
REVIEW

Stress-Induced Phenoptosis: Mechanistic Insights and Evolutionary Implications

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Received September 15, 2022

Revised November 18, 2022

Accepted November 19, 2022

Abstract—Evolution by natural selection results in biological traits that enable organismic adaptation and survival under various stressful environments. External stresses can be sometimes too severe to overcome, leading to organismic death either because of failure in adapting to such stress, or alternatively, through a regulated form of organismic death (phenoptosis). While regulated cell deaths, including apoptosis, have been extensively studied, little is known about the molecular and cellular mechanisms underlying phenoptosis and its evolutionary significance for multicellular organisms. In this article, we review documented phenomena and mechanistic evidence emerging from studies of stress-induced phenoptosis in the multicellular organism *C. elegans* and stress-induced deaths at cellular levels in organisms ranging from bacteria to mammals, focusing on abiotic and pathogen stresses. Genes and signaling pathways involved in phenoptosis appear to promote organismic death during severe stress and aging, while conferring fitness and immune defense during mild stress and early life, consistent with their antagonistic pleiotropy actions. As cell apoptosis during development can shape tissues and organs, stress-induced phenoptosis may also contribute to possible benefits at the population level, through mechanisms including kin selection, abortive infection, and soma-to-germline resource allocation. Current models can generate experimentally testable predictions and conceptual frameworks with implications for understanding both stress-induced phenoptosis and natural aging.

DOI: 10.1134/S0006297922120082

Keywords: stress, phenoptosis, *C. elegans*, aging, organismic death, antagonistic pleiotropy

INTRODUCTION

The concept of phenoptosis was originally proposed to explain certain “programmed” features of organismic death and natural aging [1, 2]. Also dubbed as “the samurai law of biology,” phenoptosis signifies gene-regulated organismic death that may confer benefits in a way “better to die than to harm.” Phenoptosis would be considered inconsequential by natural selection according to mainstream evolutionary theories, since death and aging processes occur mostly post reproduction and are not subject to selection by evolutionary forces. Indeed, the concept of phenoptosis, when discussed as a theory of natural aging, is controversial and it remains debatable whether phenoptosis can be applicable to many species, including

mammals, or limited to species with clonal population structures. It is argued that the concept of phenoptosis in certain species can be compatible with evolutionary principles under situations where programmed deaths of individuals are altruistic, by mechanisms including kin selection, defense sacrifice and resource-saving for others, to benefit the species as a population [3]. While appealing from theoretical standpoints, these ideas remain largely untested for phenoptosis as evolutionarily stable strategies in most living species.

In this article, we review documented phenomena of stress-induced deaths at the cellular level in organisms ranging from bacteria to mammals, as well as our group’s recent studies of stress-induced phenoptosis in the multicellular organism *C. elegans*. We discuss exemplar genes, pathways and mechanisms identified so far that underlie stress-induced organismic deaths for both unicellular and

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multicellular organisms. Emerging evidence suggests that these genes and signaling pathways underlying phenoptosis have pleiotropic effects, and likely evolved because of fitness-promoting effects in early life, contrasting with death or senescence-promoting effects in late life. In species with clonal populations, mechanisms for phenoptosis may also exist to benefit population as a whole under stress conditions. As such, phenoptosis can be compatible with evolutionary principles under circumstances where the organismic death is caused by well-defined acute stresses, including those from both abiotic and pathogen sources. More broadly, chronic phenoptosis may also provide explanatory power for aspects of natural aging and for conditions where aging is caused by well-defined stress types in certain species.

STRESS-INDUCED CELL DEATHS IN ORGANISMS FROM BACTERIA TO MAMMALS

Stress-induced phenoptosis in unicellular organisms, such as programmed suicidal cell death in bacteria upon bacteriophage attack, are extensively studied in mechanisms and functional significance [4-6]. Like virus for eukaryotic cells, bacteriophages represent a constant threat to bacterial replication and survival. To counteract infection by bacteriophages, bacteria have evolved numerous defense mechanisms. However, when infection by bacteriophages is too severe to overcome, a set of genetic program and cellular mechanisms act to execute the death of the infected bacterial individual. For example, the retron-type anti-phage defense system encodes an effector toxin activated upon bacteriophage infection and kills infected bacteria. Certain type III CRISPR-Cas systems are recruited if other lines of defense (retron, type I/II CRISPR-Cas or restriction enzymes) fail to kill the invading bacteriophage. Enzymes encoded by the type III CRISPR-Cas can synthesize cyclic oligoadenylates that activate RNases or use target RNA-activated proteases to degrade host proteins and RNAs, leading to bacterial death [7, 8]. Both retron and type III CRISPR-Cas systems limit growth and propagation of bacteriophages via abortive infection [4], effectively benefit the bacterial species at the population level. Thus, bacteriophage infection-induced bacterial suicidal death offers clear functional and mechanistic explanations for the existence of phenoptosis in such unicellular organisms.

In addition to the bacterial abortive infection exemplified above, the concept of stress-induced phenoptosis can extend to many other unicellular organisms and types of stress. In yeasts, programmed cell death can be triggered by severe oxidative stress from reactive oxygen species (ROS) when pro-survival responses and antioxidant defenses fail [5]. Similarly, bacteria not only encode proteins that can detoxify ROS and ROS-induced damages, but also can initiate mechanisms of self-amplifying

ROS to self-destruct when oxidative stress is too severe to overcome and causes extensive DNA damage [6, 9, 10]. Since these unicellular organisms naturally exist in densely packed clonal populations, such stress-induced programmed death or phenoptosis in unicellular organisms could be an altruistic mechanism that clears damaged cells and frees up nutrients and resources to promote the survival of healthier clones [2, 6, 11].

Stress-induced cell deaths have also been characterized in mammalian cells. Since programmed cell death, or apoptosis, was well understood and described with a role in shaping tissue morphogenesis during normal development, it has become clear that various types of stresses can also trigger programmed cell deaths in physiological and pathological processes. Such stresses include those from proteostasis imbalance in the endoplasmic reticulum (ER stress), DNA damage-causing agents, ROS, hypoxia, starvation, hypothermia, and a variety of pathogen-derived infections [12-14]. Specific signal transduction pathways have been identified to link such stresses to cell death execution, through mechanisms including apoptosis, pyroptosis, necroptosis, and ferroptosis [12, 15-17]. For example, the p38 MAPK pathway is among the most commonly involved pathways that mediate stress-induced cell death. However, its effects are highly stress-context dependent [18, 19]. Mild stress activates transient p38 phosphorylation that promotes survival, while severe stress induces its prolonged activation leading to cell death. Specific pathogen infections can also elicit diverse host stress responses, including activation of innate immune systems, inflammation, and various types of cell deaths [20-22]. Similar to abortive infection in bacteria, pathogen infection-induced cell death, such as that in mammalian dendritic cells infected by *Legionella pneumophila*, also functions to limit pathogen replication [23]. Such theme is broadly consistent with stress-induced phenoptosis in unicellular organisms, although the physiological role of stress-induced mammalian cell death is dependent on particular biological contexts and often more nuanced beyond "altruistic" mechanisms.

While stress-induced cell deaths in organisms from bacteria to mammals have been widely studied, how stress might also lead to phenoptosis in multicellular organisms is less well understood. In humans, hyper-activation of innate immune responses to viral or bacterial infections can cause inflammation and tissue injuries, leading to severe illness and death, such as that from septic shock. Such infection-induced pathogen stress has been proposed to cause organism-level phenoptosis that may protect the entire population from the spread of pathogens [24]. Although direct evidence supporting such idea in humans remains to be established, gene knockouts, neutralizing antibodies, and pharmacological agents that inhibit innate immune responses have been shown to reduce tissue injuries, organ damages,

individual mortality and even extend lifespans in animal models [25–27, p. 2]. For example, targeting the innate immune receptor TLR4 protects mice from lethal endotoxic shock and *E. coli*-induced sepsis, while mice deficient in RIPK1/3 exhibit strikingly delayed reproductive aging [28, 29, p. 4]. In addition, heat stress-induced circulatory failure, organ injury, and lethality in mice require concerted actions of ZBP1, RIPK3, MLKL, and the caspase-8-dependent necroptosis pathway [30]. These studies indicate that stress-induced organismic deaths and even aspects of chronic aging in multicellular organisms, including mammals, can be regulated by genetic programs. Nonetheless, it remains challenging to experimentally establish whether these programs reflect maladaptive pathway overreaction to severe stresses or may confer potential functional roles and adaptive values for organismic benefits at the population level.

STRESS-INDUCED PHENOPTOSIS IN *C. elegans*

C. elegans is a free-living nematode that encounters numerous microbial pathogens and diverse types of abiotic stress in its natural environment [31–34]. Pathogens known to cause death or “accelerated aging” phenotypes in *C. elegans* include those from virus (e.g., Orsay virus, Flock House virus, vesicular stomatitis virus), bacteria (e.g., *Pseudomonas*, *Legionella*, *Salmonella*, *Burkholderia*, *Yersinia*, *Streptococcus*, and *Staphylococcus*), and fungi (e.g., *Cryptococcus neoformans*, *Drechmeria coniospora*) [35–37]. Pathogenic infections can cause death or shortened lifespans in *C. elegans* through either intracellular colonization or secretion of microbial toxins. *C. elegans* recruits innate immune systems through the evolutionarily conserved p38 mitogen-activated protein kinase (MAPK), the DAF-2 insulin signaling, and transforming growth factor (TGF- β) pathways to counteract the pathogenicity of these infectious microbes [37, 38]. However, like bacteria, if pathogenic infection is too severe to overcome, *C. elegans* may activate cellular necrosis followed by organismic phenoptosis through regulatory pathways to prevent further spread of infection. Such “altruistic” behavior of *C. elegans* could be explained based on the trade-off between individual and population fitness as death or shorter lifespan of infected individuals could help restrict the transmission of infection. Although direct experimental evidence for population-level benefits of such infection-induced phenoptosis still remains lacking, several studies support that organismic deaths upon infection can be regulated by genetic programs in *C. elegans*. For example, a transcriptomic study showed that bacterial pathogen infections trigger both pathogen-specific responses and responses shared by several pathogens, including immune defense genes involved in necrotic cell death [39], which could drive organismic death [40]. Toxin-producing *Bacillus thuringiensis* triggers

cellular necrosis and organismic death through host proteases [41]. Pathogenic *P. aeruginosa* infection causes rapid death of day 9-old *C. elegans*, which can be markedly attenuated by loss of ZIP-10, a transcription factor that appears to promote immune aging [42, p. 10]. Moreover, the pathogenic bacterium *Aeromonas dhakensis* has been shown to infect and kill *C. elegans* rapidly in a manner that depends on the transcriptional induction of calreticulin and protease-encoding genes [43].

In addition to pathogen stress, many types of severe abiotic stress have also been shown to cause organismic death or shortened lifespans in *C. elegans*. Seminar work from the Gems laboratory has revealed that a cascade of the calpain-cathepsin necrosis pathway in intestinal cells can drive stress-triggered organismal death in *C. elegans* [40]. Recent studies from our laboratory have begun to elucidate the regulatory pathway underlying severe cold-thermal stress-induced phenoptosis in *C. elegans* [44, 45]. As a small-bodied ectotherm, *C. elegans* varies its body temperature along with its ambient environment and can actively reproduce during the range of 15 to 25°C. Mild hypothermia (e.g., 15°C) in *C. elegans* can extend longevity, at least in part, by activation of cytoprotective pathways and mechanisms [46, 47]. However, we found that more severe cold (e.g., 4°C shock) or freezing (e.g., transient exposure to –20°C) stresses can cause rapid organismic deaths in *C. elegans* through active regulation by genetic programs [44, 45]. Using stress-inducible GFP-based reporter systems, we carried out both forward genetic (random mutagenesis) and reverse genetic (RNAi) screens to identify genes that mediate responses to severe cold or freezing stresses in *C. elegans* [44, 45]. We found that a bZIP-type transcription factor, ZIP-10, mediates activation of a genetic program in response to severe cold stresses followed by warming. Animals deficient in ZIP-10 exhibit reduced organismic death under severe cold-warming stress conditions, consistent with a role of ZIP-10 in promoting thermal stress-induced phenoptosis in *C. elegans*. ZIP-10 appears to promote phenoptosis, at least in part, through up-regulating several protease-encoding genes in intestinal cells and its activation is gated by the actions of microRNA *mir-60* and *ISY-1*, a small-RNA-regulating factor [44]. Interestingly, several mammalian bZIP transcription factors have also been shown to promote apoptotic cell death upon exposure to stress conditions [48–50].

How are signals of severe cold-thermal stress transduced to a genetic program leading to phenoptosis in *C. elegans*? In another recent study, we have begun to address this question [45]. Through transcriptome profiling, RNAi screens and stress-responding organismic phenotype-based analysis, we established an essential role of a GPCR (FSHR-1, follicular stimulating hormone receptor related) in ZIP-10-dependent transcriptional response to severe cold-thermal stress. The *fshr-1* gene encodes the sole ortholog of glycoprotein hormone

receptor family proteins in *C. elegans* [51, 52]. Both FSHR-1 and its putative ligand FLR-2 are required for ZIP-10-dependent transcriptional responses. FLR-2/FSHR-1 appears to act through a *Gas*/cAMP/PKA signaling cascade to drive expression of genes that are ZIP-10 dependent as well as *zip-10* itself upon severe cold-thermal stress treatment. Consistent with this pathway promoting phenoptosis, loss-of-function of *fshr-1* and gain-of-function of PKA can decrease and increase organismic deaths, respectively, upon severe cold thermal stress treatment. While FSHR-1 and ZIP-10 act in the intestine, *fhr-2* is expressed primarily in neurons, indicating that severe cold-thermal stress may invoke temperature-responsive sensory neurons to regulate *fhr-2* release systemically, accompanied by local changes in intestinal membrane properties [53]. Overall, these studies suggest that GPCR signaling activates a ZIP-10-dependent genetic program, leading to systemic necrosis and organismic death in *C. elegans*. As many genes can be activated by severe cold-thermal stress in the *fshr-1* mutants, additional unidentified factors and pathways may also be involved in regulating stress-induced phenoptosis in *C. elegans*.

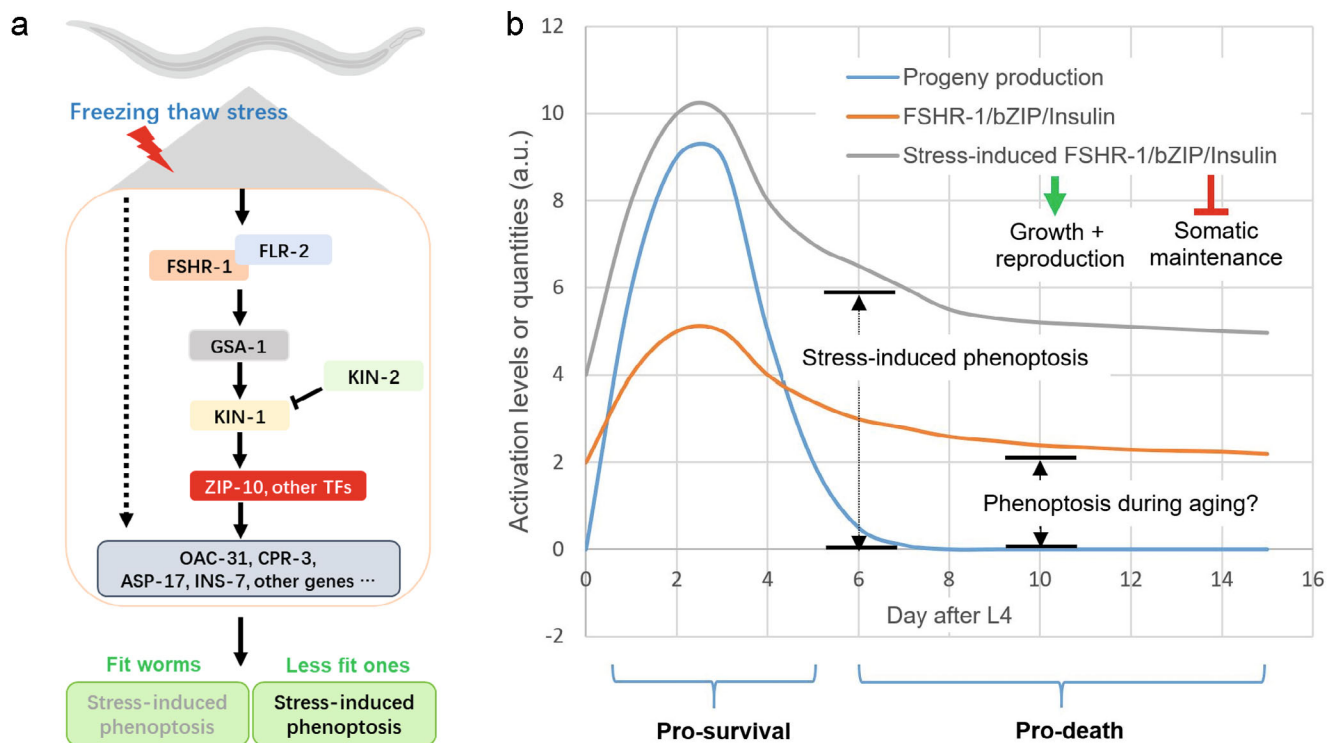
Downstream of FSHR-1 and ZIP-10, three categories of genes likely contribute to stress-induced phenoptosis. First, several ZIP-10-dependent genes encode proteases that may promote specific cleavage of unidentified targets or metabolic breakdown of proteins for tissue destruction. Reduced expression of individual protease-encoding genes only partially blocks phenoptosis, indicating that they may coordinately act in a pathway or function redundantly. Second, ZIP-10 has been shown to regulate an insulin-encoding gene *ins-7* that can drive insulin receptor signaling and antagonize DAF-16, a cytoprotective transcription factor [42, p. 10; 54, 55]. The regulation of *ins-7* by ZIP-10 may promote immunosenescence in *C. elegans* [42], consistent with roles of ZIP-10 in stress-induced phenoptosis. In addition, severe cold-thermal stress can upregulate many lipid-metabolic genes, including *oac-31* that encodes a mammalian ortholog of sterol O-acyltransferase (SOAT). SOAT plays role in lipid storage by converting accessible cholesterol into ester forms [56, 57]. A recently study suggests that cold shock induces transfer of lipids from the intestine to germline [58]. Moreover, late-life mortality in *C. elegans* has been linked to insulin-driven autophagy-mediated conversion of intestinal biomass into yolk [59]. Thus, it seems likely that *oac-31* activation by *fshr-1* under severe thermal stress condition might be linked to soma-germline trade-off to assist vitality of progeny at expense of parent survival. Moreover, aged animals appear to show markedly higher rates of phenoptosis induced by stress than younger animals. At the population level, phenoptosis of relatively aged adults may also be beneficial as limiting resources can be saved for reproductively active younger individuals under high-stress conditions. These two scenarios (“disposable soma” and “kin selection”)

are not mutually exclusive and may both contribute to potential benefits of such genetic programs underlying stress-induced phenoptosis (see more discussion below).

MODEL FOR THE PATHWAY AND POTENTIAL ROLES OF THE STRESS-INDUCED PHENOPTOSIS

Based on our current understanding, we propose a model and ideas to explain stress-induced phenoptosis in terms of both functional mechanisms and potential evolutionary implications (figure). At the mechanistic level, severe cold-thermal stress may activate a genetic program that promotes organismic death, at least in part, through the FLR-2/FSHR-1/PKA/ZIP-10 cascade (figure). While it remains unclear precisely how temperature shifts or cold-thermal stress are sensed, this pathway appears to be independent of the canonic HSF (heat-shock factor) pathway and may involve both thermal-stress sensing in neurons and change of membrane properties in intestinal cells. Similar to most signal transduction pathways, the FLR-2/FSHR-1/PKA/ZIP-10 cascade can elicit pleiotropic effects depending on the stress severity. Under nonlethal infection or mild oxidative stress conditions, both FSHR-1 and ZIP-10 can play protective roles in defending against oxidative stresses [60, 61]. Under severe cold-thermal stress conditions, these two proteins can orchestrate a genetic program promoting phenoptosis [44, 45]. Their effects are also organismic age-dependent: their death-promoting effects after severe thermal stress are particularly pronounced in older animals. Detailed mechanisms of how phenoptosis is executed remain to be further elucidated, and may involve actions of proteases, lipid metabolic enzymes and the insulin pathway. In addition, while it is still debated whether natural aging may be driven primarily by biological damage accumulation, decline of cellular maintenance programs or hyperfunction of antagonistic pleiotropy genes [62-66], these seemingly divergent causes can be considered as chronic stresses that may contribute to natural aging and organismic death via chronic stress-induced phenoptosis (figure). It is conceivable that the paradigm of cold-thermal stress-induced phenoptosis in *C. elegans* may be an acute manifestation of such chronic stress-induced phenoptosis during aging.

How does the stress-induced genetic program for phenoptosis potentially contribute to population benefits? We established a mathematical model to simulate population growth that may explain potential adaptive or beneficial functions of phenoptosis at the population level, regardless of mechanisms [45]. Simulated results from our model assuming constant parameters in a given initial population support that the number of healthy individuals in an initial population can grow faster than



Schematic model to explain how the FSHR-1/ZIP-10 pathway may underlie severe cold-thermal stress-induced phenoptosis and aging. a) Model illustrating the FLR-2/FSHR-1/PKA/bZIP regulatory pathway mediating a genetic program and transcriptional responses to severe cold-thermal stress (e.g., freezing-thaw stress, FTS), leading to stress-induced phenoptosis, more so in severely stress and less fit individuals. Dashed line indicates additional genes and pathways remain to be identified. b) Model illustrating the antagonistic pleiotropic effects of genes and pathways underlying stress-induced phenoptosis. Natural selection may drive evolution of genes and pathways that can be induced by stress and confer immune defense and growth/reproductive benefits in early life. However, when the stress stimuli become too severe to overcome and/or in late life post reproduction, many of such genes and pathways may promote the organismic death upon such stress, by activating death-executing enzymes and/or reducing somatic maintenance. Such stress-induced phenoptosis may represent an acute manifestation of chronic stress-induced natural aging, whether the chronic stress is caused by damage accumulation or hyperfunction of antagonistic pleiotropic genes

a population without stress-inducible phenoptosis, under conditions where there is competition for limited resources to reproduce or infectious spreading of pathogens among individuals. Mechanistically, stress-induced phenoptosis may act against the unfit members (less reproductive old adults, sick individuals unable to overcome severe stress or shedding infectious pathogens) to benefit the whole group at the population level.

MODEL PREDICTIONS AND FUTURE DIRECTION

Our model and simulation above generate predictions and questions that can be tested by future experiments in *C. elegans* and more broadly in other appropriate model systems. First, can late-life specific loss of cell signaling involved in early-life pro-survival responses reduce stress-induced phenoptosis and/or extend lifespans? In *C. elegans*, this can be tested by conditional genetics to manipulate expression levels or activities of genes (e.g., *fshr-1*, bZIP and insulin families) in a temporarily-specific manner. Second, can genes and path-

ways underlying stress-induced phenoptosis exhibit antagonistic pleiotropy effects over generational or even evolutionary times to confer benefits at the population level? This would involve measurements of multi-generational and population-based animal fitness in wild type and phenoptosis mutants, under an environment where resources (e.g., food or oxygen) for growth and reproduction would be limiting. Mutagenesis screens in *C. elegans* have been used as a powerful forward genetic tool, but can also be used in experimental evolution coupled with severe cold-thermal stress environments and population fitness measures, including fecundity, to help answer such question. Third, how broadly applicable is the theme of antagonistic pleiotropy for stress-induced phenoptosis when applied to other stress types, organisms with non-clonal population structure and even humans? Although the original concept of antagonistic pleiotropy did not emphasize the potentially adaptive value of post-reproductive effects, ideas of phenoptosis and antagonistic pleiotropy can be united when considering fitness benefits at the population level, if cohort competition/infection cost (μ in the population growth model [45]) is sufficiently large.

Further, as aging is considered as a progressive pathologic process, aspects of which can be driven by various types of chronic stress including bio-molecular cellular damages and inflammatory stresses, important questions arise as how and to what degrees aging pathologies are determined by stochastic accumulation of molecular damages versus hyperfunction of genes and pathways with antagonistic pleiotropy effects [62-66]. While answers to these questions may well be species-specific, exploration of these issues should help revise or refine current models and guide future studies to understand both the mechanistic basis and evolutionary implications of stress-induced phenoptosis as well as natural aging.

Contributions. Taruna Pandey, Dengke K. Ma – wrote the manuscript.

Funding. The work was supported by NIH grant 1R35GM139618, UCSF PBBR New Frontier Research (NFR) and the Packard Fellowship in Science and Engineering (D.K.M).

Ethics declarations. The authors declare no conflicts of interest. This review article does not contain any studies involving human participants or animals performed by any of the authors.

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