

# Stress, Inflammation, and Defense of Homeostasis

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Inflammation is traditionally considered a defense response induced by infection or injury. However, inflammation can also be induced by tissue stress and malfunction in the absence of infection or overt tissue damage. Here we discuss the relationship between homeostasis, stress responses, and inflammation. Stress responses have cell-autonomous and cell-extrinsic components, the latter contributing to tissue level adaptation to stress conditions. Inflammation can be thought of as the extreme end of a spectrum that ranges from homeostasis to stress response to bona fide inflammatory response. Inflammation can be triggered by two types of stimuli: extreme deviations of homeostasis or challenges that cause a disruption of homeostasis. This perspective may help to explain qualitative differences and functional outcomes of diverse inflammatory responses.

## Introduction: Homeostasis, Homeostatic Range, and Stress Responses

Homeostasis is a fundamental property of biological systems. It preserves their stability by maintaining key regulated variables within an acceptable range (Buchman, 2002). It operates at the level of the entire organism, within tissue compartments, and within individual cells. Homeostasis is best characterized at the level of the whole organism (systemic homeostasis). Here, regulated variables are well defined and include blood levels of glucose, Na<sup>+</sup>, Ca<sup>2+</sup>, and O<sub>2</sub>, blood pH and osmolarity, and core body temperature (Table 1). These variables are maintained within an acceptable dynamic range by the endocrine and autonomic nervous systems.

Tissue homeostasis has yet to be defined in terms of its regulated variables, but examples of these variables include cell number and cell composition per tissue compartment, tissue architecture (cell positioning, cell-cell interactions, and extracellular matrix abundance and composition), integrity of structural components (e.g., cell junctions and basement membrane), concentrations of O<sub>2</sub>, nutrients, and metabolic end products (e.g., CO<sub>2</sub> and urea), as well as volume, pH, temperature, and osmolarity of interstitial fluids (Table 2).

Cellular homeostasis maintains a number of regulated variables including cell volume, osmolarity, electrolyte concentration (e.g., Na<sup>+</sup>, K<sup>+</sup>, and Cl<sup>-</sup> concentrations), pH, membrane potential, and concentrations of intracellular ions, proteins, nutrients, cholesterol, oxygen, and reactive oxygen species (ROS) (Table 3).

In each of these cases and at all levels (systemic, tissue, and cellular), the regulated variables have a characteristic dynamic range that is maintained by homeostatic control systems. When regulated variables change beyond the dynamic range (as a result of external perturbations and insults), the system engages in a stress response that aims to restore homeostasis (Goldstein and Kopin, 2007).

In order to maintain homeostasis, specialized sensors constantly monitor the values of regulated variables. In systemic homeostasis these sensors include endocrine cells and sensory neurons (Table 1). In cellular homeostasis the sensors are signaling proteins that detect alterations in various core pro-

cesses, such as protein folding, levels of ROS, and nutrient availability (Table 3). Given the large number of regulated variables in cellular homeostasis, additional stress response pathways may be uncovered in the future. In principle it can be predicted that sufficient disruption in homeostasis of each regulated variable should elicit a corresponding stress response.

In tissue homeostasis the sensors for most regulated variables have not been studied and for the most part are unknown. It is not known, for example, how compartment size is sensed, how cell number and composition are measured, and how changes in the extracellular matrix (ECM) are monitored, even though it is clear that all these parameters are tightly controlled (Table 2). The only known sensors of tissue homeostasis are specialized in detecting extreme challenges such as infection and tissue injury. These sensors include tissue resident immune cells (particularly macrophages and mast cells) as well as somatosensory neurons (e.g., C-fiber nociceptors). Indeed, emerging evidence suggests that macrophages and C-fiber nociceptors may monitor and control tissue homeostasis not only at the extremes of infection and injury, but also during more common and less dramatic alterations of normal tissue states (Ahern, 2013; Basbaum et al., 2009; Mosser and Edwards, 2008; Nguyen et al., 2011; Pollard, 2009; Tracey, 2009).

Although it is well appreciated that both inflammatory and stress responses are protective reactions that defend homeostasis, the relationship between them is ambiguous. They can be viewed as distinct but overlapping components of a spectrum of system states (homeostatic state, stress response state, inflammatory state), each of which can be defined in terms of the maintenance of regulated variables. The system (organism, tissues, cells) is in a homeostatic state when the values of regulated variables are within an acceptable dynamic range. When the homeostatic capacity is insufficient to maintain these values, (e.g., due to external perturbations), a stress response is engaged. If the stress response is insufficient to defend homeostasis, an inflammatory response is induced. Both stress response and inflammation are engaged to eliminate the stressor (i.e., the source of perturbation), to promote adaptations to the stressor, and ultimately to return the system to the homeostatic state (Figure 1).

**Table 1. Representative Regulated Variables and Sensors in Systemic Homeostasis**

Regulated Variable	Sensor
Blood pressure/blood volume/Na <sup>+</sup> concentration	Aortic body (aorta), carotid body (carotid artery), atrial volume receptors (heart), juxtaglomerular apparatus (kidney)
Ca <sup>2+</sup> /Mg <sup>2+</sup> /PO <sub>4</sub> <sup>3-</sup> concentrations	Chief cells (parathyroid gland)
Glucose	Islet of Langerhans (pancreas)
Osmolarity	Circumventricular organs (hypothalamus)
pO <sub>2</sub> , pCO <sub>2</sub> , and pH	Aortic body (aorta), carotid body (carotid artery), ventrolateral medulla (medulla)
Temperature	Thermosensory neurons (skin), preoptic area (hypothalamus)

See also Costanzo (2010).

The stress and inflammatory responses can also be distinguished by the conditions that induce them. There are principally two types of stimuli eliciting these responses: the first is an extreme deviation of regulated variables from normal values, and the second is a challenge that can *cause* deviation of regulated variables but is not itself a regulated variable. Challenges in the latter category include infections, allergens, toxins, and noxious xenobiotics, all of which disrupt homeostasis and need to be sensed to elicit a protective response that aims to ultimately restore homeostasis. To distinguish between the two scenarios, we will refer to the first as a *stress response* and the second as a *defense response* (Figure 2). From this perspective the responses induced by hypoxia and heat shock, for example, are stress responses, whereas responses induced by pathogens, toxins, and tissue damage (i.e., the immune response, detoxification response, and tissue repair response) are defense responses. Stress responses are elicited by sensors (such as HIF-1 $\alpha$  and HSF-1) that monitor regulated variables (oxygen and protein folding state, respectively). Defense responses are elicited by sensors that are specialized in detecting insults that can disrupt homeostasis. Thus, pattern recognition receptors (PRRs) and xenobiotic sensors directly detect infection and noxious chemicals, respectively. Some insults, however, cannot be detected directly, because they are too diverse and unpredictable. These include most toxins and poisons as well as the majority of allergens. Sensing mechanisms in these cases are not defined but may include detection of unique noxious activ-

ities, such as disruption of tight junctions, proteolysis of ECM components, and inflammasome activation.

### Functional Categories of Stress Response Genes

The sensing mechanisms, signaling pathways, and gene expression programs controlling cellular homeostasis are well characterized. Functionally, stress response gene products can be divided into two categories depending on whether they are involved in the elimination of a stressor or in adaptation to a stress condition (Table 4). For example, gene products involved in degrading unfolded proteins, scavenging ROS, and repairing DNA damage are effectors of the stress response involved in elimination of a stressor. Stress conditions also often require specific cellular adaptations so as to minimize their negative impact: thus the unfolded protein response (UPR) not only triggers elimination of misfolded proteins but also suppresses new protein synthesis and promotes expression of chaperones to help prevent protein misfolding (the adaptation response). The genes involved in adaptation to stress are especially important when stress conditions are chronic, as is seen in long-term infection (Tabas and Glass, 2013), or when stress conditions are a normal part of specialized cellular function. For example, cells with a very high secretory demand, such as plasma cells and various exocrine and endocrine cells, experience a chronic ER stress response (Garrett et al., 2010), while kidney tubular epithelial cells experience continuous osmotic stress (Neuhofner and Beck, 2005). Consequently, these cell types develop specialized features that promote adaptation to chronic stress conditions by constitutive expression of stress-adaptation genes. In some cases the distinction between elimination and adaptation responses is less straightforward: osmotic stress triggers changes in expression of aquaporins and electrolyte transporters, and these gene products both eliminate the stressor and promote adaptation to the given stress.

### Cell-Intrinsic and Cell-Extrinsic Stress and Defense Responses

Most of what is known about cellular stress and defense responses has to do with cell-autonomous (cell-intrinsic) mechanisms of stressor elimination and stress adaptation. However, there is an equally important non-cell-autonomous (cell-extrinsic) response containing two functional gene categories. The first category of gene products regulates the extracellular compartment (e.g., ECM remodeling, cell positioning, cell-ECM contact, and cell-cell contact). Genes in the second category

**Table 2. Examples of Regulated Variables of Tissue Homeostasis**

Regulated Variable
Cell number per compartment
Cell composition (ratios of different cell types)
Cell-cell interactions
Cell positioning
ECM composition and abundance
Levels of oxygen
Levels of nutrients
Levels of metabolic waste products
Volume of interstitial fluid
pH of interstitial fluid
Electrolyte composition of the interstitial fluid
Osmolarity of interstitial fluid

**Table 3. Representative Stressors and Sensors in Cellular Homeostasis**

Stressor	Sensor
Amino acid deprivation	ATF4, mTOR (Kroemer et al., 2010; Rutkowski and Kaufman, 2003)
ATP depletion	AMPK (Sengupta et al., 2010)
ER stress	ATF6, IRE-1 $\alpha$ /XBP-1, PERK/eIF-2 $\alpha$ (Cao and Kaufman, 2012)
Genotoxic stress	p53 (Reinhardt and Schumacher, 2012)
Glucose deprivation	CHREBP (Postic et al., 2007)
Heat shock	HSF-1 (Anckar and Sistonen, 2007)
Hypoxia	HIF-1 $\alpha$ (Weidemann and Johnson, 2008)
Osmotic stress	NFAT5 (Aramburu et al., 2006)
Oxidative stress	NRF2 (Nguyen et al., 2009)
Viral infection	Receptors signaling through IRF3 (Holm et al., 2013)
Xenobiotic stress	AHR, CAR, PXR (Pascucci et al., 2008)
General environmental stress (including infection)	Receptors signaling through NF- $\kappa$ B and MAPKs (ERK, JNK, p38) (Takeuchi and Akira, 2010; Wagner and Nebreda, 2009)

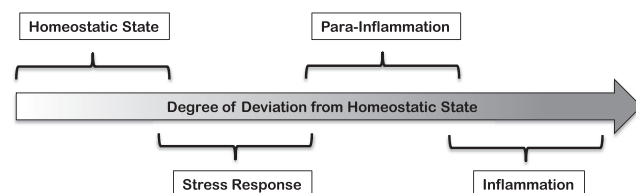
are likely involved in paracrine communication to neighboring cells, though for the most part, these genes have not been functionally defined in the context of a stress response. Most stress conditions affect populations of cells in a given compartment, rather than just individual cells. When one cell in a population is exposed to a given challenge (e.g., hypoxia or nutrient deprivation), it is likely that other cells in the same compartment will be exposed to it as well. Because of that, cells under stress produce signals that alert other cells in the vicinity to the presence of the stressor. These signals may function to induce pre-emptive responses in cells that have not yet been exposed to the challenge, making them adapt more efficiently. A well-known example of this phenomenon is provided by the antiviral defense response: virally infected cells produce type 1 interferons (IFNs) that act on neighboring cells to induce an antiviral state (Honda and Taniguchi, 2006; Levy et al., 2011).

Cell-extrinsic stress and defense responses also afford tissue-level adaptations to a challenge—adaptations that cannot be achieved at the level of individual cells. For example, hypoxia not only induces cell-autonomous adaptations, such as induction of glucose transporters and a switch to anaerobic glycolysis, but it also promotes tissue-level adaptations, such as angiogenesis, induced by cell-extrinsic signals like VEGF and other angiogenins (Shweiki et al., 1992). In this case both cell-intrinsic and -extrinsic components of the hypoxia response are induced by the same sensor, HIF-1 $\alpha$ . The cell-extrinsic stress response has many overlapping components with the tissue-level stress

response, though the two are not equivalent when the regulated variables affected under cellular versus tissue-level stress conditions are distinct. However, the cell-extrinsic response does induce tissue level adaptation to stress, as illustrated most clearly by the induction of angiogenesis upon hypoxia.

Another notable example of a cell-extrinsic stress response is the so-called radiation-induced bystander effect, in which irradiated cells induce an irradiated phenotype in nearby, untreated cells (Mothersill and Seymour, 2004). However, the signals that communicate this information are still unknown. The best available characterization of cell-extrinsic stress responses has been provided by studies in *C. elegans*, where there is evidence for systemic adaptations to cellular heat shock, oxidative stress, and genotoxic stress that are communicated either through sensory neurons or soluble factors (Durieux et al., 2011; Ermolaeva et al., 2013; Prahlad et al., 2008).

It is likely that every type of cellular stress and defense response has a cell-extrinsic component even though most have not been characterized. Indeed, global gene expression analysis indicates that various forms of stress induce large numbers of genes whose products are either known or predicted to have extracellular functions, including many secreted proteins (Table 5). Though the functions of most of these genes in the context of cellular homeostasis are unknown, they likely operate in either the extracellular compartment or a paracrine manner to induce tissue-level adaptations to stress.

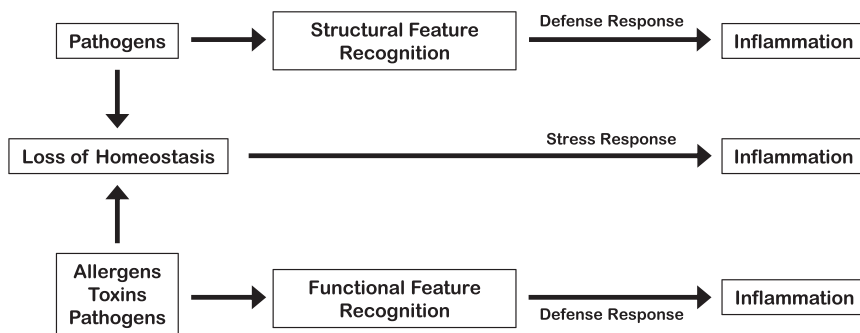


**Figure 1. An Inflammatory Spectrum**

An inflammatory response is an extreme end of the spectrum that ranges from homeostatic state to stress response, para-inflammation, and finally inflammation.

### Tissue-Level Stress Response and Para-Inflammation

While most cells can detect disruptions of tissue homeostasis, this function is performed most efficiently by specialized sensory cells, such as tissue-resident macrophages, mast cells, and sensory neurons (Figure 3). Thus, pathogen sensing is primarily delegated to macrophages (Gordon, 2007), but in addition, macrophages may also play a role in sensing more generic stressors, such as hypoxia and metabolic stress (i.e., deficit or excess in key metabolites) (Allavena et al., 2008). Macrophages are well known to produce cytokines when they sense pathogens or VEGF when they sense hypoxia, but they likely also sense other types of stressors and produce corresponding signals to



**Figure 2. Stress and Defense Response Components of Inflammation**

Inflammation can be induced by sensing extreme deviations from tissue homeostasis or by sensing the challenges that can cause extreme deviations of tissue homeostasis. The former are detected by sensors of regulated variables of cellular and tissue homeostasis. The latter can be induced upon direct recognition of structural features of agents that can disrupt tissue homeostasis (e.g., PAMP recognition by PRRs) or by detecting their conserved functional features, such as protease activity or chemical reactivity.

orchestrate tissue-level defenses and adaptations. Similarly, sensory neurons are specialized in sensing various stressors including cold and hot temperature, reactive chemicals, low pH, etc., through the use of molecular sensors such as TRP and ASIC channels (Venkatachalam and Montell, 2007). C-fiber nociceptors locally produce CGRP and Substance P upon activation by these stressors, and these neuropeptides coordinate local stress adaptations known as neuro-inflammation (Julius and Basbaum, 2001).

Similar to cellular stress and defense responses, which can be cell autonomous but may also involve cell-extrinsic components, tissue-level stress and defense responses can be tissue autonomous and/or may engage tissue-extrinsic help. These tissue-extrinsic responses involve recruitment of specialized cells either from other locations within the tissue (e.g., tissue-resident macrophages) or from the circulation (e.g., blood monocytes). Indeed, chemokines are one common component of the extracellular response to different stressors (Hitchon et al., 2002; Kanda et al., 2006; Qian et al., 2011). Tissue-extrinsic responses are particularly important when tissue-autonomous responses are insufficient to resolve the insult. They also share many features with the inflammatory response. Therefore, inflammation can be viewed as a more extreme version of the tissue-level stress response. Because the tissue-level stress response is not equivalent to the classical acute inflammatory response in that it does not necessarily involve exudate formation and neutrophil recruitment, we refer to it here as *para-inflammation* (Medzhitov, 2008). There are many examples of conditions that fall under the definition of para-inflammation in that they are clearly not normal, and yet do not include all the hallmarks of inflammation. These include aging-associated inflammation

(Goto, 2008), including age-related macular degeneration (Parmeggiani et al., 2012), as well as inflammation caused by metabolic stress, including obesity (Gregor and Hotamisligil, 2011; Odegaard and Chawla, 2013). The tissue-level stress response and para-inflammation are engaged when the level of stress is greater than what can be managed by cellular homeostatic mechanisms (as described above). However, if the level of stress is greater still, for example due to infection or tissue injury, these responses also become insufficient and a bona fide inflammatory response ensues (Figure 1).

### Inflammation

The inflammatory response is engaged when tissue-autonomous defenses are insufficient or overwhelmed. The acute inflammatory response relies upon specialized cell types (neutrophils, monocytes, eosinophils, and basophils) that are typically recruited from the circulation. The sensory cells involved in initiating the inflammatory response are the same as the ones involved in tissue-level stress and defense responses: tissue-resident macrophages, mast cells (in some tissues), and sensory neurons (mainly nociceptors). These sensory cells detect noxious insults (pathogens, toxins, irritants, etc.) either directly (e.g., through PRRs) or indirectly through their effect on tissue homeostasis (e.g., by sensing unscheduled cell death, ECM degradation products, tissue damage, etc.) (Medzhitov, 2010). Thus, according to the definition introduced above, inflammation has both a stress response component and a defense response component (Figure 2).

First, inflammation can be induced as a result of extreme deviations in regulated variables of cellular and tissue homeostasis (i.e., the stress response component of inflammation). Thus,

**Table 4. Elimination and Adaptation Responses in Cellular Homeostasis**

Stressor	Elimination Response	Adaptation Response
Amino acid deprivation	Induction of amino acid transporters	Autophagy
ER stress	Degradation of unfolded proteins	Stabilization of misfolded proteins, elimination of nonessential translation, expansion of ER compartment
Genotoxic stress	Induction of DNA repair mechanisms	Cell-cycle arrest
Glucose deprivation	Induction of glucose transporters	Use of alternative fuel sources (e.g., amino acids, lipids)
Heat shock	Degradation of unfolded proteins	Stabilization of misfolded proteins
Hypoxia	Angiogenesis	Shift to anaerobic glycolysis
Osmotic stress	Induction of aquaporins and electrolyte transporters	Induction of aquaporins and electrolyte transporters
Oxidative stress	ROS scavenging	ROS scavenging

**Table 5. Predicted Gene Products of the Cell-Extrinsic Stress Response in HeLa Cells**

Stressor	Gene Category	Secreted/Extracellular Gene Product
ER stress	Chemokine	CXCL3
	Cytokine	AIMP1, IL17RB, ISG15, LIFR, LTBP1
	ECM structural component	ADAMTSL3, COL1A2, LAMC1, NUCB2, STC2
	ECM signaling component	DKK1, FRZB, GPC3, LRCH3
	Effector enzyme	ADAM23, ARSJ, KLK11, LIPG, MMP16
	Growth factor/hormone	BMP8A, EPO, GDF15, IGFBP7, INHBA
Glucose deprivation	Chemokine	CCL20, CXCL2, CXCL3, IL8
	Cytokine	IL1A, IL6, IL11, IL18
	ECM structural component	COL5A1, CRELD2, LAMB3, MEGF6, NUCB2
	ECM signaling component	DKK1, GPC5, WNT10B
	Effector enzyme	ANG, LNPEP, LOX, LOXL2, RNASE4
	Growth factor/hormone	EGFR, GDF15, HBEGF, IGFBP3, INHBA
Heat shock	Chemokine	CCL5, CXCL9
	Cytokine	AIMP1, IL6ST, IL11, IL33, LIFR
	ECM structural component	ADAMTSL1, COL21A1, CRISP3, LAMA3, STC2
	ECM signaling component	GPC3, GPC4, LYPD6, RSPO3, WIF1
	Effector enzyme	ADAMTS5, GZMA, LOX, MMP19, PLBD1
	Growth factor/hormone	FLT3LG, HBEGF, IGF1, INHBA, EPO
Hypoxia	Chemokine	CCL2, CCL28, CXCL12, CXCL14, CXCL17
	Cytokine	IFNA1, IFNB1, IL1A, IL17A, IL33
	ECM structural component	COL2A1, CRISP3, LAMA2, MUC1, STC1
	ECM signaling component	DKK2, GPC6, RSPO1, SFRP1, WNT6
	Effector enzyme	ADAM12, ANG, ARSF, LOX, MMP11
	Growth factor/hormone	ANGPT4, ANGPTL1, GDF15, IGFBP1, INHBA
Oxidative stress	Chemokine	CCL15, CCL16
	Cytokine	CD109, FAM3C, ISG15
	ECM structural component	COL9A2, CRISPLD1, HSPG2, MMRN2, THSD4
	ECM signaling component	NXPH2, WNT5B
	Effector enzyme	ADAMTS5, KLK5, MMP16, PLBD1
	Growth factor/hormone	IGF2, INHBA, INSL6, VIP

Analysis performed on previously published gene expression data (Mense et al., 2006; Murray et al., 2004; Page et al., 2006; Saito et al., 2009). Briefly, gene expression data were obtained from the NCBI GEO database and sorted for gene products exhibiting greater than or equal to 2-fold induction. The relevant genes were then analyzed using NIAID DAVID Bioinformatics Resources 6.7 software. Genes were sorted by extracellular and secreted functional categories, and representative genes are displayed in the table.

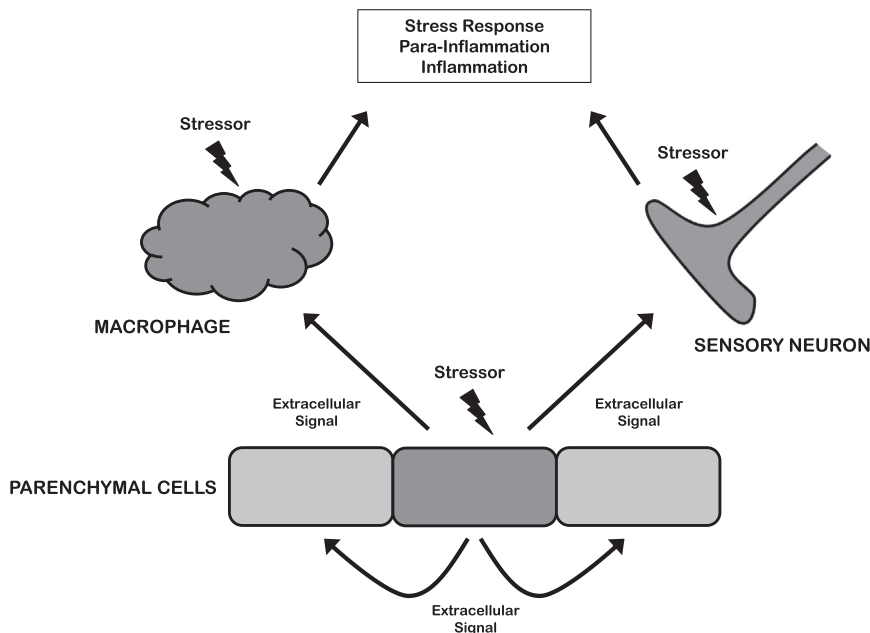
inflammation is at the extreme end of the spectrum of adaptive responses aimed to protect tissue homeostasis. Second, inflammation can be induced by agents that cause disruption of tissue homeostasis, including pathogens, toxins, and xenobiotics (i.e., the defense response component of inflammation). These agents can be sensed using two strategies: a direct mechanism, which relies upon recognition of structural features, or an indirect mechanism, which relies upon recognition of functional features.

Whenever possible, direct recognition of the disruptive agent is used to elicit the inflammatory response, even before it has a chance to cause any harm. PRRs of the innate immune system are the most prominent example of this sensing mechanism. Sensing bacterial lipopolysaccharide (LPS), for example, will elicit an inflammatory response even though LPS by itself does not cause disruption of homeostasis. The rationale for such response is that the presence of LPS in normally sterile tissues

signifies the presence of pathogens that can disrupt homeostasis and cause tissue damage. Thus, the strategy of direct recognition can detect an agent before it can cause any harm; its recognition can be dissociated from the negative consequences of its presence. As such, LPS can cause an inflammatory response regardless of whether it is present in the context of a pathogen or not.

The second strategy of recognition is used for agents that can cause disruption of homeostasis or tissue damage but cannot be sensed directly. This category includes many allergens, toxins, and poisons. These agents are sensed through recognition of functional features, such as characteristic enzymatic activity, membrane pore formation, or chemical conjugation (adduct formation). Thus, some noxious stimuli can be sensed by TRP channels on nociceptor neurons. For example, TRPA1 can detect many noxious chemicals, including formalin, acrolein





**Figure 3. Cell-Autonomous and Non-Cell-Autonomous Responses**

Cellular stress and defense responses have two components: cell autonomous (i.e., intrinsic) and non-cell autonomous (i.e., extrinsic). The former controls intracellular adaptations, while the latter modifies the extracellular environment or communicates to neighboring parenchymal cells. Stress signals also act directly on specialized cells such as macrophages and sensory neurons. These “professionals” are able to detect stress at a lower threshold than parenchymal cells, and they produce cytokines and growth factors to promote restoration of function. Stressed parenchymal cells also communicate with the specialized sensory cells through largely unknown paracrine factors.

(tear gas), isothiocyanates (mustard, horseradish, and wasabi oils), allicin (garlic), and cinnamaldehyde (cinnamon), through sensing of shared functional chemical features such as highly reactive electrophile groups (Bautista et al., 2013; Venkatchalam and Montell, 2007). The NLRP3 inflammasomes, on the other hand, monitor membrane integrity and can sense pore-forming toxins, crystals, and many other noxious stimuli (Rathinam et al., 2012). Similarly, many allergens are sensed by detection of their enzymatic activities or other functional features (Palm et al., 2012). In all these cases, functional feature recognition is coupled with the induction of a defensive inflammatory response that promotes adaptation and elimination of the noxious stimulus. In addition, this strategy of sensing is also used by nociceptors to trigger noninflammatory protective responses to low levels of noxious stimuli before they can cause much damage.

### Conclusions and Perspectives

Inflammation has traditionally been considered to be a defense response induced by infection or injury. It is increasingly appreciated, however, that chronic inflammation can accompany many pathological states without infection or injury, such as in adipose tissue of obese humans and animals (Hotamisligil, 2010). It has been shown, for example, that when the fat storage capacity of adipocytes is exceeded, an ER stress response is initiated, resulting in production of inflammatory cytokines, a condition referred to as metabolic inflammation (Hotamisligil, 2006). Recent findings along these lines increasingly suggest a close connection between inflammatory and stress responses, though the nature of that relation remains somewhat ambiguous. Here we suggest two perspectives to address this issue.

Inflammation can be viewed as the end of the spectrum of mechanisms that maintain and defend homeostasis. This spectrum is formed by homeostatic mechanisms that operate under

normal conditions: stress and defense responses that are engaged when homeostatic capacity is insufficient; para-inflammation, a tissue-level stress response that has some but not all of the characteristics of inflammation; and finally inflammation proper, which is induced when other mechanisms are insufficient or incapable to maintain homeostasis.

We distinguish two types of stimuli that can induce inflammation. The first are extreme deviations of regulated variables, which cannot be handled by homeostatic mechanisms. This type of inflammation is an extension of a stress response. The second are stimuli (including pathogens, toxins, and allergens) that are not regulated variables themselves but can affect regulated variables, thereby disrupting homeostasis. These agents can be sensed either directly through structural feature recognition, as is the case with pattern recognition, or indirectly through their functional features, such as enzymatic activities and disruption of membrane integrity. The inflammatory responses induced by the two types of stimuli are presumably qualitatively distinct. Inflammation induced by deviation of regulated variables is likely to contain homeostasis-restoring components, inflammation induced by infection is coupled with induction of antimicrobial immune responses, and inflammation induced by tissue damage involves a tissue reparative component. Future mechanistic studies should define these distinct components and their contribution to defense of homeostasis and inflammatory pathologies.

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