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Stress-Induced Evolutionary Innovation: A Mechanism for the Origin of Cell Types

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Abstract

Understanding the evolutionary role of environmentally-induced phenotypic variation (i.e., environmental plasticity) is an important issue in developmental evolution. One of the major physiological responses to environmental changes is cellular stress, which is counteracted by a generic stress reaction that detoxifies the cell, refolds proteins, and repairs DNA damage. In this paper, we elaborate on a previous finding suggesting that the cell differentiation cascade of human decidual stromal cells, a cell type critical for embryo implantation and the maintenance of pregnancy, evolved from a cellular stress reaction. We hypothesize that the stress reaction in these cells was elicited ancestrally through the inflammation caused by embryo attachment and invasion. We describe a model, Stress-Induced Evolutionary Innovation (SIEI), whereby ancestral stress reactions and their corresponding pathways can be transformed into novel structural components of body plans, such as new cell types. After reviewing similarities and differences between SIEI and the "plasticity first hypothesis" (PFH) of evolution, we argue that SIEI is a distinct form of plasticity-based evolutionary change because it leads to the origin of novel structures rather than the adaptive transformation of a pre-existing character.

Keywords: evolutionary innovation, cell type evolution, cellular stress response, evolution of gene regulation, gene regulatory network evolution, decidual cell, evolution of pregnancy

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Introduction

A "happy" cell is one that lives in relative harmony with its environment: nutritional input closely matches its metabolic need, and the nature and rate of anabolic processes is balanced with the catabolic decay and loss of cellular components. When this equilibrium is disturbed, either by a lack of nutrients or toxin-induced malfunction of its constituent components, the cell experiences stress and reacts with a stress response [1]. Cellular stress leads to the accumulation of unfolded proteins, DNA damage, and toxic side products of metabolism, such as reactive oxygen species (ROS) and other radical-like, reactive nitrogen oxides. The stress response activates genes and pathways that minimize the damage by producing enzymes that neutralize ROS (e.g., catalase or super oxide dismutase [SOD]), degrade or refold misfolded proteins (chaperones), and repair DNA damage. If these responses fail, the cell undergoes senescence or commits suicide (e.g., apoptosis). The study of all these phenomena constitutes the field of cellular stress biology, which has been separated from "normal" developmental biology and physiology for a long time. Increasingly, however, the boundary between these fields is blurring because mechanisms and agents common to the field of stress biology, such as ROS, have been found to play a role in "normal" biological processes like cell differentiation [2-5]. This overlap between stress biology and developmental biology is not coincidental. We argue that it constitutes the footprint of evolutionary processes that convert stress reactions into normal developmental and physiological processes, and give rise to evolutionary novelties (e.g., new cell types).

One of the more surprising developments in cell biology is the discovery of the role of ROS in cell differentiation. ROS are waste products of oxidative phosphorylation and thus can accumulate in the cell under stressful conditions. ROS also are produced by specialized enzymes (NADPH oxidases, e.g. NOX1, NOX2, etc.) of the cell to accomplish particular tasks, such as defense against microbes at the cell surface [6]. Nevertheless, ROS are mostly known for the damage that they can cause to cells and are seen primarily as toxic waste. However, it is now

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well established that ROS play an important part in the normal differentiation of mammalian cells, a phenomenon called "ROS signaling."

Across all multicellular domains of life, NOX-derived ROS signaling has been implicated in the differentiation of cell types. In mammals, ROS signaling has been shown to function in the maintenance and proliferation of neuronal progenitor cells [4]. Two physiological signals have been shown to induce the production of ROS: BDNF activation of NOX2 or NOX4 leads to the production of H_2O_2, which in turn inactivates PTEN, a phosphatase of PIP_3 (phosphatidylinositol-3,4,5-triphosphate), which is a signaling molecule and lipid component of the cell membrane. The inactivation of PTEN then tilts the balance of PIP_2/PIP_3 in favor of PIP_3, leading to activation of the Akt pathway that maintains neuronal progenitor cell identity. Similarly, the differentiation of mesenchymal stem cells in chondrocytes, osteocytes, and adipocytes is also regulated through the production of ROS and adjustment of their levels [7]. In angiogenesis and cardiogenesis, NOX-derived ROS promote differentiation of blood vessels and cardiomyocytes, respectively [8,9]. In *Drosophila,* ROS signaling precedes and is necessary for differentiation of hematopoietic progenitors [10], and also functions in proliferation of intestinal stem cells in the midgut [11]. In *Xenopus,* ROS function to activate the Wnt/β-catenin pathway during tail regeneration [12]. These observations, stemming from evolutionarily distant clades, suggest that pathways functioning in the generation of ROS have been utilized as an evolutionary mechanism to induce the differentiation of novel cell types.

ROS can oxidize sulfhydryl groups on proteins and turn them into $-SO_3^-$ groups (Figure 1), which creates a negatively charged residue similar to the result of phosphorylation. It is well known that, in many cases, the effect of phosphorylation can be mimicked by replacing the phosphorylated amino acid in a protein by a negatively charged amino acid like aspartic acid [13,14]. This shows that a key role of phosphorylation is to create a negative charge on the surface of proteins. Hence, it is not surprising that oxidation of –SH residues into $–SO_3^-$ can play a role similar to phosphorylation in signaling.

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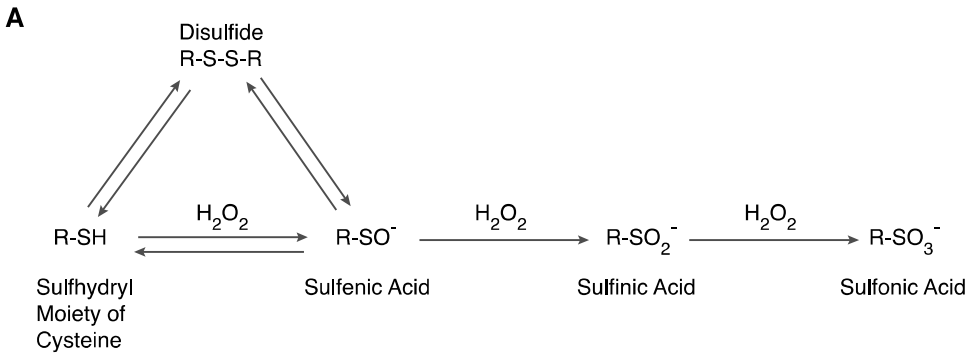

Figure 1. Oxidation pathway of sufhydryl groups of cysteine caused by ROS: -SH is oxidized by hydrogen peroxide either into di-sulfide "bridges" or various sulfo acid residues that create a negative charge on the surface of the protein and thus may have an effect similar to phosphorylation. The oxidation to sulfonic acid is essentially irreversible and commits the protein to this oxidated state.

In addition to these general considerations about the dual role of ROS signaling in normal physiology and under conditions of cellular stress, new results from a research project focused on the molecular mechanisms for the evolutionary origin of the decidual stromal cell type of eutherian mammals substantiate empirically the evolutionary significance of cellular stress responses [15]. Having encountered the significant role of stress response genes in the evolution of cell differentiation, we were prompted to reflect upon the role of stress pathways in the evolution of differentiation cascades and thus the origin of novel cell types. After reviewing these recent results, we discuss the relationship of our new model to previous analyses of the importance of plasticity in evolutionary change at a more organismal level [16,17].

Stress response and the evolution of the decidual stromal cell

The decidual stromal cell (DSC) is a cell type that evolved in the stem lineage of eutherian mammals [18] after the most recent common ancestor of marsupials and eutherian mammals (or "placental" mammals, though this a misnomer since marsupials also have placentas), and before the most recent common ancestor of eutherian mammals (Figure 2A). This inference is based on the fact that DSCs are only found in eutherian mammals and not in marsupials. Marsupials, though, do have a cell type that is homologous to the DSC, namely the endometrial

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stromal fibroblast or ESF [19], which cannot differentiate into a DSC [15]. In eutherians, and in humans specifically, the DSC differentiates from an ESF, which we label a "neo-ESF" since it can differentiate into a DSC [20]. The opossum ESF is labeled "paleo-ESF" because it cannot differentiate into a DSC. Figure 2B shows the cell type tree implying that human ESF and DSC are sister cell types, as reflected in the similarity of their transcriptomes compared to other mesenchymal cell types [21].

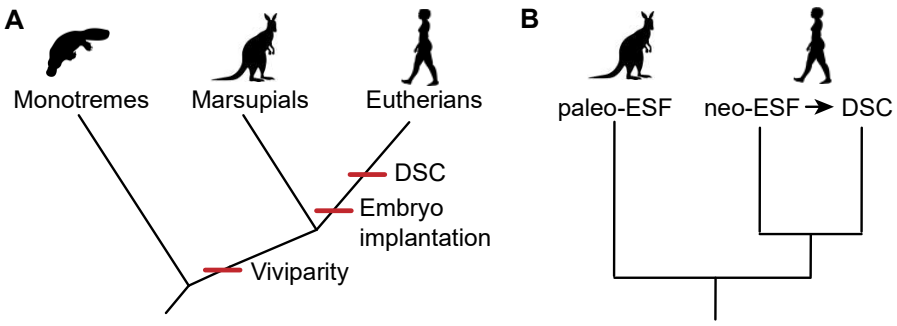

Figure 2. Evolutionary history of viviparity and the decidual stromal cell (DSC) in mammals. **A)** Large scale evolutionary history of mammals: there are three main groups (clades) of mammals. Monotremes are egg laying and likely diverged from the mammalian lineage before the evolution of viviparity, which is a shared derived characteristic of marsupials and eutherians. However, marsupials do not implant and do not have the DSC. In contrast, the ancestral situation in eutherian mammals is implantation, invasive (hemochorial) placentation, and the presence of the DSC, which is a maternal cell type essential for the accommodation of the embryo and maintenance of pregnancy. **B)** The distribution of endometrial stromal cells among therian mammals. Marsupials have an endometrial stromal fibroblast (ESF) that does not decidualize, which is referred to as "paleo-ESF". In eutherians, the ESF can differentiate into a DSC and is therefore called "neo-ESF".

Much is known about the transcription factors and signals involved in the differentiation of human DSCs [22,23]. The most salient features are that their differentiation depends on progesterone via nuclear progesterone receptor A (PGR-A) and the subsequent activation of the PKA pathway that produces cyclic adenosine monophosphate (cAMP). cAMP can be activated by prostaglandins [24], such as prostaglandin E2 (PGE2) via the prostaglandin receptors PTGER4 or PTGER2, as well as through human chorionic gonadotropin (hCG) or relaxin [22]. Comparative data, however, suggest that PGE2 may be the ancestral ligand activating the PKA pathway in these cells because hCG expression in the trophoblast is only found in humans and their close

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relatives. Other ligands have been shown to also play a role, such a EGF, IHH, BMP2, and Wnt [23,25,26]. Downstream of the cAMP signal, the transcription factor protein FOXO1 is stabilized rather than degraded and retained in the nucleus. Nuclear FOXO1 then physically interacts with a number of other transcription factors, like PGR, CEBPB, and HOXA11, and probably others as well [27,28]. It is these transcription factor complexes that then activate decidual effector genes—transcription factors that target effector genes like ZBTB16 [29,30]. Decidual marker genes in humans include prolactin (PRL), IGFBP1, and somatostatin.

In contrast, stimulating opossum ESFs with the same signaling molecules (progesterone and PGE2) leads to a mixed response [15]. On the one hand, many of the same transcription factor genes are upregulated at the transcriptional level, as observed in decidual cells, and FOXO1 protein is stabilized and retained in the nucleus. This situation is quite similar to the observed response in human DSC differentiation. On the other hand, none of the highly-induced effector genes of the human DSC are expressed in opossum paleo-ESFs after stimulation with these molecules. Instead, intracellular ROS is induced, as well as many genes related to the cellular stress response, including genes related to ROS scavenging, detoxification, and decomposition of H_2O_2 like catalase, GPX3, GPX4, SOD1, and SOD3. A model of the regulatory network induced in paleo-ESFs based on the experiments reported in Erkenbrack et al. (2018) is summarized in Figure 3A. In brief, progesterone prevents the degradation of FOXO1 protein and leads to the accumulation of FOXO1 in the cytoplasm. On the other hand, PGE2 activates the PKA pathway via the PTGER4 receptor, increasing intracellular cAMP. This, in turn, leads to the expression of NOX4 that produces intracellular ROS, which activates the oxidative stress response. FOXO1 and FOXO3 contribute to the protective function of the stress response. Figure 3B depicts a plausible reconstruction of the ancestral generic oxidative stress response. The derived stress response seen in the opossum consists of two additional pathways: (1) the production of ROS stimulated by PGE2, which in itself is not a stressor, and (2) the inhibition of FOXO1 degradation by progesterone. The latter effect could facilitate a more efficient induction of antioxidant gene expression since FOXO1 ancestrally activates these gene cassettes and now translocates to and accumulates in the nucleus.

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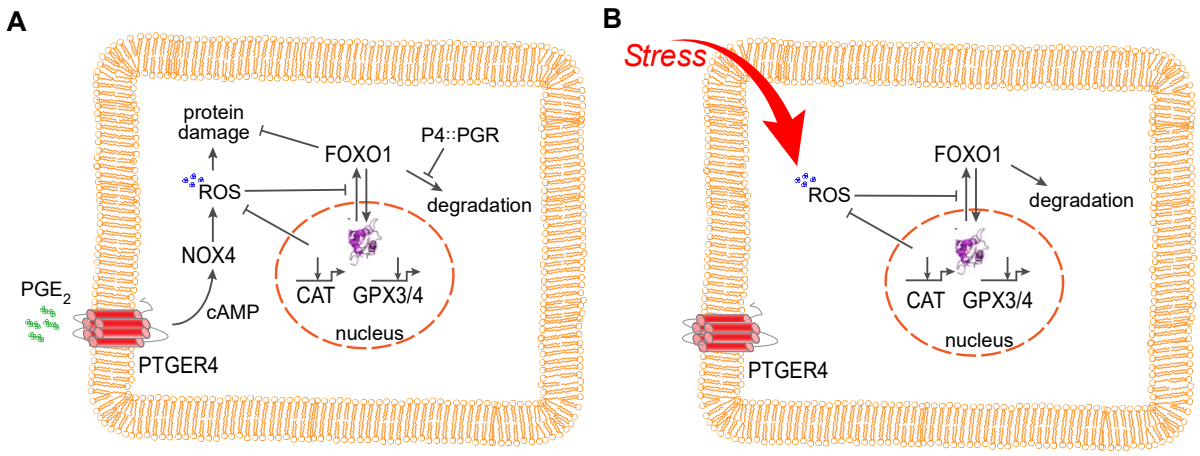

Figure 3. Regulation of FOXO1 protein activation. **A)** Regulatory network revealed in paleo-ESF of the opossum *Monodelphis domestica* (for evidence, see Erkenbrack, et al., 2018). Progesterone leads to the inhibition of degradation of FOXO1 protein, which leads to its accumulation in the cytoplasm. Presence of ROS and cAMP, as well as PGE2 through the activation of PGE2 receptor 4 (PTGER4 aka EP4) stimulation, inhibits the nuclear export of FOXO1 and thus retention of FOXO1 in the nucleus, where it positively influences the transcription of anti-oxidant enzymes like catalase and gluthathione peroxidase. In this model we assume that PGE2 acts through PKA and cAMP to induce the NADPH oxidase 4 (NOX4) to produce the cytoplasmic ROS, which is parsimonious but not yet directly shown. **B)** Ancestral activation of FOXO1 in response to ROS, through activation of ERK1/2 signaling found in many other cells. The network in the opossum ESF, as shown in A), is likely derived from this generic oxidative stress pathway by two evolutionary events. First, the evolution of NOX4 activation by PGE2, though this also could be a generic pathway since PGE2 has been shown to activate NOX4 through PTGER4 in liver cells [46]. Second, the inhibition of FOXO1 degradation by progesterone through its receptor isoform A, PGR-A. In this way, the activation of FOXO1 through the generic oxidative stress reaction becomes internalized, i.e., activated through physiological signals rather than stressors.

The notable differences between the human DSC and the opossum paleo-ESF are that the latter does not express decidual marker genes like PRL and IGFBP1, but rather activates a cellular stress response. The generic cellular stress response has two branches: one which activates genes that counteract the damaging effects of stress, like antioxidant enzymes and chaperones, and another which readies components of the apoptotic pathway in the event that the protective pathway fails. In the human DSC, components of the stress response are inhibited, including signaling pathways that activate apoptosis through JNK and P38 signaling pathways. In the human endometrium, the phosphorylated (active) form of JNK is not expressed [31] because

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of the action of a specific phosphatase, DUSP1/MEK1 [32]. Thus, in the human DSC, the generic stress response is modified so that the likelihood of apoptosis is lower than it is in the ESF.

The similarities between the human DSC and the opossum paleo-ESF are the activation of PKA, the production of ROS [33], and the activation of FOXO1 protein. Intriguingly, human DSCs produce ROS during decidualization, which plays a positive role in their differentiation [33].

Another surprising feature is that the signals which activate the cellular stress response (i.e. progesterone and PGE2) are not themselves stressors. Instead, PGE2 seems to "simulate" oxidative stress by activating NOX4, leading to some level of ROS in the cell, which in turn is activating the protective oxidative stress response. These features of the regulatory network seem to indicate that we are dealing with an "internalized" stress response, one that is activated by physiological rather than pathological signals, but which nevertheless is derived from, and thus homologous to, a reactive stress response.

Peeling away the particulars: A model of Stress-Induced Evolutionary Innovation (SIEI)

The comparison of human DSC differentiation and the response of the sister cell type in the opossum—the paleo-ESF—suggests homologies at two levels: a) the inflammatory reaction induced by embryo attachment in the opossum and the implantation reaction in the endometrium of eutherian mammals (Griffith et al., 2017); and, b) the stress reaction of the opossum ESF and differentiation pathway of the human DSC [15]. It is likely that the evolution of implantation and decidualization are not only historically associated but in fact causally intertwined. The stress reaction of the opossum ESF is likely caused by attachment-induced inflammation, and the evolution of the DSC in eutherian mammals was a key step in transforming the inflammatory attachment reaction into the process of implantation [34,35].

Overall, we have a monophyletic group of animals (i.e., a clade)—the eutherian mammals—in which two signals (progesterone and PGE2) lead to the differentiation of a cell type, the DSC.

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The DSC, in turn, interacts with the fetus to establish a sustainable fetal-maternal interface. In contrast, we have an outgroup species, the opossum, in which there is a homologous cell type—the opossum ESF—that reacts to the same signals by deploying a classical cellular stress response. The homology of opossum ESF and human DSC implies that the differentiation pathway of the DSC evolved from an ancestral stress response. In eutherians, the stress response was transformed into a novel cellular phenotype that compensates the perturbation caused by the invading embryo. There are two items to note here: 1) the different nature of the phenotypes induced in these two cells, and, 2) the stimuli that cause the deployment of the stress cascade in opossum (progesterone and prostaglandins) are not in themselves stressors.

The generic cellular stress reaction activates genes that ***protect*** against the harmful effects of stress like ROS. Examples in the opossum ESF are the upregulation of catalase and SOD to break down H_2O_2, the activation of the NRF2 signaling pathway that leads to the production of ROS-dexotifying enzymes like glutathione peroxidases (e.g., GPX3/4), and the fact that activated FOXO1 protein in the opossum ESF is protective against apoptosis (Erkenbrack, Maziarz et al., 2018). In contrast, the phenotype of the DSC is directly engaging the intruding trophoblast by both enabling and limiting trophoblast invasion, as well as modifying the reaction of the innate immune system to the perturbation caused by embryo invasion [36,37]. Therefore, the function of the DSC is not only to protect the cell from damage, like the stress reaction seen in opossum, but also to ***compensate*** for the effects of the stressor: embryo attachment, inflammation, and invasion. These observations lead to a model where the initial, environmentally-induced reaction that is protective later evolves into a phenotype that compensates for the initial stressor of implantation. This is an important feature of the SIEI model when one compares it with other models for the role of plasticity in evolution, such as the “plasticity first model” (PFH) of Levin and Pfenning (2016) and the genetic accommodation model of West-Eberhard (2003). In these models, the role of the initial plastic response is to produce an approximation of the adaptive phenotype itself. In the SIEI model, the initial plastic reaction protects and can become the target of natural selection to produce a novel compensatory phenotype later.

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The second unexpected feature of our findings in the opossum ESF is that we can induce a stress reaction with physiological stimuli (progesterone and PGE2). It is unlikely that these signals are themselves stressors, since they do not act as stressors on other cells in the body. For the opossum ESF, it is more likely that the co-activation of its progesterone receptor and PTGER4 carries information that embryo attachment and oxidative stress is likely to occur soon. In the uterus, progesterone indicates that ovulation has happened, and thus fertilized eggs are likely coming down the oviduct. PGE2 may indicate that copulation has occurred, which generically leads to transient post-copulatory inflammation in the female reproductive tract. This latter suggestion is speculative at this time because the regulation of PGE2 production in the opossum uterus has not been fully elucidated. Regardless, the point is that the stress reaction in opossum is triggered by intra-organismal signals, hormones and paracrine factors, rather than by an actual stressor. Interestingly, production of ROS in human keratinocytes has been shown to stimulate production of PGE2 [38]. Thus, it likely represents an anticipatory activation of the stress network (i.e. an internalized stress reaction), rather than being triggered by an acute stressor.

Another feature of SIEI is that the internalized stress response network creates a new target of natural selection. Only a subset of cells reacts to the internal signal and deploys a stress response. This set of cells then becomes a phenotypic target of natural selection because genetic variation that specifically affects these cells can be adaptive and subsequently fixed in the population. SIEI not only leads to an adaptive phenotype through the transformation of a stress response, but also to a new part of the organism—in this case, a novel cell type—that has its own developmental identity and differentiation pathway, derived from the original stress response.

We can summarize the above considerations with a visual model (Figure 4). Initially, some external environmental change leads to a stressed state in a subset of cells in the body (Figure 4A). When this stressor becomes a regular feature of the life cycle of the species, like reproduction or seasonal changes, natural selection will favor the deployment of an

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anticipatory stress reaction, one that is triggered by physiological signals so that these cells are poised for action when the stressor arrives (Figure 4B). Anticipatory mechanisms are widespread among organisms and seem to be adaptively favored. The most obvious example is the mobilization of nutrients from the root system of deciduous trees before the arrival of spring and the growth of leaves [39]. Another potential example is spontaneous decidualization, which is associated with menstruation. In most eutherians, decidualization depends on a signal from the embryo, but in great apes and old world monkeys (Catarrhini), as well as a few other mammals, the endometrium decidualizes even without the embryo, likely as an anticipatory mechanism because of the highly invasive nature of the placenta in these species [40].

Once the stress reaction is internalized, as it is in opossum, it can become the target of natural selection to produce a phenotype that addresses the stressor. Over time, the internalized stress reaction becomes transformed into a phenotype that not only protects but also engages the stressor itself (Figure 4C). This eventually leads to a situation that fully compensates for the influence of the stressor so that it becomes a normal part of the life cycle of the species (i.e., it is no longer a stressor). The result is twofold: a novel cell type that is specialized to deal with a specific functional challenge (the stressor) and an organism where the original stressor has become a part of the normal biology of the species.

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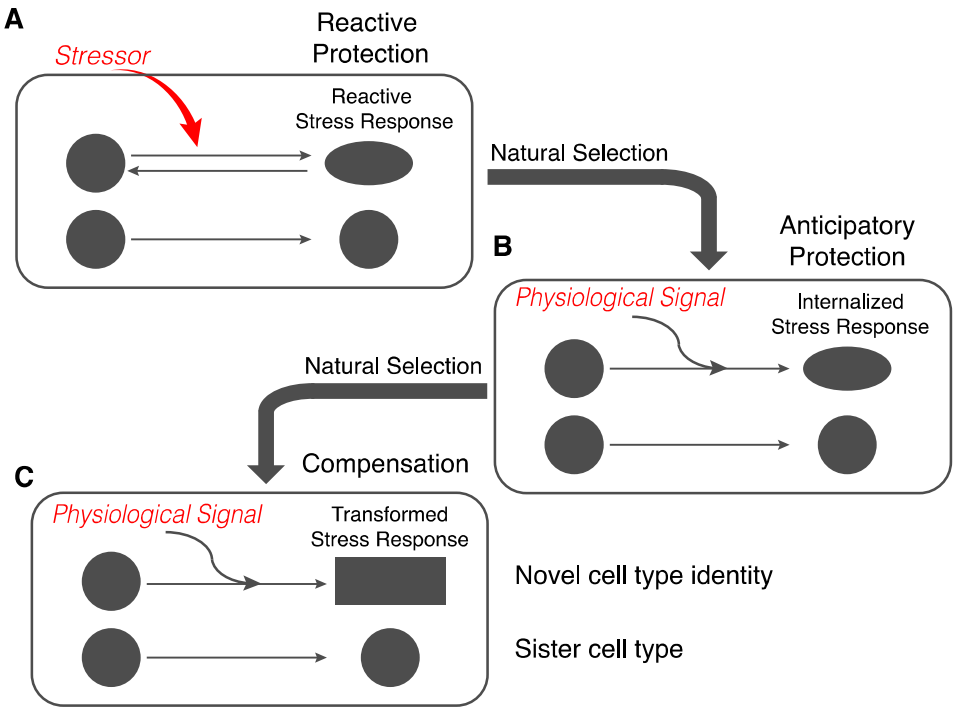

Figure 4. The model of Stress-Induced Evolutionary Innovation includes three steps. **A)** A stressor induces a generic stress response that protects the affected cells against the consequences of the stressor, such as oxidative stress. **B)** If the stress becomes frequent or predictable, then the stress reaction becomes "anticipatory protection," meaning that it is triggered by physiological signals before the stressor arrives. Note that the phenotype remains largely similar to that of the generic stress response; only the signals that elicit the response change. This is the situation we found in the opossum ESF with progesterone and prostaglandin together triggering the expression of anti-oxidant genes. One might speculate that the induction of the stress pathway by inflammatory cytokines could be an anticipatory response. **C)** Once the stress reaction is under the control of physiological rather than pathological signals, the phenotype of the affected cells can become the target of natural selection. If the stressor is routinely manifested in the life cycle of the animal, then the phenotype can evolve towards compensation. An example of this is the fact that DSCs specifically downregulate the apoptotic branch of the oxidative stress reaction [32], leading to a compensated cellular phenotype that is, to a degree, autonomous from the original stressor.

Plasticity in Evolution: Comparison of SIEI to other models

Our proposed model of SIEI is related to other models advanced to understand the role of phenotypic plasticity in evolution. We want to briefly review one of them, the plasticity first hypothesis (PFH), and then summarize the similarities and differences between PFH and SIEI.

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Models about the role of plasticity come in different flavors, including the Baldwin effect and genetic assimilation [41-43], genetic accommodation [16], and the "plasticity first hypothesis" [44,45]. Among these models, PFH is the most sophisticated and best supported empirically. Thus, we focus on it as an exemplary representative of models describing the role of phenotypic plasticity in evolution (using Levis and Pfennig 2016). According to this model (Figure 5A), the initial effect of an environmental change is to elicit a plastic response in the phenotype of individuals in the population. This response is genetically heterogeneous; individuals with different genotypes will show different responses or different degrees of plastic response. Not all of them will be equally adaptive and natural selection will eliminate genotypes exhibiting the less adaptive phenotype in the new environment. Next, there is a phase in which the more adaptive environmentally-induced phenotype is further refined by natural selection. Finally, the induced phenotype will be "assimilated" so that the development of this phenotype no longer needs the environmental stimulus; it becomes part of the "genetic heritage" of the species. There is good experimental evidence that this has occurred in nature, in particular for amphibian larvae [45].

There are two salient features of this model (Figure 5B). First, the environmental change directly induces at least an approximation of the adaptive phenotype. Hence, the role of plasticity is to (more or less) directly transform the ancestral character into a more adaptive one. Although not all individuals will be able to display the adaptive phenotype in response to the environment, this is happening in some individuals of the affected population. Second, the model explains the transformation of a character of an organism, rather than the origin of a novel character. Both of these features distinguish PFH from SIEI. The main result of an SIEI process is a novel body part, such as a cell type, that can evolve an adaptive phenotype that addresses a specific functional challenge. The main result of a PFH process is the stabilization and refinement of an adaptive, plastic character state.

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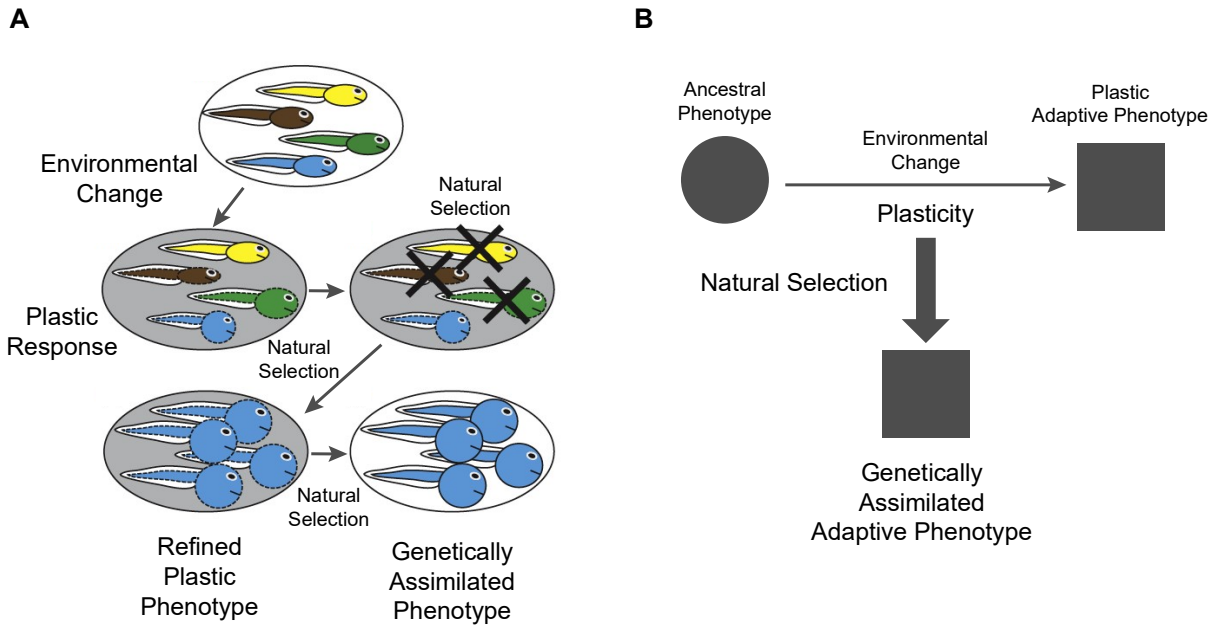

Figure 5. The plasticity first hypothesis (PFH) of adaptive evolution, modified from Figure 1 of Levis and Pfennig (2016). **A)** On the top is a population with different genotypes, indicated by different colors, and similar phenotypes (shapes). An environmental change elicits a plastic response in the phenotypes as shown here in dashed shapes. These phenotypes depend on the genotype of the individual. Since genotypes differ in their plastic responses, natural selection will select for the genotypes that have the most adaptive phenotype. The most adaptive phenotype is then further refined by natural selection, but, importantly, this phenotype is still dependent on the environment. Finally, the now refined phenotype is genetically assimilated, meaning that the environmental trigger is no longer necessary for its development, indicated here by replacing the dashed lines with solid lines. **B)** A greatly simplified schema of the structure of PFH. Plastic changes are indicated by horizontal arrow and evolution by the vertical arrow. Note that in this model the derived adaptive phenotype is more or less the immediate product of some genotype. In other words, the PFH is a model where the plastic reaction itself is producing the adaptive phenotype. The result is a transformation of the phenotype, not the origin of a novel part of the body, as in the SIEI model.

Importantly, there are similarities between PFH and SIEI. Both include environmentally-induced changes in the state of organisms, whether that be a stress response (SIEI) or a plastic adaptive phenotype (PFH). And both models postulate processes that make the induced state independent of the original stimulus: genetic assimilation of the derived plastic phenotype (PFH) and an internalized stress response (SIEI).

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Finally, there are also examples that fall somewhat between the PFH and SIEI models, such as the evolution of congenital calluses in ostriches and camels. In these cases, the derived character (the callus) is induced by the environment, like in the PFH, but it also leads to the individuation of new parts of the organism—the individual calluses at specific locations of the body—like the origin of a novel body part in SIEI. Thus, PFH and SIEI are not competing models but explain different kinds of evolutionary processes. PFH, is primarily concerned with adaptive transformations, whereas SIEI is primarily concerned with the origin of novel cell types and body parts.

Conclusions

The role of phenotypic plasticity in organismal evolution has puzzled biologists since the origin of evolutionary thought. It is now clear that phenotypic plasticity is a general biological property of most (if not all) aspects of an organism. It is also clear that evolution proceeds through a complicated interaction between natural selection and developmental processes subject to environmental plasticity. The best supported model of this kind—PFH—explains how initially plastic modifications of the phenotype can turn into genetically fixed adaptations (Levis et al., 2018). In this paper, we have described the SIEI model, which involves another potential mode of interaction between plasticity and natural selection. The SIEI model includes the hypothesis that a stress response exhibited by a group of cells in an ancestral lineage can become the target of natural selection and thereby lead to both a transformation of the stress response into an adaptive phenotype and the genetic individuation of this group of cells into a novel cell type. This model may explain the widespread correspondence between molecular mechanisms that play a role in the cellular stress response and those involved in the normal differentiation cascade of cell types. According to the SIEI model, this fact may be the footprint of an evolutionary process that transforms cellular stress reactions into developmental differentiation pathways.

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