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Abstract

Eukaryotic cells react to potentially dangerous perturbations of the intracellular or extracellular microenvironment by activating rapid (transcription-independent) mechanisms that attempt to restore homeostasis. If such perturbations persist, cells may still try to cope with stress by activating delayed and robust (transcription-dependent) adaptive systems, or they may actively engage in cellular suicide. This regulated form of cell death can manifest with various morphological, biochemical and immunological correlates, and constitutes an ultimate attempt of stressed cells to maintain organismal homeostasis. Here, we dissect the general organization of adaptive cellular responses to stress, their intimate connection with regulated cell death, and how the latter operates for the preservation of organismal homeostasis.

Introduction

One of the features that enabled life was the ability of primordial cells (or their precursor) to demarcate a portion of space within a semi-impermeable barrier, hence withdrawing themselves from the chemical and physical conditions that governed the (micro)environment while preserving a possibility to exchange molecules with it [1]. Such a partial confinement *de facto* established a primitive sort of homeostatic control, progressively allowing proto-cellular components, perhaps including ribozymes, to catalyze the first biochemical reactions and to self-propagate in an ever more controlled milieu [2]. Modern cells have evolved not only a highly refined version of that primordial barrier (the plasma membrane), but also sophisticated systems for the preservation of intracellular and extracellular homeostasis [3-6]. The pharmacological or genetic blockade of such mechanisms renders cells way more susceptible to succumb to relatively mild challenges, demonstrating that adaptive stress responses generally play crucial cytoprotective functions [4]. However, the acquisition of multicellularity (in its largest meaning) has brought about a superior need: the preservation of "supracellular" homeostasis. Thus, unicellular organisms that live in colonies, like *Saccharomyces cerevisiae*, respond to otherwise unbearable stress conditions (*e.g.*, persistent nutrient deprivation) by activating a program of cellular suicide that involves most (but not all) cells, which *de facto* provides the surviving components of the colony with substrates that may ensure their survival [7-9]. Similarly, animal and plant cells that are unable to restore cellular homeostasis by means of adaptive stress responses actively commit suicide [4, 10]. Such instances of regulated cell death (RCD) can manifest with various morphological, biochemical and immunological correlates [11-14], and constitute an ultimate attempt of stressed cells to preserve the integrity of the whole organism [15]. RCD preserves organismal homeostasis not only because it ensures the elimination of cells that have been damaged beyond recovery, but also because

(stressed and) dying cells emit a wide panel of molecules that signal locally (via paracrine circuitries) and systemically (via endocrine circuitries) the state of danger.

Here, we discuss the general organization of cellular responses to stress, their intimate connection with various forms of RCD, and how the latter contribute to the maintenance of organismal homeostasis in modern eukaryotes.

Cellular responses to stress

Modern eukaryotes are provided with a large panel of stress sensors, which constantly monitor indicators of intracellular or extracellular homeostasis, such as cytoplasmic ATP levels, growth factor availability, DNA stand breaks and oxygen tension [16, 17]. Sensors of this type are present in virtually all subcellular compartments, depending on the conditions they are capable of detecting [18, 19]. For instance, decreased ATP concentrations (which are paralleled by increased AMP levels), are sensed by the AMP-activated protein kinase (AMPK) complex, which is mostly localized to the cytosol [20, 21], whereas limited growth factor availability is detected at the outer leaflet of the plasma membrane, where various growth factor receptors are expressed [22, 23]. Stress sensors are responsible for the initiation of one or multiple signaling pathways that ultimately activate the mechanisms that execute adaptive stress responses. This can occur according to two functionally opposed paradigms. On the one hand, some sensors are constitutively turned off, and respond to perturbations of homeostasis with an increase in activity. This is the case of AMPK [20, 21]. On the other hand, some sensors are constitutively turned on, and respond to microenvironmental fluctuations with a decrease in activity. This is the case of various growth factor receptors, including the epidermal growth factor receptor (EGFR) [22, 23].

Irrespective of this distinction, stress sensors can operate at two distinct levels, generally depending on the duration of the (de)activating stimulus. On the one hand, they engage a signal transduction pathway that relies on (1) a ready-made molecular machinery, and (2) post-translational modifications only. This is important because it ensures a rapid reaction to stress. On the other hand, they initiate the synthesis of novel components of the molecular apparatus of response to stress, which is important to sustain cellular adaptation over time, if needed. Of note, such a delayed response is generally launched

along with its rapid counterpart, yet comes into action only later, unless homeostasis has been restored in the meanwhile (**Figure 1**).

The DNA damage response mediated by the serine/threonine kinase ATM and tumor protein 53 (TP53, also known as p53) well exemplifies such an organization of adaptive responses to stress. ATM is recruited to DNA double-strand breaks by a multiprotein complex including MRE11 homolog A (MRE11A), nibrin (NBN) and RAD50 homolog (RAD50), where it becomes activated by trans- and auto-phosphorylation on S1981 [24]. Among various substrates, active ATM phosphorylates TP53 on S15 and checkpoint kinase 2 (CHEK2) on T68, resulting in the CHEK2-dependent phosphorylation of TP53 on S20 [24]. Phosphorylated TP53 has reduced affinity for the E3 ubiquitin protein ligase MDM2, and hence accumulates in the nucleus in the form of transcriptionally active tetramers [25, 26]. Since cytoplasmic p53 tonically inhibits autophagy by physically interacting with RB1-inducible coiled-coil 1 (RB1CC1), the accumulation of TP53 in the nucleus has two consequences: (1) it unleashes a rapid autophagic response that is required for the optimal handling of DNA damage [27, 28], and (2) alongside, it initiates the TP53-dependent synthesis of cell cycle-arresting proteins, like cyclin-dependent kinase inhibitor 1A (CDKN1A, best known as $p21^{Cip1}$), which allow the DNA repair machinery to operate [29, 30]. If DNA can be fully repaired, the activation state and expression levels of all these proteins return to baseline conditions, and the adaptive response to stress is shut down [25].

Failing adaptation and regulated cell death

Adaptive responses to stress are not always successful, and when homeostasis is irremediably lost the cell commits suicide. Interestingly, stress-induced RCD is generally triggered by the very same sensors that detect homeostatic perturbations, implying that such sensors are not only connected to the systems that attempt to repair damage and recover homeostasis, but also to the molecular machinery that controls RCD. This also indicated that there are molecular circuitries that operate as switches and *de facto* convert a cytoprotective signal into the induction of RCD (**Figure 1**). This situation is well exemplified by the cellular reaction initiated at the endoplasmic reticulum (ER) upon the accumulation of misfolded proteins, the so-called “unfolded protein response” (UPR) [5].

One important sensor of misfolded proteins in the ER lumen is heat shock 70kDa protein 5 (HSPA5, best known as GRP78 or BIP). In physiological conditions, GRP78 binds, hence inhibiting, various signal transducers of the ER membrane, including (but not limited to) eukaryotic translation initiation factor 2 alpha kinase 3 (EIF2AK3, best known as PERK) [6, 31]. As unfolded proteins accumulate, however, they compete with EIF2AK3 for GRP78 binding, resulting in PERK activation and the consequent phosphorylation of eukaryotic translation initiation factor 2 alpha (eIF2α) in the cytosol [32]. This causes a generalized arrest of Cap-dependent translation [33], coupled to the selective translation of mRNAs bearing internal ribosomal entry sites, including the mRNA coding for GRP78 itself [34], or exploiting alternative, upstream open-reading frames (ORFs), such as the mRNA encoding activating transcription factor 4 (ATF4) [35]. A reduced rate of protein translation combined with the increased availability of GRP78 may allow for the re-establishment of reticular homeostasis, a process that is marked by the dephosphorylation of eIF2α and by the restoration of normal ATF4 levels [36]. Of note, eIF2α dephosphorylation is also required for failing UPRs to emit an RCD-inducing

signal [37]. In the latter case, however, the levels of ATF4 and other UPR-activated transcription factors like DNA-damage-inducible transcript 3 (DDIT3, best known as CHOP) remain elevated, resulting in overwhelming protein synthesis in the presence of dephosphorylated eIF2α [38].

Interestingly, cellular stress sensors generally dispatch signals that actively inhibit RCD as cells attempt to restore homeostasis. However, when adaptation fails, such signals cease and cells succumb to RCD. Two models have been proposed to explain this phenomenon [39]. One possibility is indeed that stress sensors dispatch both RCD-inhibiting and RCD-inducing signals as soon as they are activated, and the latter overcome the former when adaptation fails. Another possibility is that stress sensors initially deliver only RCD-inhibiting signals, and when adaptation fails these are substituted by their RCD-promoting counterparts (**Figure 2**). Experimental arguments in clear favor of one model over the other are missing, and most likely they both apply (at least to some degree) in specific circumstances. Irrespective of the mechanisms whereby failing adaptation to stress initiates RCD, this also constitutes an adaptive response, but at the organismal level.

Regulated cell death and organismal homeostasis

Cells in which adaptive stress responses have failed are damaged beyond recovery, and must be eliminated because (1) they have probably lost their function, and/or (2) they may constitute a threat to the entire organism. For instance, cells with unrepaired DNA are prone to accumulate somatic mutations as they divide, thereby standing at risk for malignant transformation [40]. It is therefore not surprising that cells from higher eukaryotes have evolved the capacity to commit suicide for the sake of organismal homeostasis [15]. However, this is not the only way whereby the transition from the adaptive arm of stress responses to the activation of RCD contributes to the maintenance of the entire organism. Indeed, both stressed and dying cells emit a large panel of signals that alert other cells of danger, including various cytokines and so-called "damage-associated molecular patterns" (DAMPs) [41-43].

This concept is well exemplified by viral infection. Virtually all cells respond to cytosolic double-stranded RNA and other nucleotides of microbial origin by producing elevated amounts of type I interferon (IFN) [44]. By binding to homodimeric or heterodimeric receptors on hitherto unaffected cells, type I IFN renders them relatively resistant to infection, hence exerting a crucial cytoprotective effect [44]. Moreover, type I IFN stimulates the synthesis of chemoattractants for T lymphocytes, such as chemokine (C-X-C motif) ligand 10 (CXCL10) [45]. After such a wave of type I IFN synthesis, infected cells often commit suicide, hence interrupting the viral cycle and limiting viral dissemination [46]. Moreover, cells succumbing to infection release several DAMPs, including ATP, mitochondrial DNA and the non-histone chromatin-binding protein high-mobility group box 1 (HMGB1) [47-49]. Altogether, these factors promote the activation of various myeloid and lymphoid cell populations, hence boosting the immunological protection of the entire organism against viral infection [50, 51]. Thus, RCD contributes to the maintenance of organismal homeostasis in response to viral infection in

several ways. Accordingly, several viruses have evolved strategies to manipulate the machinery that controls RCD to their benefit [46].

Conclusions and perspectives

Eukaryotic cells respond to stress by activating various systems that attempt to repair damage and restore cellular homeostasis while preventing RCD. When such responses fail, cells damaged beyond repair actively undergo RCD, which constitutes a mechanism for the maintenance of organismal homeostasis. It is becoming increasingly clear that preventing the regulated demise of post-mitotic cells is a difficult therapeutic objective [39]. Patients with ischemic or traumatic disorders, indeed, are generally treated hours after the initial perturbation of homeostasis, when a majority of affected cells have irremediably committed to die. Therapeutic interventions should therefore aim at protecting neighboring cells, which are still in the adaptive phase of the stress response, and/or at controlling the signals emitted by affected cells as they die [51, 52]. Such a therapeutic paradigm may maximize the benefit that ischemia and trauma patients obtain from treatment.

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Legends to Figures

Figure 1. **General organization of stress responses in modern eukaryotes.** Eukaryotic cells generally respond to perturbations of intracellular or extracellular homeostasis by simultaneously activating a rapid mechanism of adaptation, relying on ready-made components and post-translational modifications, as well as a transcription-dependent system, which comes into action, if needed, to support adaptation over time. Alongside, stress sensors also dispatch signals that inhibit regulated cell death (RCD). If adaptation fails and homeostasis cannot be recovered, however, the signals dispatched by stress sensors become lethal, and cells undergo RCD.

Figure 2. **Alternative models for the transition between the adaptive and lethal phase of stress responses.** At least theoretically, failing stress responses can result in the activation of regulated cell death (RCD) via two mechanisms. **A.** Stress sensors initially dispatch RCD-inhibiting as well as RCD-promoting signals, and RCD intervenes when the latter overcome the former. **B.** Stress sensors initially dispatch RCD-inhibiting signals, which cease as adaptation fails. Alongside, stress sensors become able to dispatch RCD-promoting signals, which eventually cause RCD.

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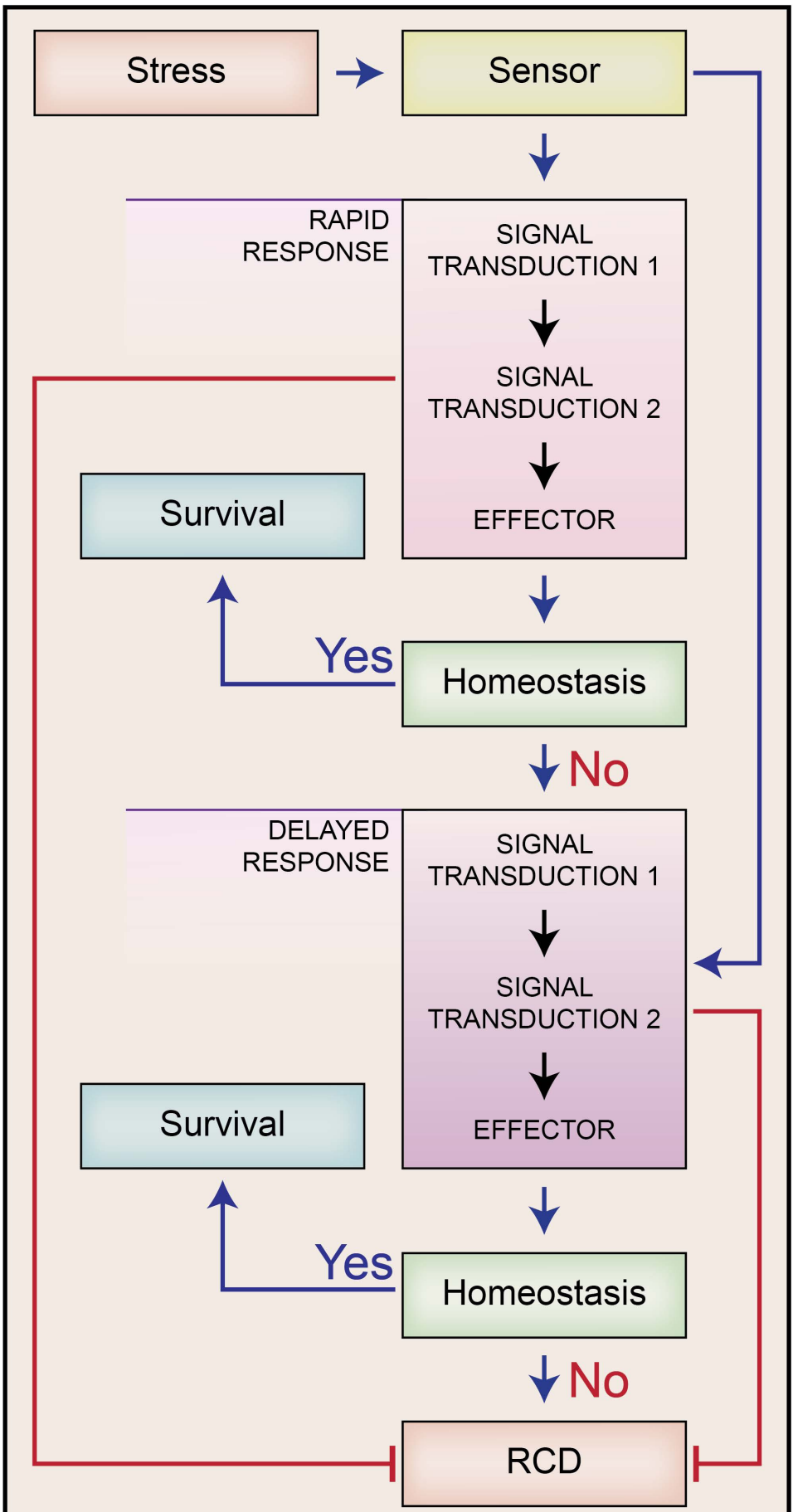
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EFFECTOR
Survival
Yes
Homeostasis
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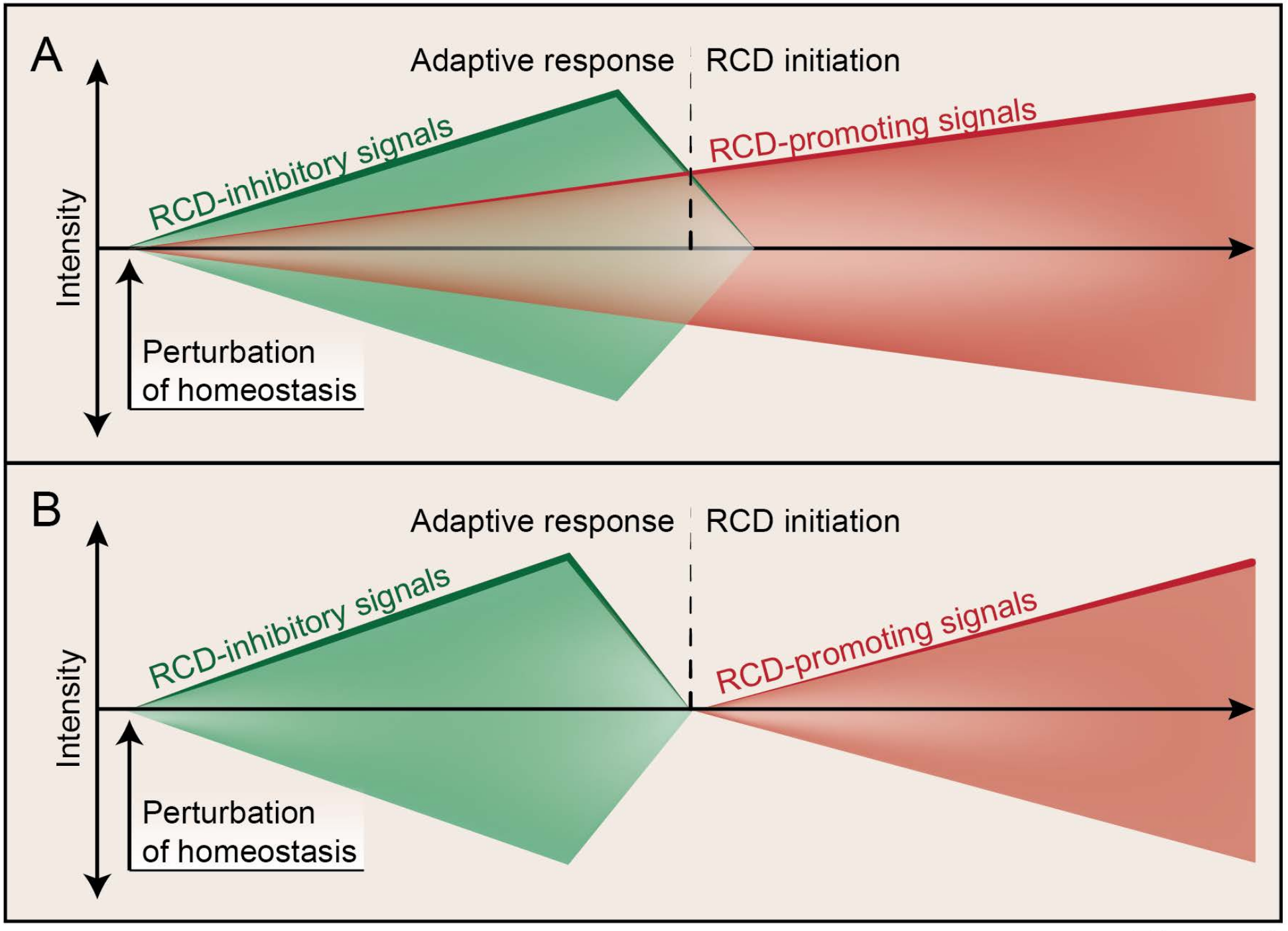
SIGNAL TRANSDUCTION 2
EFFECTOR
Survival
Yes
Homeostasis
No
RCD

Figure 1


A
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Intensity
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B
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Intensity
Perturbation
of homeostasis

Figure 2