB-domain proteins (for C1s/C1r, Uegdf, BMP-related) (Ermolaeva and Schumacher, 2014b). How such genes exert signaling activity in somatic tissues remains to be investigated. In fact, little is known about the immune effector mechanisms in *C. elegans*.

The elevated stress resistance associated with an innate immune response appears to be a highly conserved feature. Even the human immune system not only defends the organisms but also harms host tissue in its rampage against pathogenic invaders. Therefore, a stress resistance program is intricately woven into the activity of immune defense. Similar to human immune defenses, *C. elegans* requires the activation of reactive oxygen species (ROS) defense during the course of intestinal infections (Hoeven et al., 2011). The ROS defense is mediated by the SKN-1 transcription factor, which also function in longevity assurance and responds not only to ROS but also to starvation, an important environmental factor that leads to lifespan extension in the worms (An et al., 2005; Bishop and Guarente, 2007). Not only SKN-1, but also the *bona fide* longevity assurance factor DAF-16, regulates longevity and at the same time elevates pathogen resistance (Garsin et al., 2003). Whether the tissue maintenance that is part of the longevity assurance program simply happens to

elevate the ability to withstand infections or whether certain aspects of the DAF-16-mediated longevity assurance program specifically attack the invaders is not conclusively determined.

A distinct effect on cellular maintenance and pathogen defense has been observed in experiments that investigated proteostasis during an immune response. The inability to trigger the endoplasmic reticulum unfolded protein response (UPR^{ER}) owing to a mutation in *xbp-1* led to larval lethality during infection with the most widely employed bacterial pathogen *Pseudomonas aeruginosa* (PA) in *C. elegans* (Richardson et al., 2010). Strikingly, the lethality could be circumvented when the central innate immune signaling pathway was abrogated by a mutation in PMK-1. Therefore, the UPR^{ER} was not part of the immune defense but rather functioned as an immune response tolerance mechanism. Indeed, the *C. elegans* innate immune response is comprised of a large number of immune peptides that carry signal peptides targeted to the secretory pathway (Troemel et al., 2006). Therefore, immune signaling leads to a shift of the cellular proteome towards secreted defense peptides that are passed through the ER and the Golgi apparatus. Protein folding in the ER appears thus to be essential for tolerating the production of the battery of immune peptides.

Indeed, even the ubiquitin proteasome system (UPS) can become overloaded during an immune response. This was observed when *C. elegans* expressing the UPS model substrate (composed of GFP tagged with a ubiquitin moiety that after polyubiquitination is degraded by the UPS (Segref et al., 2011)) was cultured on immunogenic *Bacillus subtilis* (Ermolaeva et al., 2013). Initially, the immune response leads to activation of the UPS, likely to support coping with the proteome shift towards the immune program; likewise, the UPS activation is essential for the GDISR-mediated stress resistance. However, upon culturing on immunogenic bacteria for extended periods of time, the levels of the model substrates were strongly elevated. The UPS activation is also required for the lifespan extension for instance upon germline ablation (Vilchez et al., 2012). Taken together, longevity assurance and immune signaling are intricately intertwined.

Outlook: inflammatory DNA damage signaling in mammals

Also in humans, there is ample evidence that immune signaling responds to DNA damage. Examples range from the UV response in the skin to the senescence-associated secretory phenotype (SASP). The consequences of immune signaling, however, are far more complex. For instance, SASP can promote inflammation and cancer cell growth, but has also been implicated in tissue remodeling required for wound healing (Demaria et al., 2014; Krtolica et al., 2001). The inflammatory responses to DNA damage are thought to cause tissue degeneration with aging and, indeed, in several mammalian models of accelerated aging due to diverse forms of genome instability, reducing immune signaling by NFκB inhibition could alleviate the pathology (Osorio et al., 2012; Tilstra et al., 2012). The inflammatory signaling, however, also constitutes a vicious cycle as it aggravates genome instability, for instance, by harming telomere maintenance (Jurk et al., 2014). It will be highly interesting to further investigate the role of stress resistance mechanisms such as proteostasis in tolerating genome instability and preserving tissue functioning.

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Figure 1. Responses to DNA damage in diverse species share common features to ensure species preservation.

The responses of three organisms to DNA damage are summarized in parallel to demonstrate the universality of the logical framework of how DNA damage responses can promote the preservation of species, despite vast divergence in the molecular mechanisms.