Tissue Damage Control in Disease Tolerance

Miguel P. Soares, Raffaella Gozzelino and Sebastian Weis
Instituto Gulbenkian de Ciência, Oeiras, Portugal

Correspondence to mpsoares@igc.gulbenkian.pt

Keywords: Tissue damage control, disease tolerance, stress-response, damage-response, infection.

ABSTRACT

Immune driven resistance mechanisms are the prevailing host defense strategy against infection. In contrast, disease tolerance mechanisms limit disease severity by preventing tissue damage or ameliorating tissue function without interfering with pathogen load. Here we propose that tissue damage control underlies many of the protective effects of disease tolerance. We explore the mechanisms of cellular adaptation that underlie tissue damage control in response to infection as well as sterile inflammation, integrating both stress and damage responses. Finally, we discuss the potential impact of targeting these mechanisms in the treatment of disease.

INTRODUCTION

Immunity refers to the inherent ability of any given organism to protect itself from disease and more specifically from infectious diseases. The immune system is part of an evolutionarily conserved host defense strategy against infection that recognizes, destroys and/or expels invading pathogens. Host resistance to infection refers to this immune-driven defense strategy, which carries a negative impact on pathogens. This is distinct from antimicrobial resistance, which refers to the pathogen's capacity to evolve towards becoming refractory to the detrimental effects imposed by host resistance mechanisms or by antimicrobial agents.

It is widely accepted that immune-driven resistance mechanisms are the prevailing, if not the only, host defense strategy against infections. This notion is strongly supported by the overwhelming success of medical interventions targeting resistance mechanisms, in terms of reducing the global burden imposed by infectious diseases on mankind[1]. This is illustrated by vaccination, where pre-emptive induction of immune-driven host resistance mechanisms provides robust and often long-lasting protection against

infectious diseases. Another related and highly successful therapeutic approach consists in the use of antimicrobial drugs, e.g. antibiotics, which can be perceived as providing pharmacologic-driven resistance as the means to limit the severity of infectious diseases.

In some instances however, immune- and/or pharmacologic-driven resistance mechanisms are not sufficient *per se* to prevent morbidity and/or mortality associated with infectious diseases, regardless of their capacity to exert a negative impact on pathogens. Moreover, microorganisms can evolve resistance mechanisms against host immunity[2] as well as against antimicrobial drugs and produce compounds[3] that increase their virulence[2]. These factors may in part explain why in some cases therapeutic approaches targeting resistance mechanisms fail to overcome the morbidity and mortality of infectious diseases such as: i) severe forms of malaria associated with *Plasmodium* infection, i.e. 600,000 deaths/year[4], ii) severe sepsis associated with polymicrobial infections, i.e. 750,000 cases/year in the US alone[5] or iii) respiratory infections such as pneumonia, associated with *influenza* virus infections, i.e. 500,000 deaths/year[6], among others. We will argue that in these and probably other cases, a second host defense strategy may play a major role in limiting disease severity, namely, disease tolerance[7-9].

Immune-driven resistance mechanisms likely co-evolved with disease tolerance mechanisms as genetically distinct defense strategies required to limit the severity of infectious diseases. In contrast to host resistance, disease tolerance mechanisms limit disease severity without affecting the host's pathogen load[7-9], by protecting the infected host from tissue damage (*Box 1&2*). Here we propose that tissue damage control is a prevailing mechanism underlying the protective effects of disease tolerance. We explore the mechanisms underlying tissue damage control, and discuss the potential impact of targeting such mechanisms in the treatment of infectious diseases and possibly other immune mediated inflammatory conditions as well.

TISSUE DAMAGE CONTROL AND DISEASE TOLERANCE

We will refer to cells and/or soluble molecules contributing to host resistance mechanisms as the host's immune system (*Fig.1*). Cells and/or soluble molecules involved in maintaining the integrity of epithelial barriers have a dual protective effect against pathogens, i.e. to provide a physical barrier that prevents pathogen systemic access and to modulate microbial communities at the epithelial interface via the

production of anti-microbial peptides, among other molecules[10] (*Fig.1*). All other host cells and/or soluble molecules that do not exert a negative impact on pathogens will be referred hereby as the host´s parenchyma (*Fig.1*). While parenchyma cells, tissues and organs do not contribute directly to resistance mechanisms, they are a critical component in maintenance of homeostasis, i.e. health[11,12]. Thus, impaired parenchyma function likely underlies the disruption of homeostasis associated with the pathogenesis of infectious diseases.

The host´s immune system drives resistance to infection via a series of mechanisms that rely initially on pathogen sensing via cognate binding of pathogen associated molecular patterns (PAMP) by host pattern recognition receptors (PRR)[13]. In addition, other classes of sensors may recognize molecular patterns associated with pathogen's effector activities rather than the pathogen itself, i.e. the guard hypothesis[14] (*Fig.1*). This hypothesis was raised initially in the context of host-pathogen interactions in plants, in which resistance genes were found to protect the infected host from disease caused by virulence genes encoded by pathogens. The initial assumption was that the products of resistance genes would interact directly and neutralize virulence factors. It became apparent however, that resistance genes also act as a PRR, recognizing virulence factors and activating immune-driven resistance mechanisms[14,15]. An alternative explanation, i.e. the guard hypothesis, proposes that the products of host resistance genes interact physically with host proteins, once these are targeted by virulence factors[14,15]. This hypothesis is supported by the finding that host resistance genes encode a family of proteins containing leucine-rich repeats (LRR), which are typically involved in protein-protein interactions. Moreover, these were shown to interact physically with host proteins modified posttranslationally by virulence factors to prevent disease severity[14,15]. The evolutionary conserved nature of these resistance genes suggests that a similar defense mechanism may be operational in animals[14,16]

Pathogen sensors are essential to activate innate and adaptive immune responses[17,18], driving the effector phase of host resistance to infection[13]. Host resistance mechanisms act in a pathogen-class specific manner destroying certain classes of pathogens, i.e. bacteria, viruses, fungi and protozoan parasites while expelling others, i.e. helminthes.

Pathogens also express toxins that can elicit varying levels of stress and dysfunction to host cells, tissues and organs, eventually leading to programmed cell death, tissue damage and organ dysfunction. These include pore-forming toxins that can compromise

the integrity of plasma membranes as well as intracellular membranes, disrupting cellular homeostasis[19]. Toxins and other virulence factors are perceived as a central mechanism of pathogenicity associated with infectious diseases (*Fig.1*). This pathogenic effect is countered essentially via host resistance mechanisms that reduce pathogen load and limit the damaging effects of the associated toxins and virulence factors (*Fig.1*). However, resistance mechanisms *per se* can impose varying levels of stress, dysfunction and eventually damage to the host parenchyma. This phenomenon referred as immunopathology, plays a central role in the pathogenesis of many infectious diseases (*Fig.1*)[7-9]. Of note, not all resistance mechanisms are potentially damaging to the host, with some having low if any associated toxicity, e.g. anti-microbial peptides, while others are potentially highly damaging, e.g. hypochlorous acid produced by activated polymorphonuclear (PMN) cells.

Depending on the extent of damage imposed to host cells and tissues by microbial toxins and/or host resistance mechanisms, desequestration of intracellular damage-associated molecular patterns, e.g. heat shock proteins (HSP), adenosine triphosphate (ATP), high mobility group box 1 protein (HMGB1), mitochondrial DNA, hemoglobin or heme, can occur and engage host PRR[20]. This phenomenon, referred as sterile inflammation can reinforce resistance mechanisms but also immunopathology[20,21].

While host resistance mechanisms are central to clear invading pathogens, controlling the severity of infectious diseases requires an additional host defense strategy that limits the extent of tissue damage imposed during infection, a protective mechanism referred as disease tolerance (*Box 1&2*; *Fig.1*)[7-9]. This requirement for a tight coupling of host resistance mechanisms to an additional protective strategy enforcing disease tolerance is well illustrated for the regulation of host iron metabolism during infection (*Box 3*). It is worth noting that disease tolerance describes a biological phenomenon quite distinct from immunological tolerance, which has as a hallmark the protection of self tissues from immune attack. While the two may be linked functionally, for example in their ability to limit tissue damage, they act via distinct effector mechanisms.

We posit that disease tolerance relies on a number of cellular and systemic adaptive responses that protect host parenchyma tissues from stress, dysfunction and/or damage, and will refer to these protective mechanisms as tissue damage control (*Fig.1*). In contrast to host resistance mechanisms, tissue damage control limits host disease severity without interfering with pathogen load (*Fig.1*)[7-9]. This countervailing protective

response should be required to limit the pathogenic effect associated not only with toxins expressed by pathogens but also with some potentially damaging host resistance mechanisms. Thus, tissue damage control acts as an inherent component of host defense against infection, required to decouple potentially deleterious immune-driven resistance mechanisms from disease severity.

One should consider that when tissue damage control mechanisms operate on cells of the host immune system, these can act in a immunoregulatory manner[22,23] that impacts on host resistance mechanisms (*Fig.1*)[24]. Moreover, when exerted in epithelial cells, tissue damage control should enforce barrier function and thus prevent pathogen access to host tissues (*Fig.1*)[10]. This is in keeping with the notion that tissue damage control is an integral component of host defense mechanisms against infection, which regulates not only disease tolerance but also resistance and barrier function mechanisms when acting on parenchyma, immune cells or barrier epithelial cells, respectively.

Tissue damage control can be enforced via different mechanisms including: i) neutralization of toxins and other virulence factors, ii) immunoregulatory mechanisms limiting the damaging effects of host resistance mechanisms and/or iii) cellular and systemic adaptive responses limiting the deleterious effects associated with different forms of stress and damage imposed by pathogens and/or host resistance mechanisms (*Fig.1*). Failure of any of these regulatory mechanisms to prevent tissue damage is expected to exacerbate stress, dysfunction and/or tissue damage and as such the severity of infectious diseases, presumably without interfering with pathogen load (*Fig.1*). We will focus in the next sections on the molecular basis of cellular and systemic adaptive responses limiting tissue damage imposed during infection, i.e. tissue damage control.

ADAPTIVE RESPONSES UNDERLYING TISSUE DAMAGE CONTROL

Tissue damage control is regulated by a number of evolutionary conserved adaptive responses acting in a cell autonomous and systemic level to preserve the functional integrity of the host tissues[7,25]. We will discriminate two types of adaptive responses, namely stress-responses and damage-responses. This distinction is based on two criteria: 1) the sensors used to activate the corresponding adaptive responses, and 2) their biologic outputs. Stress-responses are triggered by sensors that respond to environmental cues such as those related to variations of oxygen tension, redox status,

osmolarity, metabolite concentration, toxins, etc (*Fig.2*). Stress-sensors and the ensuing responses can in principle be triggered in the absence of cellular damage. These aim essentially at maintaining cellular function, while preventing different forms of stress from causing cellular damage. This occurs via activation of specific stress-responsive programs, which provide metabolic adaptation to the environmental changes driving different forms of stress while reducing, whenever possible, those forms of stress. Damage-responses on the other hand are triggered by sensors that respond to different forms of cellular damage. These include damage to macromolecules, i.e. DNA, proteins or lipids and to organelles, i.e. mitochondria, endoplasmic reticulum (ER), Golgi apparatus or lysosomes. Damage-sensors and their issuing responses are triggered in the context of cellular stress - the underlying cause of damage - but in contrast to stress-responses, they aim essentially at maintaining cellular function and repairing ongoing macromolecular and/or organelle damage.

Assuming that different classes of pathogens, i.e. viruses, fungi, bacteria, protozoan and eukaryotic parasites, might elicit distinct forms of stress and damage, the sensors for those forms of stress and damage and their corresponding responses should report on those classes of pathogens, a concept originally proposed by Ruslan Medzhitov in discussions at scientific conferences. This suggests as well that stress- and damage-responses are functionally integrated within inflammatory responses, likely fine-tuning host immunity to specific classes of pathogens[12]. In keeping with this notion, signal transduction pathways triggered by PRR or associated with immunoregulatory mechanisms exerted by specific immune cell types and/or involving interleukins can modulate different stress- and damage-responses, and *vice versa* and as such regulate tissue damage control and disease tolerance. While this added level of complexity should not be ignored, here we focus instead on the mechanisms through which tissue damage control impacts on defense against disease.

STRESS-RESPONSES AND TISSUE DAMAGE CONTROL

Stress-responses emerged at an early stage of evolution as the means to provide ancestral forms of life with the possibility of adaptation to environmental changes[25-27]. In general, such environmental changes are related to essential components of homeostasis, such as i) oxygen tension ii) cellular redox iii) osmolarity and iv) glucose or ATP/ADP cellular concentrations, disturbance of which leads to, respectively, hyperoxia or hypoxia, oxidative stress, osmotic stress and metabolic stress (*Fig.2*).

The common outcome of stress-responses is metabolic adaptation, which enables the maintenance of cellular, tissue and organ function under different forms of stress[25]. Metabolic adaptation aims at preserving core cellular functions at the expense of accessory ones, while minimizing macromolecular and organelle damage[25-27]. This is achieved via the expression of a number of immediate-early responsive genes coupled to broad inhibition of protein synthesis[28], repressing non-essential gene functions[29]. An illustrative rather than comprehensive overview of different stress-responses potentially regulating tissue damage control is provided in *Fig.3*.

Systemic spreading of pathogens from the initial site of infection is countered by an immediate host response characterized by the activation of the clotting cascade associated with platelet activation/aggregation and recruitment of activated PMN and monocyte/macrophages (Mø). One of the "trade offs" of this defense strategy is local deregulation of microvascular circulation, eventually leading to hypoxia, which depending on the tissue can have more or less severe pathologic consequences[7]. Hypoxia triggers an evolutionarily conserved stress-response regulated by the transcription factor hypoxia-inducible factor 1 alpha (HIF-1α)(*Fig.3*)[30]. When activated in immune cells, HIF-1α can promote resistance to infection (reviewed in[32,33]). In some instances, activation of HIF-1α in immune cells can compromise disease tolerance, as suggested by the observation that HIF-1α deletion in myeloid cells exacerbates lethality from endotoxic shock in mice[31]. Whether adaptive responses to hypoxia in parenchyma tissues, such as orchestrated by HIF-1α, promote tissue damage control and disease tolerance remains to be tested.

Resistance mechanisms often rely on targeting pathogens for oxidative damage via PMN cell and Mø activation[34]. The "trade-off" of this defense strategy includes oxidative stress imposed on host tissues, possibly leading to tissue damage, organ dysfunction and disease. This is likely counteracted by an adaptive cellular response regulated by the evolutionarily conserved transcription factor nuclear factor-erythroid 2-related factor 2 (NRF2)[35,36]. Activation of NRF2 provides tissue damage control and disease tolerance to malaria caused by *Plasmodium* infection[37,38] and presumably to sepsis caused by polymicrobial infections in mice[39]. When activated in cellular components of host immunity, NRF2 modulates resistance to infection, as demonstrated for *Salmonella* infection in mice[40] (*Box.3*).

Some forms of stress associated with infection can decrease mitochondrial ATP output, reducing cellular ATP availability. This is sensed by the infected host via the

evolutionarily conserved AMP-activated protein kinase (AMPK), which adjusts cellular metabolism to available energy (*Fig.3*)[41]. While it is likely that when activated in the host parenchyma this adaptive response should confer some level of tissue damage control and disease tolerance, this remains to be established. Expression of AMPK in immune cells exerts immunoregulatory effects that modulate resistance mechanisms[22,23].

Infection is often associated with local or systemic "growth factor" deprivation, whether associated or not to oxidative and metabolic stress. This is sensed by the infected host via activation of the evolutionarily conserved Forkhead box O (FOXO) family of transcription factors[42] (*Fig.3*). Activation of FOXO during *Mycobacterium* infection in flies is essential to provide metabolic adaptation, e.g. regulation of glycogen and triglyceride synthesis, and to limit host disease severity, irrespectively of pathogen load[43]. Thus, FOXO regulates a stress-responsive program that confers disease tolerance to infection in flies[8]. Whether the same is true in mammals remains to be tested. Moreover, when activated in cellular components of the host immune system, FOXO family members also exert immunoregulatory effects that can impact on resistance mechanisms[22,23].

Maintenance of cellular osmolarity is a central component of homeostasis and perturbations of osmolarity associated with systemic infections are probably sensed and counteracted by osmoregulatory stress-responses, which provide systemic as well cellular adaptation to higher or lower than physiologic osmolarity[44,45] (*Fig.3*). These stress-responses can act both systemically and in a cell autonomous manner[44,45], presumably contributing to tissue damage control and disease tolerance, although this remains to be established.

Another stress-response possibly regulating disease tolerance relies on the recognition of exogenous and/or endogenous ligands by the evolutionary conserved ligand-activated transcription factor aryl hydrocarbon receptor (AhR), best known for its involvement in orchestrating a stress-response to xenobiotics[46]. Several studies have shown that activation of this stress-response acts in a immunoregulatory manner that maintains barrier tissue function and limits the pathogenesis of immune mediated inflammatory conditions (*reviewed in*[47]). A recent study, published while this review was in preparation, proposes that activation of AhR by L-kynurenine, an endogenous intermediate product of the host tryptophan catabolism, confers disease tolerance to bacterial infections[48].

Microbial toxins, such as bacterial pore forming toxins[19], are another form of stress,

sensed via several host stress sensors including those belonging to the Nod like receptor protein (NLRP) family[19,49]. Activation of NLRP3 by pore forming toxins triggers interleukin (IL)-1b secretion, a pro-inflammatory cytokine that activates the stress-responsive p38 MAPK and the c-Jun N-terminal kinase (JNK) signal transduction pathways, which are protective against pore forming toxins[50]. Presumably, osmoregulatory stress-responses are also involved in adaptive responses to pore forming toxins, given that these can disrupt cellular osmolarity[50].

In some cases stress-responses are maladaptive, that is, they fail *per se* to provide sufficient level of metabolic adaptation to different forms of stress, allowing therefore the accumulation of macromolecular and organelle damage in cells. This is sensed and countered by damage-responses (*Fig.2*).

DAMAGE-RESPONSES AND TISSUE DAMAGE CONTROL

Cells have distinct sensors that trigger specific damage-responses associated with different types of cellular damage. These share as a common biologic output repair of macromolecular and/or organelle damage, aiming at maintenance of cellular function within the boundaries of essential outputs and at the expense of accessory ones. An illustrative rather than comprehensive overview of damage-responses possibly involved in tissue damage control is provided (*Fig.4*).

Accumulation of misfolded proteins is a form of macromolecular damage associated with different forms of stress[51]. When misfolded proteins accumulate in the cytosol or in the ER these trigger two distinct damage-responses, namely the heat shock response[52,53] and the unfolded protein response (UPR)[51,54,55], respectively (*Fig.4*). The hallmarks of these proteotoxic responses are: i) broad suppression of protein synthesis and ii) transcriptional up-regulation of a subset of immediate early-responsive genes that escape translational repression, and repair protein damage and/or destroy unfolded proteins[29,51]. To what extent the heat shock and the UPR impact the severity of infectious diseases is not clear. While the expression of heat shock factor 1 (HSF-1) has been associated with some level of host protection against *Listeria monocytogenes* infection[56] as well as against endotoxic shock[57] in mice, whether this occurs via a mechanism involving tissue damage control and disease tolerance remains to be established. The UPR on the other hand confers tissue damage control in mice; the expression of X-box binding protein 1 (XBP1) by gut epithelial cells is required to sustain epithelial barrier integrity and anti-microbial activity, preventing gut epithelial damage

and colitis[58]. Expression of XBP1 also protects *Caenorhabditis elegans* against *Pseudomonas aeruginosa* infection without interfering with pathogen load[59], arguing for an evolutionarily conserved role for the UPR in the regulation of tissue damage control in barrier epithelia and presumably elsewhere. It is likely that the salutary effects exerted by the UPR in gut epithelial cells relate both to protection from damage imposed by host resistance mechanisms[59] and also by pathogens[58], such triggered by bacterial pore forming toxins that can disrupt the gut epithelium[10,19].

DNA damage arising from infections[60] must be promptly repaired to avoid accumulation of mutations and genomic instability, i.e. the hallmarks of tumorogenesis and cancer. This notion is in keeping with the growing recognition that a number of cancers are directly or indirectly associated with history of infection[60]. Pharmacologic targeting of DNA-damage-responses regulated by the Ser/Thr protein kinase ataxia telangiectasia-mutated (ATM)[61] provides a robust protective response against severe sepsis elicited by polymicrobial infection in mice[62] (*Fig. 4*). This protective effect acts via a mechanism that does not interfere with host pathogen load, conferring tissue damage control and disease tolerance to sepsis[62]. More specifically, DNA-damage-responses appear to act predominately at the level of the lung epithelium to confer tissue damage control, arguing for a central pathologic role exerted by damage to the lung epithelium in the pathogenesis of severe sepsis[62]. Whether ATM and/or other regulators of DNA damage-responses act under pathophysiologic conditions to confer tissue damage control during different types of infection is likely, but this remains to be established (*Fig. 4*).

Lipid damage is another form of macromolecular damage associated with different types of stress, including lipid peroxidation driven by a self-propagating oxidative chain-reaction catalyzed by divalent metals such as iron contained inside the lipophilic ring of heme[63]. Lipid peroxidation can impair membrane functions and promote tissue damage, compromising disease tolerance, as illustrated for *influenza* virus infection in mice[64]. Presumably effector mechanisms that restrain lipid peroxidation, such as for example mediated by glutathione peroxidase 4 (GPX4)[65] or by the lipophilic antioxidant bilirubin[66] (*reviewed in*[67]), should promote tissue damage control and in turn disease tolerance, but this remains to be established.

Autophagy is an evolutionarily conserved damage-response triggered by organelle damage driven by different forms of stress including redox and metabolic stress, hypoxia or protein unfolding as well as driven by PRR signaling (*Fig. 4*) (reviewed in[68]). Damaged

organelles are captured by the vesicular system and fused to lysosomes, initiating their degradation while promoting recycling of their components. Autophagy and its manipulation by pathogens modulates host resistance mechanisms[68]. More recently autophagy has also been shown to modulate tissue damage control and disease tolerance, as illustrated in the context of polymicrobial infection in mice[62]. Briefly, pharmacologic induction of DNA-damage response by anthracyclines, a group of chemotherapeutic agents that activate DNA damage-responses involving ATM, provides robust protection against severe sepsis in mice[62]. This salutary effect acts via a mechanism involving two components of the autophagy damage response, namely the autophagy protein microtubule-associated protein 1 light chain-3B (LC3B) and the autophagy-related protein 7 (Atg7)[62]. Specific inhibition of Atg7 in the lung is sufficient to impair the protective effect of anthracyclines while Atg7 overexpression in the lung is protective against severe sepsis[62]. This argues strongly for the notion of autophagy providing tissue damage control in parenchyma tissues, i.e. the lung epithelium, and conferring disease tolerance to sepsis.

When damage-responses are maladaptive, that is, fail to provide a sufficient level of damage repair to enforce tissue damage control, the default outcome is programmed cell death leading eventually to irreversible tissue damage, organ dysfunction and severe disease (*Fig.2* and *Box 3*). We propose that the pathogenesis of infectious diseases is regulated to a large extent by the relative capacity of different stress- and/or damage-responses to provide metabolic adaptation and damage repair, at sufficient levels as to avoid cytotoxicity, tissue damage and disease (*Fig.2*). While we have argued that tissue damage control mechanisms are a central component of disease tolerance, this does not exclude other mechanisms from contributing to disease tolerance. One of such mechanisms is likely to involve tissue repair via compensatory proliferation of stem cells[69].

Stress- and damage responses must be tightly regulated during infection, so that cellular function can be restored to full capacity as soon as the cause of stress and damage, i.e. the pathogen, is eliminated by host resistance mechanisms. Moreover, it has been argued that in a similar manner to host resistance mechanisms, tissue damage control and disease tolerance operate in a pathogen-class specific manner, a notion proposed originally by Ruslan Medzhitov in scientific conferences, and demonstrated experimentally in the context of protozoan/bacterial[70] as well as viral/bacterial co-infection[71] in mice. This imposes again the existence of a stringent regulatory

mechanism controlling stress- and damage-responses that allows for host protection against non-overlapping classes of pathogens.

TISSUE DAMAGE CONTROL IN NON-COMMUNICABLE DISEASES

Stress- and damage-responses also exert protective effects against non-communicable diseases in which inflammation or misdirected immunity act as the underlying cause of pathology. In keeping with this notion the stress-responsive program regulated by NRF2 is protective against organ ischemia and reperfusion injury (IRI), via a mechanism involving the expression of several effector genes, including the stress-responsive enzyme heme oxygenase-1 (HO-1, encoded by the *HMOX1* gene)[72] and the iron sequestering protein ferritin heart/heavy chain (encoded by the *FTH* gene)[73](*Box 3*). This salutary effect is also observed in the context of heart and brain IRI[72], presumably limiting the pathogenesis of myocardial infarction and stroke, the two major non-communicable diseases in terms of global impact on human morbidity and mortality. Other adaptive responses conferring protection against IRI include the metabolic stress-response regulated by AMPK[74] and the UPR[75]. Moreover ischemic pre-conditioning, a hormesis-like protective response against IRI (*Box 4*)[76], acts via a mechanism involving HIF-1α[30]. Stress-responses regulated by NRF2[77] and HIF-1α[32] also prevent the rejection of transplanted organs via a mechanism involving tissue damage control, and driven most probably by HO-1 expression[72]. Transplanted organs can also undergo a hormesis-like response[76] (*Box 4*) termed accommodation[78], which prevents graft rejection via a mechanism involving again the expression of HO-1[79].

Autoimmune diseases are another group of non-communicable diseases in which stress- and damage-responses can act in a salutary manner. This is illustrated by the oxidative stress-response regulated by NRF2, which prevents the onset of diabetes[80], systemic lupus erythematosus[81], rheumatoid arthritis[82] and multiple sclerosis[83] in murine models for these diseases. Damage responses also exert protective effects against autoimmune diseases, as illustrated for the UPR in the context of type 1 diabetes, where impaired expression of the the UPR components activating transcription factor 6 (ATF6) and XBP1 in β-cells of the pancreas are associated with disease progression in both mice and humans[84]. Importantly, targeting the UPR pharmacologically in β-cells inhibits the pathogenesis of experimental type 1 diabetes in mice, a salutary effect associated with β-cell cytoprotection and reduced inflammatory infiltrates[84]. The UPR also exerts protective effects against autoimmune neuroinflammation, as illustrated in mice for the

expression of the UPR component protein kinase RNA-like ER kinase (PERK) in olygodendrocytes[85]. As referred above, expression of the UPR component XBP1 in intestinal epithelial cells inhibits colitis in mice while hypomorphic variants of the human XBP1 allele are associated with susceptibility to inflammatory bowel disease[58]. It is worth noticing that the salutary effects exerted by the UPR against the pathogenesis of these immune-mediated inflammatory diseases appear to act essentially in parenchyma cells in which protein synthesis is overabundant, as illustrated for β-cells, oligodendrocyte an intestinal epithelial cells, which produce high levels of insulin, myelin and mucins, respectively. Whether hormesis-like responses (*Box 4*)[76] involving stress- or damage-responses confer protection against autoimmunity remains to be established.

THERAPEUTIC TARGETING OF TISSUE DAMAGE CONTROL

The widespread and often uncontrolled usage of anti-microbial drugs and in particular antibiotics, in the treatment of infectious diseases led to the selection of multidrug-resistant pathogens[1]. Targeting tissue damage control and disease tolerance might be a major therapeutic option when treating infectious diseases caused by multidrug resistant pathogens. This therapeutic approach, referred as supportive therapy, is already widely used in severe sepsis, severe forms of malaria, severe diarrheal diseases, severe febrile illness as well as fatal hemorrhagic fevers. Presumably a more rational development of pharmacologic agents targeting specifically central regulators of different stress- or damage-responses, e.g. NRF2[35], HIF1-α[32], AMPK or ATM[62], conferring tissue damage control should be of therapeutic value in the treatment of these pathologic conditions. The same rationale can be applied to the treatment of non-communicable diseases in which inflammation and/or immunity act as the underlying cause of disease. In support of this notion, pharmacologic use of anti-oxidants confers disease tolerance to *Plasmodium* infection in mice[86,87]. Also, activation of DNA damage responses and autophagy by anthracyclines - involving ATM, LC3B, ATG7 - confers disease tolerance to polymicrobial infections, acting therapeutically against severe sepsis in mice[62]. Pharmacologic administration of amphiregulin, an epithelial growth factor family member, confers disease tolerance to bacterial pneumonia after *influenza* virus infection in mice[71] and as mentioned above pharmacologic induction of the UPR in β-cells also provides tissue damage control and mitigates the pathogenesis of type-1 diabetes in mice[84]. These findings argue strongly for the potential therapeutic targeting of these stress- and damage-responses outside the specific

context of infectious diseases.

CONCLUDING REMARKS

Vaccination and anti-microbial drugs resulted in global protection of mankind against a variety of pathogens. These approaches however, failed to confer robust protection against insidious infectious diseases that remain a major cause of morbidity and mortality worldwide. Moreover the emergence of a growing number of highly virulent multidrug-resistance pathogens compromises the current therapeutic handling of infectious diseases. In these cases, disease tolerance may play a major role that is often not considered in terms of our understanding of the pathogenesis of infectious diseases or their treatment. Therefore, a fuller understanding of disease tolerance and underlying mechanisms, including tissue damage control, is of clear basic and clinical relevance.

A major challenge is to identify and characterize the molecular mechanisms regulating disease tolerance to specific classes of pathogens. Assuming that disease severity reflects more or less pronounced disruption of homeostasis one should monitor in a quantitative manner “homeostatic parameters” as read-outs of disease driven by infection. Such “homeostatic parameters” include those related to the functional outputs of vital organs essential for maintenance of homeostasis, including the heart/vascular, lung, kidney, liver and brain. This approach used in a daily basis clinically should be adapted to experimental systems addressing at molecular level the mechanism underlying disease tolerance. The expectation is that disease severity will be reflected by quantitative variations of those parameters and that mechanisms controlling disease tolerance should modulate those parameters within the boundaries of homeostasis, without interfering with pathogen load. Another major challenge is the identification and characterization of the functional points of integration between immune-driven resistance and tissue damage control mechanisms regulating disease tolerance. The prediction is that immunoregulatory mechanisms will modulate stress- and damage-responses and hence tissue damage control and disease tolerance. It is expected that these endeavors will enable further understanding of host-pathogen interactions and the rational targeting of disease tolerance mechanisms in the treatment of infectious diseases.

BOX 1:

An historical perspective of disease tolerance: Disease tolerance was first recognized as a plant defense strategy against infection[88,89], with its original description dating back to as early as the end of the XIX century[90]. The concept was refined by mid XX century, as the ability to sustain infection without a concomitant reduction in host fitness[89]. These studies posit that disease tolerance does not rely on reducing host pathogen load for preservation of health[88] but instead acts via mechanisms that limit parenchyma damage[89]. While the concept of disease tolerance was rapidly expanded to different types of infection in plants[89], it took over a century to extrapolate this notion beyond the plant literature. This was achieved by a series of studies on the immune response of *Drosophila melanogaster* to infection, which revealed that loss of function mutations in genes encoding inflammatory cytokines, e.g. the tumor necrosis factor (*TNF*) homolog *eiger* or in genes controlling metabolic stress-responses, i.e. forkhead box transcription factor (*FOXO*) and *AKT* (*Fig.3*) modulate host survival without interfering with pathogen load[8,9,43]. These and other studies revealed the involvement of specific genes in the regulation of “endurance” to infection, now referred as disease tolerance by analogy to the plant literature[8,9], while the same phenomenon is often referred to as "resilience" as well[91]. Contemporary with these studies is the finding that a symbiont of flies, i.e. the intracellular bacteria *Wolbachia*, regulates not only host resistance but also disease tolerance to viral infections[92]. In addition to demonstrating that disease tolerance is operational in flies, these studies revealed that host interaction with a given microbe can regulate disease tolerance and as such the pathologic impact of infection by other pathogens[92]. Again contemporary to these studies, is the finding that disease tolerance also occurs in animals, including worms[59] as well as mice[86,93]. Overall, these studies “opened the way” to the cellular and molecular characterization of the mechanisms involved in disease tolerance, which have now started to become elucidated, and shown to rely on evolutionarily conserved stress- and damage-responsive programs that adapt and maintain host parenchyma function during infection (*Fig.3&4*).

BOX 2:

Disease tolerance in mammals: Disease tolerance was first demonstrated formally in mammals, and interpreted as such, in the context of *Plasmodium* infection[93], the causative agent of malaria. Namely, mice from different genetic backgrounds were found to develop varying levels of disease severity, irrespectively of their corresponding pathogen loads[93]. This observation and the conceptual framework under which it was interpreted were instrumental in extrapolating the notion that genetically encoded mechanisms confer disease tolerance mammals[93]. Contemporary to this study, is the finding that the *Kcnj8* gene, encoding the ATP-sensitive potassium (K_{ATP}) channel Kir6.1, is essential for protection against viral infections in mice, without interfering with pathogen load[94].

The cellular and molecular mechanisms regulating tissue damage control and disease tolerance remain poorly understood. In the specific context of *Plasmodium* infection[93] these have been linked functionally to a evolutionary conserved stress-responsive and cytoprotective program that provides metabolic adaptation to cellular iron overload[87,95]. Two effector genes have been functionally implicated, namely the heme catabolizing enzyme HO-1[86,96,97] and the ferritin heart/heavy chain (FTH)[87,95]. These provide a systemic adaptive response to tissue iron overload in the infected host, which prevents cytotoxicity and tissue damage caused by the accumulation of iron-heme during the blood stage of *Plasmodium* infection[86,96,97]. The same stress-responsive program is involved in conferring tissue damage control and disease tolerance to severe sepsis driven by polymicrobial infection[98].

Assuming that unfettered cytotoxicity is a common underlying mechanism driving tissue damage during infection, stress- and damage-response that confer tissue damage control and disease tolerance to infection should protect host parenchyma cells from programmed cell death. In support of this notion is the finding that deletion of the RIP kinase 3 (RIPK3) gene, a master regulator of programmed cell death by necroptosis[99], is sufficient *per se* to confer tissue damage control and disease tolerance to systemic polymicrobial infection in mice[100]. Moreover, deletion of the *Birc3* (cIAP2) gene, encoding a E3 ubiquitin ligase that suppresses necroptosis, impairs tissue damage control and disease tolerance to *influenza* virus infection in mice[101]. These findings suggest that stress- and damage-responses conferring tissue damage control may target directly or indirectly the RIPK1/3-driven necroptosis signal transduction pathway to confer disease tolerance or resistance to infection, a hypothesis that remains to be tested.

BOX 3:

Metabolic adaptation to iron overload and disease tolerance. Based on its relative abundance and ability to exchange electrons with a number of donor/acceptor molecules iron is at the center stage of many vital biological functions. Pathogens rely strictly on iron acquisition for the progression of infection, evolving strategies that fuel host iron into their own metabolic pathways[102]. It follows that host strategies that deny pathogen access to iron are a central and evolutionarily conserved host resistance mechanism[95,102,103]. This defense strategy relies to a large extent on the expression of: i) hepcidin antimicrobial peptide gene (*HAMP*), a master regulator of systemic iron metabolic adaptation during infection that reduces iron acquisition from diet and suppresses iron cellular export[103], ii) lipocalin-2, a soluble iron chelator encoded by the *LCN2* gene that prevents extracellular pathogens from accessing iron[104] and iii) natural resistance associated macrophage protein function (*NRAMP-1*), an intracellular iron transporter encoded by the *SLC11A1* gene, that removes iron from phagolysosomes and limits iron supply to intracellular pathogens[105].

Systemic regulation of pathogen access to host iron has a major "trade off", namely, host tissue iron overload compromising host parenchyma function[95]. Moreover, systemic disruption of cellular iron export can interrupt iron supply to hemoglobin synthesis and erythropoiesis, causing anemia of chronic disease[106]. Therefore systemic modulation of host iron metabolism during infection provides a paradigm for the requirement of an integrated host defense strategy in which resistance mechanisms must be coupled to tissue damage control as to limit the severity of infectious diseases[87,95]. This is accomplished via metabolic adaptation to tissue iron overload, via a mechanism involving the expression of ferritins[87,95].

Ferritins are multimeric nanocage-like structures made of FTH (heavy/heart) and FTL (light/liver) chains, that can incorporate up to 4,500 iron atoms in the form of inorganic ferrihydrite aggregates[107]. FTH ferroxidase activity converts reactive iron (Fe^{2+}) into inert iron (Fe^{3+}) that does not partake in the production of free radicals via the Fenton chemistry[95]. This anti-oxidant effect confers tissue damage control and disease tolerance to infection in mammals[87,95] as well as in plants[108], arguing for the evolutionarily conserved nature of this host defense strategy.

BOX 4:

Overlapping protection, evolution and hormesis. There is an overlapping profile of gene expression associated different stress- and damage-responses in evolutionary disparate organisms[25-27,53]. This argues for the involvement of a core number of evolutionarily conserved effector genes in the regulation of those stress- and damage-responses and as such on the regulation of tissue damage control and disease tolerance. Presumably, stress- and damage-responses evolved from ancestral forms of life where they provided adaptation to environmental changes[26] being co-opted through evolution to provide host protection against infection[25,27]. These ancestral adaptive responses preceded most probably those underlying host resistance mechanisms, co-evolving thereafter to decouple potentially damaging resistance mechanisms from tissue damage and disease severity. This is in keeping with the notion that some host resistance mechanisms can *per se* elicit cellular stress and damage, which in the absence of a countervailing protective response would be pathogenic. We propose that stress- and damage-responses conferring tissue damage control and disease tolerance to infection are required to decouple potentially deleterious resistance mechanisms from disease severity. The overlap of signal transduction pathways and profiles of gene expression associated with different stress- and damage-responses (*Fig.2-4*) also argues for some level of cross-protection against seemingly unrelated forms of stress and damage[68]. This phenomenon known as hormesis[76], is also referred as pre-conditioning in the context of organ IRI, or energy restriction in the context of ageing as well as accommodation in the context of organ transplantation[78]. The shared principle being that sub-toxic forms of stress and/or damage can elicit adaptive responses in cells, tissues, organs or organisms that are protective against subsequent exposure to toxic levels of the same or unrelated forms of stress and/or damage[76]. The impact of this phenomenon for infectious diseases is supported by the finding that the protective effect exerted by sickle hemoglobin against malaria, relies on a hormesis-like effect involving the activation of the stress-response regulated by NRF2 and providing tissue damage control and disease tolerance to *Plasmodium* infection[97]. A similar effect has been assigned to the protective effect of nitric oxide against the development of severe malaria in mice[38]. This suggests that targeting hormesis-like mechanisms may be used as a strategy induce tissue damage control and disease tolerance to other types of infection, a notion supported by the protective effect exerted by pharmacologic targeting of the DNA damage-responses against severe sepsis in mice[62].

FIGURE LEGENDS:

Figure 1: Tissue damage control in host microbe interactions. Homeostasis is governed to a large extent by parenchyma tissues that do not exert a negative impact (-|) on pathogens. Toxins and other virulence factors expressed by pathogens can elicit cellular stress and damage to the host parenchyma (lighting bolt arrow), disrupting homeostasis. This is a major driver in the pathogenicity of infectious diseases. Recognition of pathogens (PRR/PAMP) activates (->) the host innate and adaptive immune response, reducing pathogen load and hence pathogenicity. This defense strategy, called host resistance to infection, can have a direct negative impact (-|) on host parenchyma (immunopathology) or an indirect negative impact (-|) in combination with toxins. This is another major driving force in the pathogenesis of infectious diseases. Tissue damage control refers to a protective mechanism that limits the extent of stress and damage imposed to host cells by toxins and other virulence factors as well as by host resistance mechanisms. When exerted in parenchyma, tissue damage control reduces disease severity without interfering with pathogen load, and is said to confer disease tolerance to infection. Toxins and virulence factors as well as host resistance mechanisms (not depicted in *figure*) can exert a negative impact (-|) on host epithelial cells, disrupting barrier functions. When exerted in host epithelial cells, tissue damage control enforces barrier function, contributing to host resistance mechanisms. Toxins and virulence factors can also exert a negative impact (-|) on components of the host immune system, impairing resistance to infection. Therefore, when exerted in the immune system, tissue damage control can act in an immunoregulatory manner and modulate resistance mechanisms.

Figure 2: Stress- and damage-responses: Circles indicate signal transduction pathways regulating specific gene profiles, as triggered by different sensors represented by rectangles. Activation of stress- and damage-responses provides tissue damage control and disease tolerance to systemic infections. When stress-responses are maladaptive, that is, when these fail to provide sufficient levels of metabolic adaptation to different forms of stress, the result is macromolecular, i.e. protein, lipid, DNA, and/or organelle damage. This triggers a functionally different set of adaptive responses that are no longer aimed at providing metabolic adaptation but instead aim at repairing macromolecular and/or organelle damage, i.e. damage repair. Damage responses, act presumably as a second layer of tissue damage control to enforce disease tolerance.

When damage-responses are maladaptive, that is, fail to provide sufficient macromolecular and/or organelle damage repair, the default program is programmed cell death, leading to tissue damage, organ dysfunction and eventually to disease.

Figure 3: Stress-response pathways: Stress-responses are controlled by a number of master regulators (red rectangles) that provide cellular adaptation to specific forms of stress. **Hypoxia** is sensed by the prolyl hydroxylase (PHD)2, which uses O_2 to hydroxylate two proline residues in the transcription factor HIF-1α. This promotes the recruitment of the E3 ubiquitin ligase von Hippel-Lindau (VHL/Cul3), ubiquitinating (green circle; Ub) and targeting HIF-1α for proteolytic degradation by the 26s proteasome pathway[30]. PHD2 activity is inhibited when O_2 pressure (pO_2) decreases bellow physiologic levels, i.e. hypoxia. This releases HIF-1α from VHL, allowing for HIF-1α nuclear translocation and binding to DNA hypoxia responsive elements (HRE) in the promoter of effector genes regulating metabolic adaptation to hypoxia[30]. **Oxidative stress** is sensed by the Kelch-like ECH-associated protein 1 (Keap1) that controls the activation of the transcription factor NRF2, a member of the Cap'n'collar basic leucine zipper family of transcription factors that acts as a master regulator of cellular adaptive responses to oxidative stress[36]. Under homeostasis, Keap1 acts as an ubiquitin E3 ligase, targeting NRF2 for ubiquitination (green circle; Ub) and proteolytic degradation by the 26s proteasome pathway[35]. Oxidative stress causes several sulfhydryl groups in Keap1 to form disulfide bounds, inhibiting its ubiquitin E3 ligase activity and releasing NRF2, which associated with small Maf proteins[109] and undergoes nuclear translocation, binding to the DNA antioxidant responsive elements (ARE) in the promoter of genes regulating adaptation to oxidative stress[35]. **Metabolic stress.** Cellular AMP, ADP and ATP concentrations are maintained at constant levels by different mechanisms regulating ATP production in the mitochondria and ATP consumption. Moreover, adenylate kinase (ADK) catalyzes the conversion of 2 ADP into ATP + AMP. When cellular ATP concentration decreases, ADP to ATP ratio increases displacing the reaction catalyzed by adelylate kinase towards ATP and AMP. This is sensed by AMPK, which orchestrates a cellular adaptive response promoting catabolic pathways generating ATP while switching-off ATP consumption[41]. **Multiple forms of stress** can be sensed by the evolutionarily conserved Forkhead box O (FOXO) family of transcription factors[42]. Under homeostasis, FOXO activity is suppressed via the

insulin-signaling transduction pathway involving PI3K and AKT and promoting sustained FOXO binding to 14.3.3[42]. Inhibition of PI3K and AKT is associated with activation of upstream stress-activated mitogen activated protein kinases (MAPK), including the Jun N-terminal kinase (JNK). These trigger FOXO post-translational modifications (PTM) promoting its nuclear translocation and binding to specific DNA motifs in the promoter of genes that confer adaptation to multiple forms of stress. **Osmotic stress** elicits an immediate adaptive response modulating cellular volume and intracellular concentrations of inorganic ions and macromolecules, via a mechanism involving the aquaporin "water channels" (AQP) and solute carrier channels (SLC). Prolonged osmotic stress is sensed by the protein kinase A-anchoring protein 13 or Brx[45], which activate MAPK. These include the p38 MAPK that targets the transcription factor nuclear factor of activated T-cells 5 (NFAT5), also know as the tonicity-responsive element binding protein (TonEBP). Phosphorylated NFAT5 dimerizes and undergoes nuclear translocation binding to DNA osmotic response elements (ORE), in the promoter of osmoregulatory genes[44]. A recent study proposes that activation of the xenobiotic stress-response regulated by AhR confers disease tolerance to bacterial infections[48] (not illustrated).

Figure 4: Damage response pathways. Damage-responses are controlled by a number of macromolecular and organelle damage sensors. These activate specific genetic programs providing cellular adaptation to different forms of cellular damage. **Unfolded protein response (UPR).** Accumulation of misfolded proteins in the ER lumen is sensed by the binding immunoglobulin protein (BiP)/78 kDa glucose-regulated protein (GRP-78) chaperone and the inositol requiring protein-1 (IRE1), two master regulators of the UPR[54,55]. Dimerization and release of GRP78, de-repress IRE1 activity[55], which splices X-box binding protein 1 (XBP1) mRNA, promoting XBP1 translation, nuclear translocation and binding to DNA X-box elements in the promoter of effector genes regulating the UPR. Binding of GRP-78 to unfolded proteins in the ER lumen also triggers the activation of the protein kinase RNA-like ER kinase (PERK) and the transcription factor-6 (ATF6). PERK represses mRNA translation[55] and activates different substrates, including NRF2, which regulates the expression of several effector genes that provide disease tolerance to infection. ATF6 also induces the transcription of different genes contributing to the UPR, including *XBP1*. **Heat shock response**. Accumulation of misfolded proteins in the cytoplasm, as a result of cellular exposure to

higher than physiologic temperatures, i.e. fever, or other forms of stress associated with infection is sensed by heat shock proteins (HSP), e.g. chaperones[52]. Under homeostasis, components of the Hsp90 chaperone family repress the transcription factor heat shock factor 1 (HSF1), the master regulator of the heat shock response. Misfolded proteins recruit Hsp90. This releases HSF1, which homotrimerizes and undergoes nuclear translocation, binding to DNA heat shock elements (HSE) in the promoter of different classes of HSP genes. **DNA damage**. DNA double strand breaks, one of the most deleterious forms of DNA damage, are sensed by the Mre11/Rad50/Nbs1 complex, which activates ATM, a master regulator of the double stranded DNA damage-response[61]. Under homeostasis ATM exists essentially as a homodimer, dissociating into active monomers in response to DNA double strand breaks[61]. ATM orchestrates an adaptive cellular response involving substrate proteins that regulate cell cycle progression, metabolic adaptation or programmed cell death[61]. **Autophagy** relies on the cellular vesicular system initiated by a process of nucleation of damaged organelles, elongation and maturation leading to lysosome (Lys) fusion, and allowing for degradation and recycling of their components[68].

REFERENCES

1 Fauci, A.S. and Morens, D.M. (2012) The perpetual challenge of infectious diseases. *N Engl J Med* 366 (5), 454-461

2 Miskinyte, M. *et al.* (2013) The genetic basis of Escherichia coli pathoadaptation to macrophages. *PLoS Pathog* 9 (12), e1003802

3 Perfeito, L. *et al.* (2007) Adaptive mutations in bacteria: high rate and small effects. *Science* 317 (5839), 813-815

4 Cunnington, A.J. *et al.* (2013) Piecing together the puzzle of severe malaria. *Sci Transl Med* 5 (211), 211ps218

5 Angus, D.C. and van der Poll, T. (2013) Severe sepsis and septic shock. *N Engl J Med* 369 (9), 840-851

6 Almond, M.H. *et al.* (2012) Influenza-related pneumonia. *Clin Med* 12 (1), 67-70

7 Medzhitov, R. *et al.* (2012) Disease Tolerance as a Defense Strategy. *Science* 335, 936-941

8 Ayres, J.S. and Schneider, D.S. (2012) Tolerance of infections. *Annu Rev Immunol* 30, 271-294

9 Schneider, D.S. and Ayres, J.S. (2008) Two ways to survive infection: what resistance and tolerance can teach us about treating infectious diseases. *Nat Rev Immunol* 8 (11), 889-895

10 Marchiando, A.M. *et al.* (2010) Epithelial barriers in homeostasis and disease. *Annu Rev Pathol* 5, 119-144

11 Buchman, T.G. (2002) The community of the self. *Nature* 420 (6912), 246-251

12 Chovatiya, R. and Medzhitov, R. (2014) Stress, inflammation, and defense of homeostasis. *Mol Cell* 54 (2), 281-288

13 Medzhitov, R. (2008) Origin and physiological roles of inflammation. *Nature* 454 (7203), 428-435

14 Dangl, J.L. and Jones, J.D. (2001) Plant pathogens and integrated defence responses to infection. *Nature* 411 (6839), 826-833

15 Chisholm, S.T. *et al.* (2006) Host-microbe interactions: shaping the evolution of the plant immune response. *Cell* 124 (4), 803-814

16 Vance, R.E. *et al.* (2009) Patterns of pathogenesis: discrimination of pathogenic and nonpathogenic microbes by the innate immune system. *Cell Host Microbe* 6 (1), 10-21

17 Lemaitre, B. *et al.* (1996) The dorsoventral regulatory gene cassette spatzle/Toll/cactus controls the potent antifungal response in Drosophila adults. *Cell* 86 (6), 973-983

18 Medzhitov, R. *et al.* (1997) A human homologue of the Drosophila Toll protein signals activation of adaptive immunity. *Nature* 388 (6640), 394-397

19 Los, F.C. *et al.* (2013) Role of pore-forming toxins in bacterial infectious diseases. *Microbiol Mol Biol Rev* 77 (2), 173-207

20 Chen, G.Y. and Nunez, G. (2010) Sterile inflammation: sensing and reacting to damage. *Nat Rev Immunol* 10 (12), 826-837

21 Zelenay, S. and Reis e Sousa, C. (2013) Adaptive immunity after cell death. *Trends Immunol* 34 (7), 329-335

22 Pearce, E.L. *et al.* (2013) Fueling immunity: insights into metabolism and lymphocyte function. *Science* 342 (6155), 1242454

23 O'Neill, L.A. and Hardie, D.G. (2013) Metabolism of inflammation limited by AMPK and pseudo-starvation. *Nature* 493 (7432), 346-355

24 Silva-Gomes, S. *et al.* (2013) Heme catabolism by heme oxygenase-1 confers host resistance to Mycobacterium infection. *Infect Immun* 81 (7), 2536-2545

25 Kultz, D. (2005) Molecular and evolutionary basis of the cellular stress response. *Annu Rev Physiol* 67, 225-257
26 Lopez-Maury, L. *et al.* (2008) Tuning gene expression to changing environments: from rapid responses to evolutionary adaptation. *Nat Rev Genet* 9 (8), 583-593
27 Kultz, D. (2003) Evolution of the cellular stress proteome: from monophyletic origin to ubiquitous function. *J Exp Biol* 206 (Pt 18), 3119-3124
28 Lemaitre, B. and Girardin, S.E. (2013) Translation inhibition and metabolic stress pathways in the host response to bacterial pathogens. *Nat Rev Microbiol* 11 (6), 365-369
29 Spriggs, K.A. *et al.* (2010) Translational regulation of gene expression during conditions of cell stress. *Mol Cell* 40 (2), 228-237
30 Semenza, G.L. (2012) Hypoxia-inducible factors in physiology and medicine. *Cell* 148 (3), 399-408
31 Peyssonnaux, C. *et al.* (2007) Cutting edge: Essential role of hypoxia inducible factor-1alpha in development of lipopolysaccharide-induced sepsis. *J Immunol* 178 (12), 7516-7519
32 Scholz, C.C. and Taylor, C.T. (2013) Targeting the HIF pathway in inflammation and immunity. *Curr Opin Pharmacol* 13 (4), 646-653
33 Nizet, V. and Johnson, R.S. (2009) Interdependence of hypoxic and innate immune responses. *Nat Rev Immunol* 9 (9), 609-617
34 Holmstrom, K.M. and Finkel, T. Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nat Rev Mol Cell Biol* 15 (6), 411-421
35 Hayes, J.D. and Dinkova-Kostova, A.T. (2014) The Nrf2 regulatory network provides an interface between redox and intermediary metabolism. *Trends Biochem Sci*
36 Sykiotis, G.P. and Bohmann, D. (2010) Stress-activated cap'n'collar transcription factors in aging and human disease. *Sci Signal* 3 (112), re3
37 Ferreira, A. *et al.* (2008) A central role for free heme in the pathogenesis of severe malaria: the missing link? *J Mol Med* 86 (10), 1097-1111
38 Jeney, V. *et al.* (2014) Control of Disease Tolerance to Malaria by Nitric Oxide and Carbon Monoxide. *Cell Reports*
39 Thimmulappa, R.K. *et al.* (2006) Nrf2 is a critical regulator of the innate immune response and survival during experimental sepsis. *J Clin Invest* 116 (4), 984-995
40 Nairz, M. *et al.* (2013) Nitric oxide-mediated regulation of ferroportin-1 controls macrophage iron homeostasis and immune function in Salmonella infection. *J Exp Med* 210 (5), 855-873
41 Hardie, D.G. *et al.* (2012) AMPK: a nutrient and energy sensor that maintains energy homeostasis. *Nat Rev Mol Cell Biol* 13 (4), 251-262
42 Eijkelenboom, A. and Burgering, B.M. (2013) FOXOs: signalling integrators for homeostasis maintenance. *Nat Rev Mol Cell Biol* 14 (2), 83-97
43 Dionne, M.S. *et al.* (2006) Akt and FOXO dysregulation contribute to infection-induced wasting in Drosophila. *Curr Biol* 16 (20), 1977-1985
44 Brocker, C. *et al.* (2012) The role of hyperosmotic stress in inflammation and disease. *Biomol Concepts* 3 (4), 345-364
45 Kino, T. *et al.* (2009) Brx mediates the response of lymphocytes to osmotic stress through the activation of NFAT5. *Sci Signal* 2 (57), ra5
46 Denison, M.S. and Nagy, S.R. (2003) Activation of the aryl hydrocarbon receptor by structurally diverse exogenous and endogenous chemicals. *Annu Rev Pharmacol Toxicol* 43, 309-334

47 Stockinger, B. *et al.* (2014) The aryl hydrocarbon receptor: multitasking in the immune system. *Annu Rev Immunol* 32, 403-432
48 Bessede, A. *et al.* (2014) Aryl hydrocarbon receptor control of a disease tolerance defence pathway. *Nature* 511 (7508), 184-190
49 Franchi, L. *et al.* (2012) Sensing and reacting to microbes through the inflammasomes. *Nat Immunol* 13 (4), 325-332
50 Kao, C.Y. *et al.* (2011) Global functional analyses of cellular responses to pore-forming toxins. *PLoS Pathog* 7 (3), e1001314
51 Buchberger, A. *et al.* (2010) Protein quality control in the cytosol and the endoplasmic reticulum: brothers in arms. *Mol Cell* 40 (2), 238-252
52 Lindquist, S. (1986) The heat-shock response. *Annu Rev Biochem* 55, 1151-1191
53 Richter, K. *et al.* (2010) The heat shock response: life on the verge of death. *Mol Cell* 40 (2), 253-266
54 Xu, C. *et al.* (2005) Endoplasmic reticulum stress: cell life and death decisions. *J Clin Invest* 115 (10), 2656-2664
55 Hotamisligil, G.S. (2010) Endoplasmic reticulum stress and the inflammatory basis of metabolic disease. *Cell* 140 (6), 900-917
56 Murapa, P. *et al.* (2011) Heat shock factor 1 protects mice from rapid death during Listeria monocytogenes infection by regulating expression of tumor necrosis factor alpha during fever. *Infect Immun* 79 (1), 177-184
57 Xiao, X. *et al.* (1999) HSF1 is required for extra-embryonic development, postnatal growth and protection during inflammatory responses in mice. *EMBO J* 18 (21), 5943-5952
58 Kaser, A. *et al.* (2008) XBP1 links ER stress to intestinal inflammation and confers genetic risk for human inflammatory bowel disease. *Cell* 134 (5), 743-756
59 Richardson, C.E. *et al.* (2010) An essential role for XBP-1 in host protection against immune activation in C. elegans. *Nature* 463 (7284), 1092-1095
60 Weitzman, M.D. and Weitzman, J.B. (2014) What's the Damage? The Impact of Pathogens on Pathways that Maintain Host Genome Integrity. *Cell Host Microbe* 15 (3), 283-294
61 Shiloh, Y. and Ziv, Y. (2013) The ATM protein kinase: regulating the cellular response to genotoxic stress, and more. *Nat Rev Mol Cell Biol* 14 (4), 197-210
62 Figueiredo, N. *et al.* (2013) Anthracyclines induce DNA damage response-mediated protection against severe sepsis. *Immunity* 39 (5), 874-884
63 Repetto, M. *et al.* (2012) Lipid Peroxidation: Chemical Mechanism, Biological Implications and Analytical Determination. In *Biochemistry, Genetics and Molecular Biology* (Catala, A., ed), INTECH
64 Imai, Y. *et al.* (2008) Identification of oxidative stress and Toll-like receptor 4 signaling as a key pathway of acute lung injury. *Cell* 133 (2), 235-249
65 Seiler, A. *et al.* (2008) Glutathione peroxidase 4 senses and translates oxidative stress into 12/15-lipoxygenase dependent- and AIF-mediated cell death. *Cell Metab* 8 (3), 237-248
66 Stocker, R. *et al.* (1987) Bilirubin is an antioxidant of possible physiological importance. *Science* 235 (4792), 1043-1046
67 Gozzelino, R. *et al.* (2010) Mechanisms of cell protection by heme oxygenase-1. *Annu Rev Pharmacol Toxicol* 50, 323-354
68 Kroemer, G. *et al.* (2010) Autophagy and the integrated stress response. *Mol Cell* 40 (2), 280-293
69 Buchon, N. *et al.* (2013) Gut homeostasis in a microbial world: insights from Drosophila melanogaster. *Nat Rev Microbiol* 11 (9), 615-626

70 Cunnington, A.J. *et al.* (2012) Malaria impairs resistance to Salmonella through heme- and heme oxygenase-dependent dysfunctional granulocyte mobilization. *Nat Med* 18 (1), 120-127
71 Jamieson, A.M. *et al.* Influenza virus-induced glucocorticoids compromise innate host defense against a secondary bacterial infection. *Cell Host Microbe* 7 (2), 103-114
72 Soares, M.P. and Bach, F.H. (2009) Heme oxygenase-1: from biology to therapeutic potential. *Trends Mol Med* 15, 50-58
73 Berberat, P.O. *et al.* (2003) Heavy chain ferritin acts as an antiapoptotic gene that protects livers from ischemia reperfusion injury. *FASEB Journal* 17 (12), 1724-1726
74 Russell, R.R., 3rd *et al.* (2004) AMP-activated protein kinase mediates ischemic glucose uptake and prevents postischemic cardiac dysfunction, apoptosis, and injury. *J Clin Invest* 114 (4), 495-503
75 Bailly-Maitre, B. *et al.* (2006) Cytoprotective gene bi-1 is required for intrinsic protection from endoplasmic reticulum stress and ischemia-reperfusion injury. *Proc Natl Acad Sci U S A* 103 (8), 2809-2814
76 Kaiser, J. (2003) Hormesis. Sipping from a poisoned chalice. *Science* 302 (5644), 376-379
77 Ke, B. *et al.* (2013) KEAP1-NRF2 complex in ischemia-induced hepatocellular damage of mouse liver transplants. *J Hepatol* 59 (6), 1200-1207
78 Soares, M.P. *et al.* (1999) Accommodation. *Immunology Today* 20 (10), 434-437
79 Soares, M.P. *et al.* (1998) Expression of heme oxygenase-1 can determine cardiac xenograft survival. *Nat Med* 4 (9), 1073-1077
80 Uruno, A. *et al.* (2013) The Keap1-Nrf2 system prevents onset of diabetes mellitus. *Mol Cell Biol* 33 (15), 2996-3010
81 Jiang, T. *et al.* (2014) Nrf2 suppresses lupus nephritis through inhibition of oxidative injury and the NF-kappaB-mediated inflammatory response. *Kidney Int* 85 (2), 333-343
82 Wruck, C.J. *et al.* (2011) Role of oxidative stress in rheumatoid arthritis: insights from the Nrf2-knockout mice. *Ann Rheum Dis* 70 (5), 844-850
83 Johnson, D.A. *et al.* (2010) The absence of the pro-antioxidant transcription factor Nrf2 exacerbates experimental autoimmune encephalomyelitis. *Toxicol Sci* 114 (2), 237-246
84 Engin, F. *et al.* (2013) Restoration of the unfolded protein response in pancreatic beta cells protects mice against type 1 diabetes. *Sci Transl Med* 5 (211), 211ra156
85 Hussien, Y. *et al.* (2014) Genetic inactivation of PERK signaling in mouse oligodendrocytes: Normal developmental myelination with increased susceptibility to inflammatory demyelination. *Glia*
86 Seixas, E. *et al.* (2009) Heme oxygenase-1 affords protection against noncerebral forms of severe malaria. *Proc Natl Acad Sci U S A* 106 (37), 15837-15842
87 Gozzelino, R. *et al.* (2012) Metabolic adaptation to tissue iron overload confers tolerance to malaria. *Cell Host Microbe* 12 (5), 693-704
88 Caldwell, R.M. *et al.* (1958) Tolerance to Cereal Leaf Rusts. *Science* 128 (3326), 714-715
89 Schaefer, J.F. (1971) Tolerance to plant disease. *Annual Reviews of Phytopathology* 9, 235-252

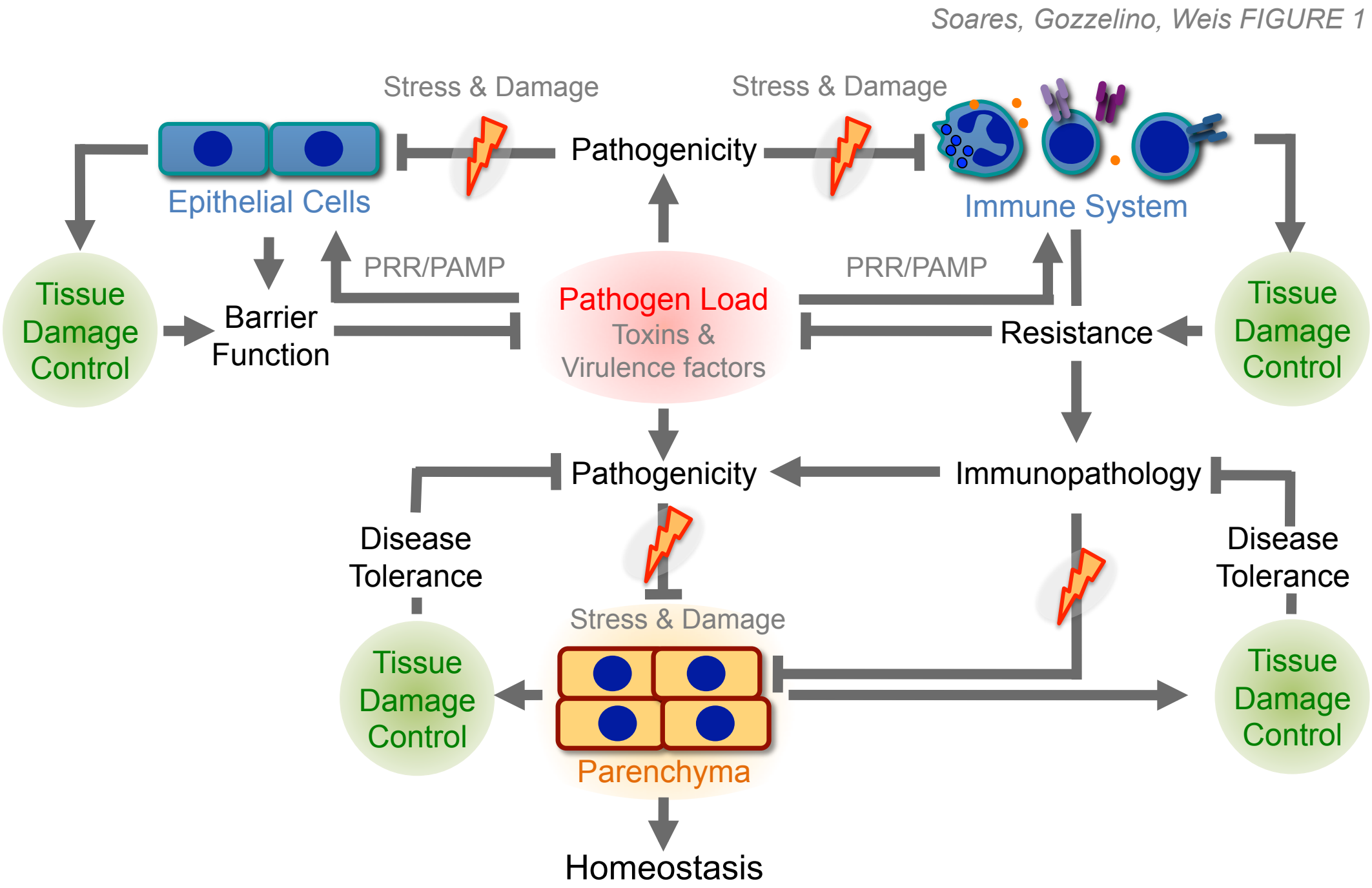
90 Cobb, N.A. (1894) Contributions to aneconomic knowledge of Australian rusts (Uredineae) In *Agr. Gas. N. S. W.* , pp. 239-250 Sydney : C. Potter, govt. printer, 1894
91 Ferrandon, D. (2013) The complementary facets of epithelial host defenses in the genetic model organism Drosophila melanogaster: from resistance to resilience. *Curr Opin Immunol* 25 (1), 59-70
92 Teixeira, L. *et al.* (2008) The bacterial symbiont Wolbachia induces resistance to RNA viral infections in Drosophila melanogaster. *PLoS Biol* 6 (12), e2
93 Raberg, L. *et al.* (2007) Disentangling genetic variation for resistance and tolerance to infectious diseases in animals. *Science* 318 (5851), 812-814
94 Croker, B. *et al.* (2007) ATP-sensitive potassium channels mediate survival during infection in mammals and insects. *Nat Genet* 39 (12), 1453-1460
95 Gozzelino, R. and Soares, M.P. (2013) Coupling Heme and Iron Metabolism via Ferritin H Chain. *Antioxid Redox Signal*
96 Pamplona, A. *et al.* (2007) Heme oxygenase-1 and carbon monoxide suppress the pathogenesis of experimental cerebral malaria. *Nat Med* 13 (6), 703-710
97 Ferreira, A. *et al.* (2011) Sickle Hemoglobin Confers Tolerance to Plasmodium Infection. *Cell* 145 (April 29), 398–409
98 Larsen, R. *et al.* (2010) A central role for free heme in the pathogenesis of severe sepsis. *Sci Transl Med* 2 (51), 51ra71
99 Hitomi, J. *et al.* (2008) Identification of a molecular signaling network that regulates a cellular necrotic cell death pathway. *Cell* 135 (7), 1311-1323
100 Duprez, L. *et al.* (2011) RIP kinase-dependent necrosis drives lethal systemic inflammatory response syndrome. *Immunity* 35 (6), 908-918
101 Rodrigue-Gervais, I.G. *et al.* (2014) Cellular inhibitor of apoptosis protein cIAP2 protects against pulmonary tissue necrosis during influenza virus infection to promote host survival. *Cell Host Microbe* 15 (1), 23-35
102 Nairz, M. *et al.* (2010) The struggle for iron - a metal at the host-pathogen interface. *Cell Microbiol* 12 (12), 1691-1702
103 Drakesmith, H. and Prentice, A.M. (2012) Hepcidin and the iron-infection axis. *Science* 338 (6108), 768-772
104 Flo, T.H. *et al.* (2004) Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron. *Nature* 432 (7019), 917-921
105 Fritsche, G. *et al.* (2007) Modulation of macrophage iron transport by Nramp1 (Slc11a1). *Immunobiology* 212 (9-10), 751-757
106 Weiss, G. and Goodnough, L.T. (2005) Anemia of chronic disease. *N Engl J Med* 352 (10), 1011-1023
107 Harrison, P.M. and Arosio, P. (1996) Ferritins - Molecular Properties, Iron Storage Function and Cellular Regulation. *Biochimica et Biophysica Acta - Bioenergetics* 1275 (3), 161-203
108 Deak, M. *et al.* (1999) Plants ectopically expressing the iron-binding protein, ferritin, are tolerant to oxidative damage and pathogens. *Nat Biotechnol* 17 (2), 192-196
109 Motohashi, H. *et al.* (1997) The world according to Maf. *Nucleic Acids Res* 25 (15), 2953-2959

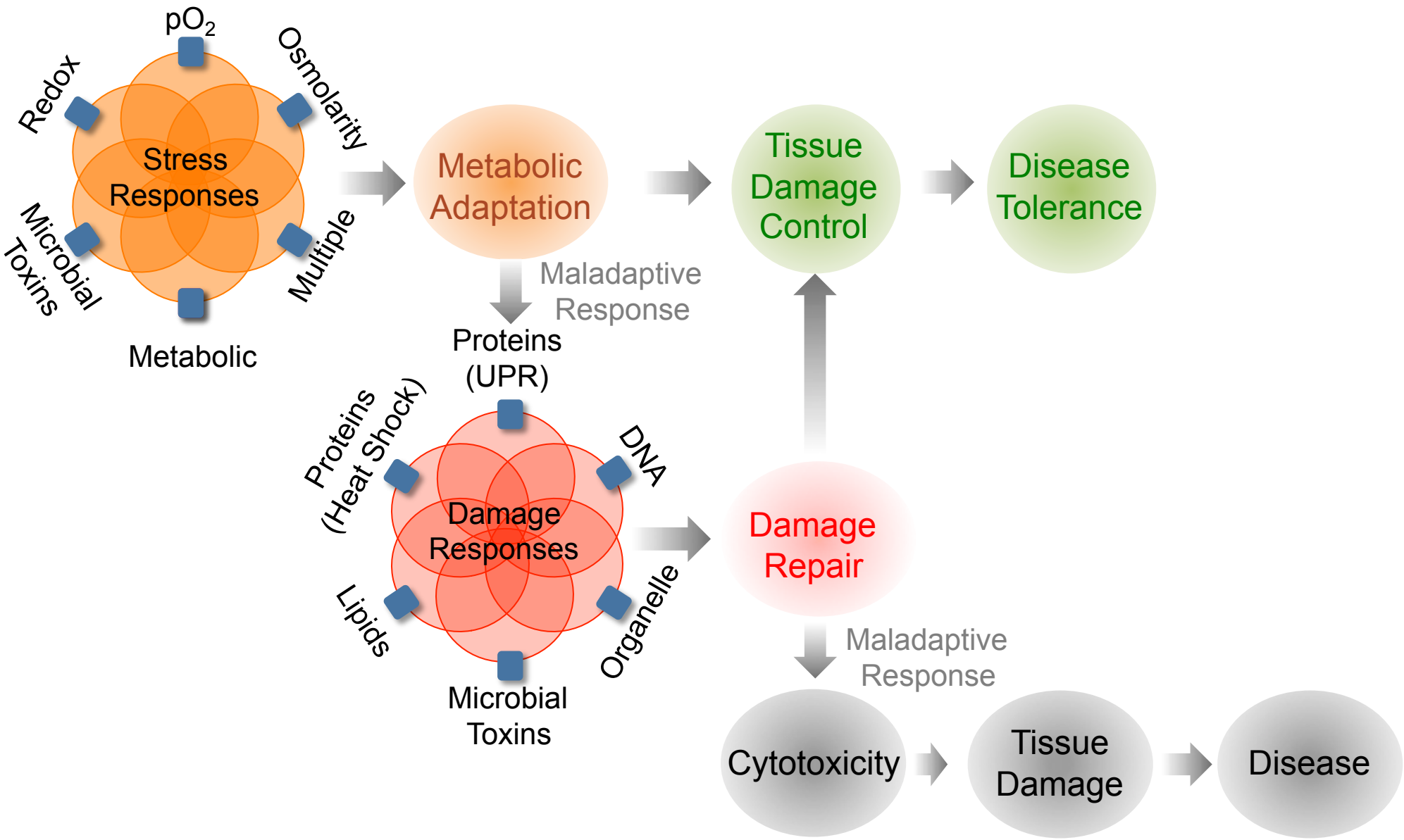
ABBREVIATION:

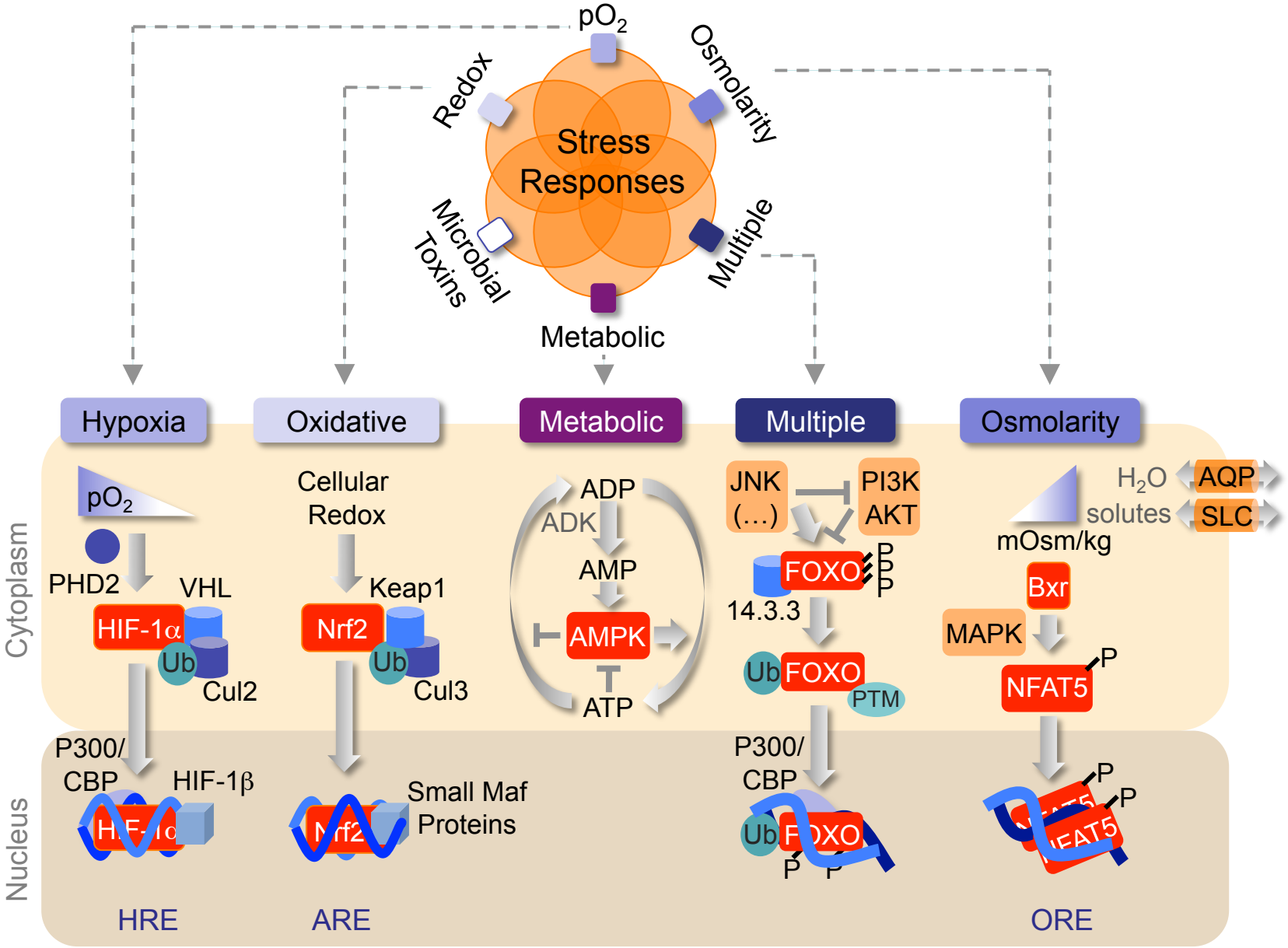
ADK: adenylate kinase; **AMPK**: AMP-activated protein kinase; **AQP**: aquaporin; **ARE**: antioxidant responsive elements; **ATF6**: activating transcription factor-6; **ATM**: ataxia-telangiectasia mutated; **CBP**: CREB binding protein; **CO**: Carbon Monoxide; **CREB**: cAMP response element-binding protein; **ER**: endoplasmic reticulum; **Fe**: iron; **FOXO**: Forkhead box O; **FTH**: ferritin heart/heavy chain; **FTL**: ferritin liver/light chain; **GRP-78**: glucose-regulated protein; **HAMP**: hepcidin antimicrobial peptide gene; **HIF-1α**: hypoxia-inducible factor 1 alpha; **HO-1**: HMOX1/heme oxygnease-1; **HRE**: hypoxia responsive elements; **HSE**: heat shock elements; **HSF1**: heat shock factor 1; **HSP**: heat shock proteins; **IRE1**: inositol requiring protein-1 ; **IRI**: ischemia and reperfusion injury; **JNK**: Jun N-terminal kinase; **Keap1**: Kelch-like ECH-associated protein 1; **MAPK**: mitogen activated protein kinases; **NFAT5**: nuclear factor of activated T-cells 5; NRAMP-1 natural resistance associated macrophage protein function; **NRF2**: nuclear factor-erythroid 2-related factor 2; **ORE**: osmotic response elements; **PAMP**: pathogen associated molecular patterns; **PERK**: protein kinase RNA–like endoplasmic reticulum kinase; **PHD2**: prolyl hydroxylase 2; **PRR**: pattern recognition receptors; **PTM**: post-translational modifications; **HSP**: small heat shock proteins; **SLC**: solute carrier channels; TNF: tumor necrosis factor; **TonEBP**: tonicity-responsive element binding protein; **Ub**: ubiquitinating; **UPR**: unfolded protein response; **VHL/Cul3**: von Hippel-Lindau; **XBP1**: X-box binding protein 1.

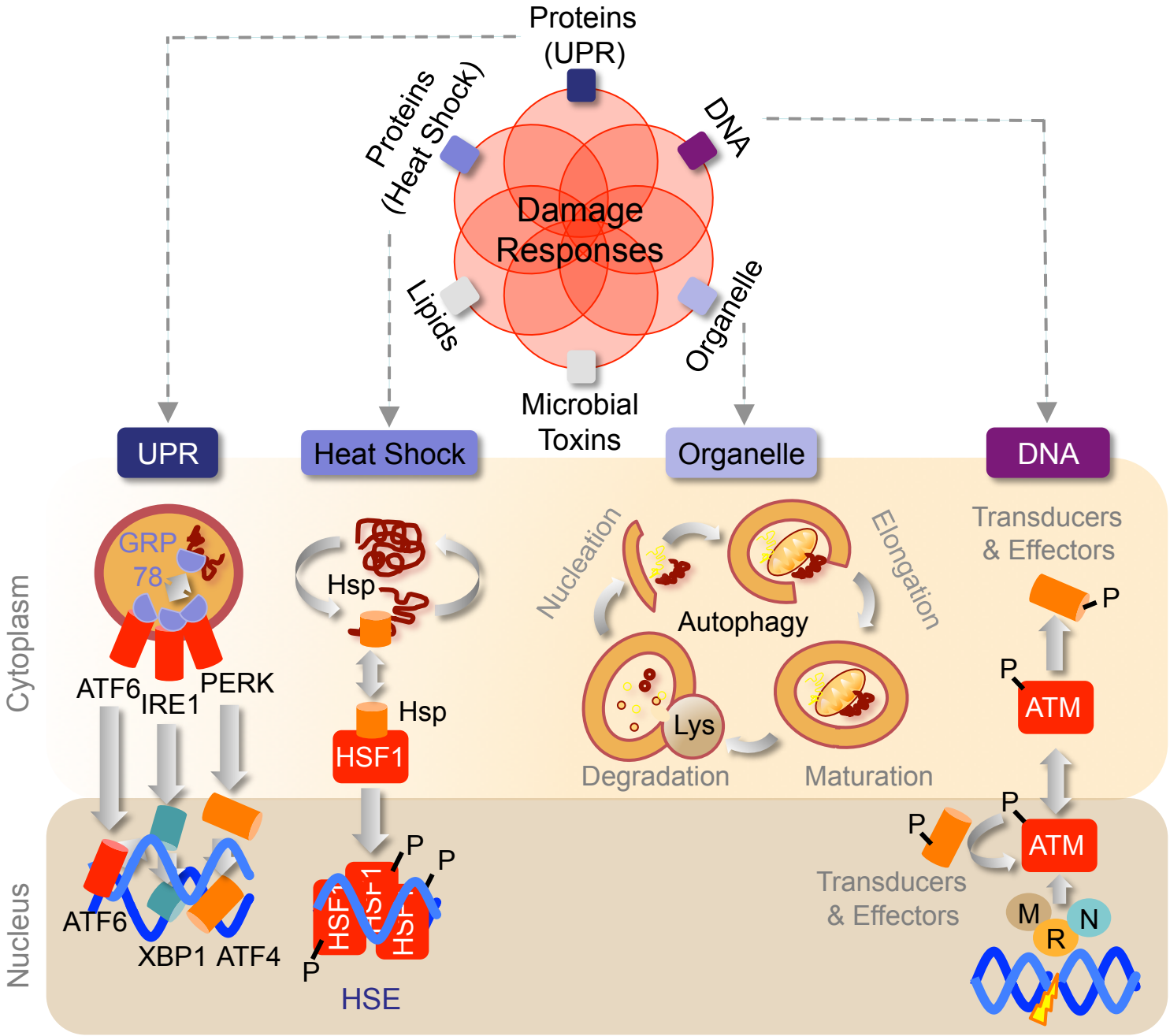
ACKNOWLEDGEMENTS: The authors are indebted to Jonathan Howard and Luis Teixeira (Instituto Gulbenkian de Ciência) as well as Damian Trujillo (Stanford University) for revision, input and comments to the manuscript. Support by Fundação para a Ciência e Tecnologia grants PTDC/SAU-TOX/116627/2010, HMSP-ICT/0022/2010 to MPS and SFRH/BPD/44256/2008 to RG, European Community 7th Framework Grant ERC-2011-AdG. 294709-DAMAGECONTROL to MPS and Deutsche Forschungsgemeinschaft (DFG) to SW.

Figure


Soares, Gozzelino, Weis FIGURE 1
Stress & Damage
Stress & Damage
Pathogenicity
Epithelial Cells
Immune System
Tissue Damage Control
Barrier Function
PRR/PAMP
PRR/PAMP
Pathogen Load
Toxins & Virulence factors
Resistance
Tissue Damage Control
Pathogenicity
Immunopathology
Disease Tolerance
Disease Tolerance
Stress & Damage
Tissue Damage Control
Tissue Damage Control
Parenchyma
Homeostasis


pO_2
Redox
Osmolarity
Stress Responses
Microbial Toxins
Multiple
Metabolic
Metabolic Adaptation
Tissue Damage Control
Disease Tolerance
Maladaptive Response
Proteins (UPR)
Proteins (Heat Shock)
DNA
Damage Responses
Lipids
Organelle
Microbial Toxins
Damage Repair
Maladaptive Response
Cytotoxicity
Tissue Damage
Disease


pO2
Redox
Osmolarity
Stress Responses
Microbial Toxins
Multiple
Metabolic
Hypoxia
Oxidative
Metabolic
Multiple
Osmolarity
Cytoplasm
Nucleus
pO2
PHD2
VHL
HIF-1α
Ub
Cul2
P300/ CBP
HIF-1β
HRE
Cellular Redox
Keap1
Nrf2
Ub
Cul3
Small Maf Proteins
ARE
ADP
ADK
AMP
AMPK
ATP
JNK (…)
PI3K AKT
FOXO
P
14.3.3
Ub
FOXO
PTM
P300/ CBP
Ub
FOXO
P
H2O
AQP
solutes
SLC
mOsm/kg
Bxr
MAPK
NFAT5
P
ORE


Proteins
(UPR)
Proteins
(Heat Shock)
DNA
Damage
Responses
Lipids
Organelle
Microbial
Toxins
UPR
Heat Shock
Organelle
DNA
Cytoplasm
Nucleus
GRP
78
ATF6
IRE1
PERK
Hsp
Hsp
HSF1
Nucleation
Elongation
Autophagy
Lys
Degradation
Maturation
Transducers
& Effectors
P
P
ATM
ATF6
XBP1
ATF4
HSF1
HSF1
HSF1
P
P
P
HSE
P
P
ATM
Transducers
& Effectors
M
N
R