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Disease Tolerance as an Inherent Component of Immunity

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Abstract

Pathogenic organisms exert a negative impact on host health, revealed by the clinical signs of infectious diseases. Immunity limits the severity of infectious diseases through resistance mechanisms that sense and target pathogens for containment, killing, or expulsion. These resistance mechanisms are viewed as the prevailing function of immunity. Under pathophysiologic conditions, however, immunity arises in response to infections that carry health and fitness costs to the host. Therefore, additional defense mechanisms are required to limit these costs, before immunity becomes operational as well as thereafter to avoid immunopathology. These are tissue damage control mechanisms that adjust the metabolic output of host tissues to different forms of stress and damage associated with infection. Disease tolerance is the term used to define this defense strategy, which does not exert a direct impact on pathogens but is essential to limit the health and fitness costs of infection. Under this argument, we propose that disease tolerance is an inherent component of immunity.

INTRODUCTION

Disease tolerance was first described a century and a half ago (1, 2), as an inherent component of plant immunity (3, 4). Over the last decade it has become apparent that this evolutionarily conserved defense strategy is also operational in animals, as demonstrated in flies (5, 6) and mammals, including rodents (7, 8) and humans (9). There are now multiple examples where disease tolerance appears to play a central role in conferring host protection against viral, bacterial, protozoan, and fungal infections (**Tables 1**, **2**).

Likely because "tolerance" is a term used to define several fundamental properties of immunity, the concept of disease tolerance and its associated terminology are often misinterpreted. Etymologically, tolerance can be traced back to Old French (fourteenth century): *tolerance*, from the Latin *tolerantia*, which referred to the capacity to bear, endure, or tolerate, i.e., *tolerare*. As disease tolerance denotes this capacity to bear, endure, or tolerate an infection, this terminology honors the early meaning of the word tolerance, used in the initial description of a defense strategy that limits the negative impact of infection on host health and fitness without exerting a direct impact on pathogens (3, 4) (**Figure 1**).

By definition, disease tolerance relates to a process that mitigates disease. However, the World Health Organization ambiguously defines disease as opposition to health: "a state of complete physical, mental and social well-being, not merely the absence of disease or infirmity" (10). To avoid this ambiguity, in the original description in plants (1, 2), disease tolerance was inferred from variations in host fitness, a precisely quantifiable parameter defined by the capacity to yield progeny. Of note, fitness is often interchangeable with health, considering that healthy individuals are more likely to yield progeny (3, 11).

Table 1 Contribution of stress and damage responses to disease tolerance to infection

Pathogen class	Stress/damage response	Effector[a]	Pathogen	Effect on disease tolerance	Ref.
Viruses	Xenobiotic stress	***Ahr***	Herpes simplex	↑	231
	Metabolic stress	Glucose	Influenza	↑	52
		Ppara	Influenza	↓	52
		Zinc	HIV[b]	↑	186
		SCFAs	Influenza	↑	232
	UPR	***Chop***	Influenza	↓	52
	Cell proliferation and growth	*Areg*	Influenza	↑	131
Bacteria	Oxidative stress	***Hmox1***	CLP	↑	58
		Fth	CLP	↑	23
		Nrf2	LPS	↑	233
		Mt1	*Helicobacter pylori*	↑	234
	Hypoxic stress	*Hif1a*	*Streptococcus pneumoniae*	↓	235
			Staphylococcus aureus	↓	235
	Osmotic stress	***Nfat5***	LPS	↓	236
	Xenobiotic stress	***Ahr***	LPS	↑	37
			Salmonella Typhimurium		
			Group B *Streptococcus*		

(*Continued*)

Table 1 (*Continued*)

Pathogen class	Stress/damage response	Effector[a]	Pathogen	Effect on disease tolerance	Ref.
	Proteotoxic stress	***Hsf1***	*Listeria monocytogenes*	↑	237
	Genotoxic stress	***P21***	LPS	↑	238
		P53	LPS	↑	239
			Streptococcus pneumoniae	↑	240
			Klebsiella pneumoniae	↑	240
	Metabolic stress	***mTor***	LPS	↓	241
			LPS	↓	242
		Gcn2	LPS	↓	243
		G6pc1	CLP	↑	23
		Srebf1	LPS	↑	244
		Anorexia	*Salmonella enterica* Typhimurium$^{\Delta slrP}$	↓	16
	DNA damage	***Atm***	CLP	↑	245
	UPR	***Chop***	LPS	↑	51
		Atf3	LPS	↑	246
	Programmed cell death	*Pfif*	*Mycobacterium tuberculosis*	↑	86
	Several	***Sirt***	LPS	↑	247
Protozoa	Oxidative stress	***Hmox1***	*Plasmodium* spp.	↑	8, 9, 17, 56, 57
		Fth	*Plasmodium chabaudi*	↑	9
			Plasmodium vivax[b]	↑	9
		Sickle Hb	*Plasmodium berghei*	↑	17
		Nrf2	*Plasmodium berghei*	↑	17, 57
		Glucose	*Plasmodium chabaudi*	↑	191
			Plasmodium berghei		
	Several	***Sirt1***	*Trypanosoma cruzi*	↑	248

Abbreviations: CLP, cecal ligation and puncture; *Fth*, ferritin heavy chain; LPS, lipopolysaccharide; *Mt1*, Metallothionein 1; *Ppara*, peroxisome proliferator activated receptor alpha; SCFA, short-chain fatty acid; *Sirt*, Sirtuin; UPR, unfolded protein response.

[a]Genes in bold are components of the transcriptional stress and damage response network.

[b]Human; when not indicated, host is mouse.

TISSUE DAMAGE CONTROL

Disease tolerance is driven by tissue damage control mechanisms, which support the functional output of parenchyma tissues and maintain vital homeostatic parameters within a dynamic range compatible with host survival to infection (3, 12, 13) (**Figure 1**). Tissue damage control mechanisms are regulated by a number of evolutionarily conserved stress and damage responses (12, 14), which limit the negative impact of different forms of stress and damage emanating either

Table 2 Individual contributions of immunoregulatory genes to disease tolerance to infection

Pathogen class	Immune response	Effector[a]	Pathogen	Effect on disease tolerance	Ref.
Viruses	Cytokines	*Il22*	Influenza	↑	117
			Dengue virus	↑	116
Bacteria	Innate immunity	*cRel*	CLP	↑	249
		Tlr2	*Streptococcus suis*	↓	250
	Adaptive immunity	*Ctla4*	*Mycobacterium tuberculosis*	↓	251
		Pdl1	CLP	↓	252
	Cytokines and cytokine receptors	*Ifnar1*	*Streptococcus pyogenes*	↑	253
		Il22	*Citrobacter rodentium*	↑	254
	Toxin neutralization	*Atg16l*	*Staphylococcus aureus*	↑	255
		Adam10	*Staphylococcus aureus*	↓	256
Protozoa	Innate immunity	*Myd88*	*Plasmodium berghei*	↓	257
		Tlr2/9	*Plasmodium berghei*	↓	257
		PMN cells	*Plasmodium berghei*	↑	89
		Pdl1/Ctla4	*Plasmodium berghei*	↓	105
	Cytokines and cytokine receptors	*Ifng*	*Plasmodium berghei*	↓	258
		Lta	*Plasmodium berghei*	↓	259
		St2/Il33r	*Plasmodium berghei*	↓	260
		Il6ra	*Plasmodium chabaudi*	↓	261
		Il10	*Plasmodium chabaudi*	↑	100
		Il22	*Plasmodium chabaudi*	↑	114
			Leishmania major	↑	115
	Toxins	*Pl*GPI	*Plasmodium berghei*	↓	262
		*Pb*Hmgb2	*Plasmodium berghei*	↓	263
Fungi	Signaling	*Ifnar1*	*Candida albicans*	↑	264
		Il17c	*Candida albicans*	↓	265
	Toxin	*Af*Ppo	*Aspergillus fumigatus*	↑	266
Helminths	Innate immunity	*Myd88*	*Trichinella spiralis*	↓	267
	Signaling	*St2/IL33R*	*Trichinella spiralis*	↓	267
		Il4ra	*Schistosoma mansoni*	↑	268

Abbreviations: *Af*Ppo, *A. fumigatus* dioxygenase; *Ifnar1*, IFN-α receptor 1; *Adam10*, ADAM metallopeptidase domain 10; *Atg16l*, autophagy related 16 like; *Pb*Hmgb2, *P. berghei* eukaryotic high-mobility-group-box 2; *Pl*GPI, *P. falciparum* glycosylphosphatidylinositol; PMN, polymorphonuclear.

[a]Genes in bold are components of the transcriptional stress and damage response network.

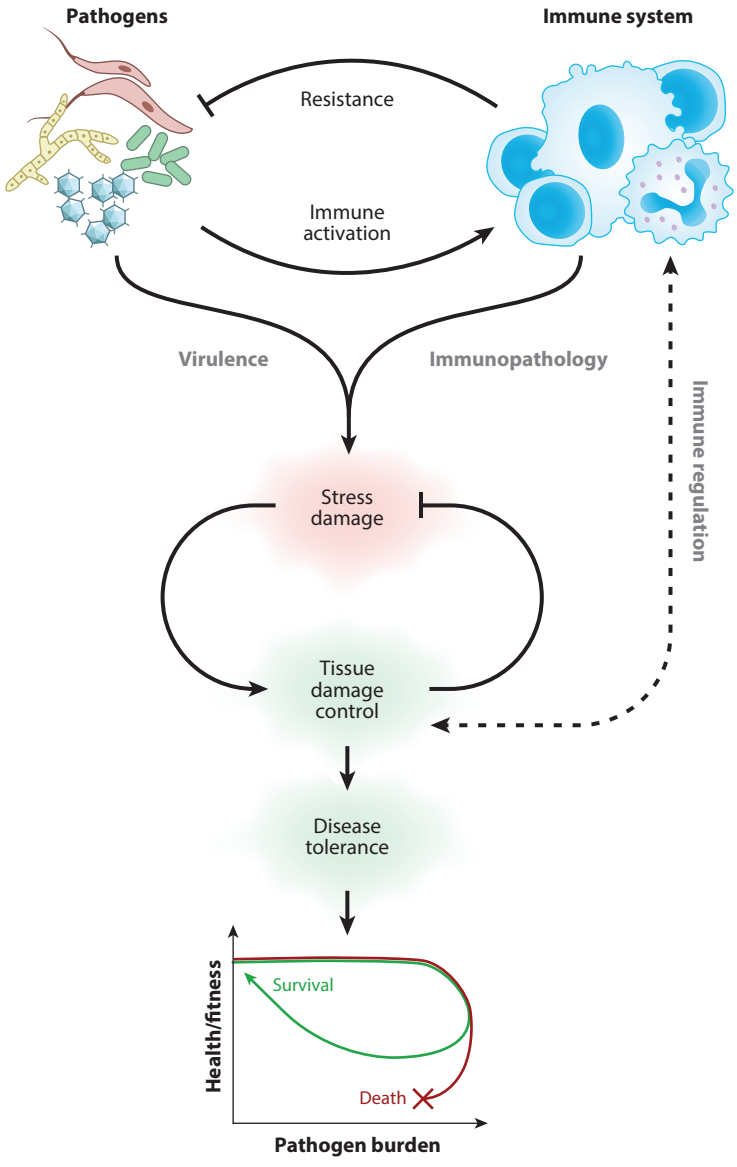


Figure 1

Host-pathogen interactions are usually summarized by the activation of the host immune system by pathogens, triggering a response that provides resistance to infection. This does not take into consideration the different forms of stress and damage imposed on host parenchyma tissues, by pathogens (virulence) or immune-driven resistance mechanisms (immunopathology). The countervailing response to these processes, referred to as tissue damage control, underlies the establishment of disease tolerance to infection. Disease tolerance is inferred when variations between host health or fitness parameters occur independently of pathogen load over time, as revealed by the corresponding disease trajectories (223). Of note, tissue damage control limits immunopathology and therefore might enable resistance mechanisms to operate in a more robust or prolonged manner to reduce pathogen load.

directly from pathogens, i.e., toxins, or indirectly from immune-driven resistance mechanisms, i.e., immunopathology. The nature and organization of these stress and damage responses, and how these contribute functionally to establish disease tolerance to infection, remain unclear.

Stress responses sense and react to variations in environmental cues, providing a level of metabolic adaptation required to sustain core cellular functional outputs, to the detriment of accessory ones (12, 14). When metabolic adaptation is insufficient, damage responses sense and react to damage imposed on different cellular components, repairing or replacing cellular macromolecules and organelles to sustain core cellular functional outputs (12, 14).

Stress and damage responses are controlled by a number of evolutionarily conserved transcriptional master regulators (12, 14). These can induce or repress the expression of specific sets of effector genes, which provide cellular adaptation to different forms of stress or damage associated with infection (12, 14). Ultimately, it is the expression of these stress- and damage-responsive genes that confers tissue damage control and establishes disease tolerance to infection.

COUPLING DISEASE TOLERANCE AND RESISTANCE TO INFECTION

Infectious diseases are associated with the development of sickness behavior, encompassing malaise, loss of appetite (anorexia), social withdrawal, and lethargy (11, 15). By promoting host health, disease tolerance should counter this behavioral response and in doing so limit its proposed protective effects against pathogen transmission (11). As such, disease tolerance should, per se, favor the spread of infectious diseases at a population level. In support of this notion, some bacterial pathogens such as *Salmonella enterica* Typhimurium can promote host disease tolerance as a strategy to favor their transmission (16). This suggests that genes, or genetic variations, promoting disease tolerance should be selected against through evolution; this does not, however, appear to be the case (17), indicating that the evolutionary trade-off imposed by disease tolerance is somehow mitigated. This occurs most likely by coupling disease tolerance to resistance mechanisms that clear pathogens at an individual level and prevent their transmission at a population level. There are several possible scenarios via which this might occur.

First, stress and damage responses enforcing tissue damage control should enable immune-driven resistance mechanisms to operate under negligible immunopathology (3, 18) (**Figures 1**, **2**). Presumably, this allows for resistance mechanisms to operate in a more robust manner and achieve pathogen clearance, a prerequisite to halt disease transmission. This argues that tissue damage control mechanisms operating in parenchyma tissues must act in concert with immune-driven resistance mechanisms to limit the health and fitness costs of infection, at individual and population levels.

Second, stress and damage responses regulate how parenchyma tissues respond to cytokines and other cues emanating from immune cells, functionally integrating resistance and disease tolerance to infection. Namely, pathogen sensing via pattern recognition receptors (PRRs) triggers the secretion of cytokines, e.g., IL-1β, TNF, IL-6, IL-10, or IL-22, which act systemically via their corresponding receptors expressed in parenchyma tissues. For example, TNF, IL-6, and IL-22 signal in hepatocytes to trigger the acute phase response, characterized by the production of components of the complement cascade as well as C-reactive, serum amyloid, and mannose-binding proteins, which target pathogens for clearance by the complement cascade and phagocytosis. Hepcidin is another central component of the acute phase response. It acts as a master regulator of iron metabolism and restricts extracellular pathogens from accessing this essential micronutrient (19)—a resistance mechanism known as nutritional immunity (20, 21). Similar to hepcidin, the induction of other iron-regulatory genes in response to cytokines

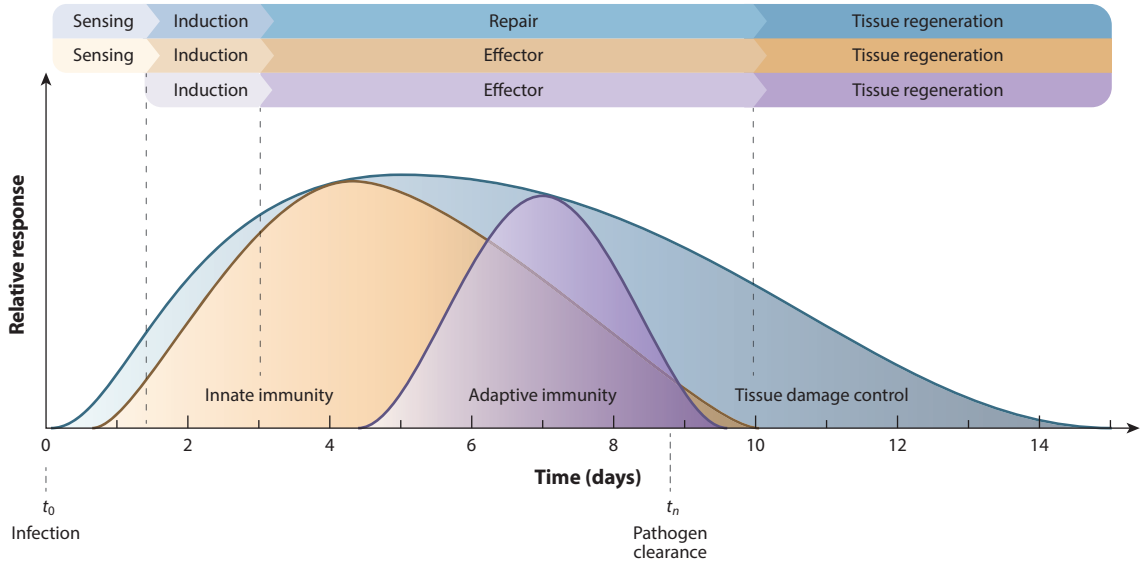


Figure 2

Tissue damage control as a component of immunity. Pathogens impose different forms of stress and damage on host cells. This is likely countered via stress and damage responses, which confer tissue damage control; that is, they adjust host metabolism to different forms of stress and damage imposed by pathogens. Innate immunity (*orange*) affords an early resistance mechanism, coupled over time to activation of adaptive immunity (*violet*), which provides high-affinity targeting of pathogens for containment, expulsion, or killing. While highly advantageous in reducing the health and fitness costs of infection, innate and adaptive immunity can cause immunopathology. This trade-off is countered via stress and damage responses that confer tissue damage control (*blue*), alongside tissue regeneration responses, to establish disease tolerance to infection.

such as TNF, IL-6, and IL-22 should also contribute to integrate resistance and disease tolerance (22).

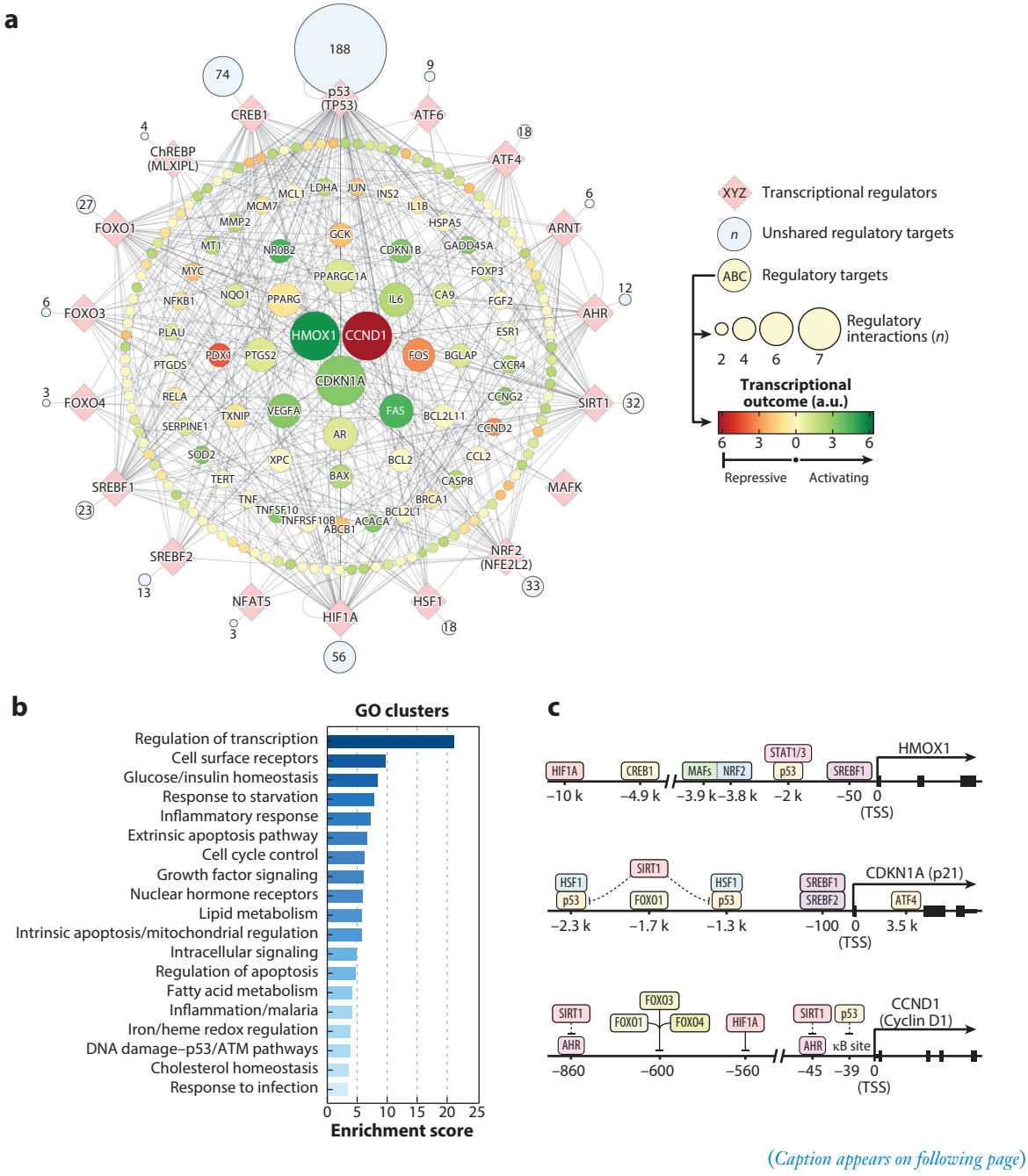
Third, stress and damage responses modulate how cytokines and other factors affect host metabolism. As an example, TNF and IL-6 regulate liver glucose production, which exerts a major impact on organismal glucose homeostasis in response to infection (23). This may also impact directly on pathogens that use glucose as a major carbon source as well as on activated leukocytes, which undergo a metabolic switch toward glycolysis, presumably regulating resistance to infection (24).

Considering that stress and damage responses underlying tissue damage control can modulate resistance to infection, this strengthens the case that disease tolerance is an integral component of immunity (**Figures 1**, **2**). Understanding how stress and damage responses operate is therefore critical to understand how disease tolerance and resistance are integrated functionally as components of immunity to confer protection against infection.

ORGANIZATION OF THE TRANSCRIPTIONAL STRESS AND DAMAGE RESPONSE NETWORK

Stress and damage responses evolved most likely from ancestral forms of life where these provided organismal adaptation to variation of homeostatic parameters beyond viable thresholds (25–28). Infections are often associated with wide variations of host homeostatic parameters (12, 14, 28), which are sensed and reacted upon by a transcriptional stress and damage response

network (**Figure 3**). This network regulates the expression of a number of effector genes (25–27) that confer tissue damage control and establish disease tolerance to infection (**Table 1**). The molecular details on how these stress and damage responses operate have been described elsewhere (12, 14) and are briefly summarized below.



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

The transcriptional stress and damage response network. (*a*) Regulatory relationships (*lines*) between stress- or damage-responsive transcriptional master regulators (*pink diamonds*) and effector genes (*inner circles*). Node size is proportional to the number of transcriptional regulators converging upon the node. Each node refers to a core effector gene, upon which at least two of the transcriptional master regulators act. Induction and repression of gene expression are indicated by green and red, respectively, calculated as the sum of the described regulatory relationships for any given node (activating = 1, repressive = −1). Light blue circles represent genes regulated by a single (private) transcriptional master regulator, and *n* is the number of genes regulated. Human and mouse data were extracted from the TRRUST database, version 2 (224). (*b*) Gene ontology term enrichment analysis using DAVID functional annotation clustering (225). The list of target genes from panel *a* regulated by two or more transcriptional regulators was used, and analysis was performed against a *Homo sapiens* background list, using default settings (similarity term overlap = 4, similarity threshold = 0.35, initial and final group membership = 4, multiple linkage threshold = 0.5, EASE = 1.0). Clusters with no overlapping designations are shown. (*c*) Promoter regions of core effector genes with the highest number of transcriptional regulators (from panel *a*), and the respective binding sites and/or regions required for transcriptional regulation. Abbreviations: DAVID, Database for Annotation, Visualization and Integrated Discovery; EASE, Expression Analysis Systematic Explorer (modified Fisher exact test); GO, gene ontology; κB site, Rel/NF-κB binding site; TRRUST, Transcriptional Regulatory Relationships Unraveled by Sentence-Based Text Mining; TSS, transcriptional start site.

Oxidative stress, often associated with infection, is sensed by the host via different mechanisms, including KEAP1 (Kelch-like ECH-associated protein 1), a constitutive repressor of the transcriptional master regulator of oxidative stress, NRF2 [nuclear factor (erythroid-derived 2)-like 2]. This allows NRF2 to associate with small musculoaponeurotic fibrosarcoma (sMAF) proteins and regulate the expression of effector genes (29, 30) (**Figure 3**), establishing disease tolerance to infection (**Table 1**).

Hypoxia is another form of stress often associated with infection, characterized by lower than physiologic supply of O_2 (31). This is sensed by host prolyl hydroxylases, which act as constitutive repressors of the hypoxia-inducible factor (HIF) family of transcription factors (31). Hypoxia relieves the repressive effect of prolyl hydroxylases, promoting the transcription of HIF-regulated effector genes (**Figure 3**), modulating resistance (32), and compromising disease tolerance to bacterial infection when expressed by myeloid cells (**Table 1**).

Systemic infections can be associated with variations in solute concentration in plasma (33), which are sensed by guanine nucleotide exchange factor BRX/AKAP13 (protein kinase A–anchoring protein 13). This triggers the activation of the transcription factor NFAT5 (nuclear factor of activated T cells 5) (34), which regulates the transcription of effector genes (**Figure 3**), establishing disease tolerance to infection (**Table 1**).

Xenobiotic molecules expressed by pathogens can be sensed via AHR (aryl hydrocarbon receptor) (35), which undergoes ligand-binding-induced nuclear translocation with ARNT (AHR nuclear translocator) (36). This complex drives the transcription of effector genes (**Figure 3**) regulating resistance (35) and disease tolerance (37) to infection (**Table 1**).

Infections can be associated with anorexia of infection, a hallmark of sickness behavior characterized by a reduction of appetite (11, 15). This can lead to variations in glycemia, which activate the protein phosphatase 2A (PP2A), promoting nuclear translocation of the factor carbohydrate response element–binding protein (ChREBP) and driving the transcription of target genes (**Figure 3**), including glycolytic genes (38). In addition, variations in glycemia can lead to activation of gluconeogenic transcriptional programs by cAMP responsive element binding protein 1 (CREB1) (39) (**Figure 3**). Relative concentrations of different amino acids are sensed by mammalian target of rapamycin (mTOR) (40), the general control nonderepressible 2 (GCN2) kinase (40), or activating transcription factor 3 (ATF3) and ATF4 (41) (**Figure 3**). The involvement of these sensors in the establishment of disease tolerance to infection is not clear, with GCN2 dampening gut inflammation (42) while promoting endotoxic shock (**Table 1**).

Availability of free fatty acids is monitored by free fatty acid receptor 1 (FFAR1) and FFAR4 (40), with FFAR2 and FFAR3 sensing short-chain fatty acids (SCFAs) (43) and cholesterol levels being sensed by sterol regulatory element–binding transcription factor 1 (SREBF1) and SREBF1 cleavage–activating protein (SCAP) complex (40). The stress response activated by SREBF1 (**Figure 3**) is required to resolve endotoxic shock in mice and may therefore contribute to establishing disease tolerance to bacterial infections (**Table 1**).

The insulin receptor signaling transduction pathway is another component of the stress and damage response network (**Figure 3**), which activates constitutively phosphatidylinositol 3-kinase (PI3K) and AKT, repressing the activity of the forkhead box O (FOXO) family of transcription factors (44). In the absence of insulin or other growth factor receptor signaling, mitogen-activated protein kinases (MAPKs) inhibit PI3K and AKT, promoting FOXO activation and the expression of genes conferring metabolic adaptation and establishing disease tolerance, as illustrated for *Mycobacterium marinum* infection in flies (45).

When metabolic adaptation is insufficient, per se, to mitigate the deleterious effects inherent to different forms of stress, the ensuing event is damage to cellular macromolecules, including DNA, protein, and lipids, and organelles, ultimately compromising tissue function (12). This activates components of the transcriptional stress and damage response network (**Figure 3**), as described in detail elsewhere (12, 14). For example, proteotoxic damage activates the unfolded protein response (UPR) (46, 47) and the heat shock response (47, 48) (**Figure 3**). The UPR relies on the activation of signaling pathways involving inositol-requiring enzyme 1 (IRE1), X-box-binding protein 1 (XBP1), and the double-stranded-RNA-activated protein kinase (PKR)–like endoplasmic reticulum (ER) kinase (PERK)-ATF4 branch and ATF6 (46, 47). These are essential to promote protein refolding in the ER and to sustain cellular homeostasis. The heat shock response repairs misfolded cytosolic proteins and is regulated by the heat shock factor (HSF) family of transcription factors (48, 49) (**Figure 3**). These induce the transcription of several chaperones among other heat shock–responsive genes. Both the UPR and the heat shock response contribute toward disease tolerance (**Table 1**): XBP1 is required to establish disease tolerance to *Pseudomonas aeruginosa* infection of *Caenorhabditis elegans* (50). C/EBP homologous protein (CHOP), a transcription factor activated by PERK, prevents kidney failure in response to lipopolysaccharide in mice, suggesting that it might promote disease tolerance to bacterial infections (51). In contrast, CHOP compromises disease tolerance to influenza virus infection in mice (52) (**Table 1**), consistent with the notion that stress and damage responses act in a pathogen-class-specific manner to establish disease tolerance to infection (3).

Different types of DNA damage activate specific DNA damage responses, as illustrated by the one sensing double-strand breaks by MRE11-RAD50-NBS1 (MRN). This protein complex triggers the activation of the PI3K-related kinase ataxia telangiectasia mutated (ATM) (53), which sets off a phosphorylation cascade that activates p53, a critical component of the transcriptional stress and damage network that reacts to genotoxic stress and damage (53, 54) (**Figure 3**). This DNA damage response promotes tissue damage control and disease tolerance to infection (**Table 1**).

The transcriptional stress and damage response network can also be regulated via epigenetic modifications, as provided by the sirtuin family of histone deacetylases (HDACs) (55). These regulate the transcription of core effector genes in the network (**Figure 3**), which contribute to the establishment of disease tolerance to infection (**Table 1**).

One striking feature in the transcriptional stress and damage response network is that a restricted number of effector genes can be regulated by up to 7 of the 18 transcription factors included in the network (**Figure 3**). This suggests that there is a hierarchical structure among the effector genes, with core genes at the center stage of the network, likely playing a central role in

the establishment of disease tolerance to infection. In strong support of this concept, heme oxygenase 1 (HO-1, encoded by *HMOX1*), a heme-catabolizing enzyme that confers tissue damage control and contributes critically to establish disease tolerance to infection (17, 56–58), is one of those core effector genes (**Table 1**).

The reason why increasing heme catabolism appears to be at the core of the transcriptional stress and damage response network is not clear (59, 60). One reason for this may be that while heme acts as a prosthetic group of hemoproteins supporting vital biologic functions (59), different forms of stress and damage can release heme from those hemoproteins (59). The resulting labile heme can be cytotoxic and pathogenic (59), and presumably, therefore, HO-1 induction is required to counter these effects. Moreover, heme catabolism by HO-1 generates equimolar amounts of the gasotransmitter carbon monoxide (CO), iron, and bilirubin, all of which can exert salutary effects (61). Specifically, CO can bind with high avidity to reduced iron in the heme groups of hemoproteins, preventing heme release and further generation of labile heme (56, 59). This mechanism of action of CO contributes to explaining, for example, how sickle hemoglobin establishes disease tolerance to malaria (17) (**Table 1**). Moreover, CO also acts as a signal transduction molecule, exerting immunoregulatory (62), cytoprotective (63), and antiproliferative (64) effects that can contribute to establishing disease tolerance to infection. While cytotoxic per se, the labile iron generated via heme catabolism by HO-1 induces posttranscriptionally the expression of ferritin, which neutralizes labile iron and in doing so plays a critical role in the establishment of disease tolerance to infection, as illustrated for sepsis (23) or malaria (9) (**Table 1**). Finally, biliverdin reductase converts biliverdin into bilirubin, a potent lipophilic antioxidant (65), which may also contribute to establishing disease tolerance to infection.

There are two additional core effector genes in the transcriptional stress and damage response network, namely, the cell cycle regulators cyclin D1 (CCND1) and cyclin-dependent kinase inhibitor 1A (CDKN1A), also known as p21 (**Figure 3**). Cell cycle progression is regulated at specific checkpoints, ensuring that transition between different phases of the cell cycle is allowed only when, for example, replication errors or faulty aspects of mitosis are successfully repaired (66). Progression through the G1 phase of the cell cycle is controlled by cyclins, including cyclin D1 (67). Moreover, stress and damage responses are associated with cell cycle arrest by CDKN1A/p21 (68). The critical role of cell cycle arrest in allowing the repair of cellular macromolecules, in the context of different damage responses, is well established for DNA damage repair (69). To what extent this is also required in the context of other damage responses remains to be established. While there is, to the best of our knowledge, no experimental evidence that p21 affects the establishment of disease tolerance to infection, there is circumstantial evidence to suggest that this is the case. For example, the antiproliferative effect of CO, generated via heme catabolism by HO-1, relies on the induction of p21 (64). Moreover, p21 regulates macrophage activation and is protective against endotoxic shock (**Table 1**). Presumably, inhibition of cyclin D1 acts, concomitantly with p21 upregulation, to arrest cell cycle progression, providing tissue damage control, as illustrated for ischemia reperfusion injury (70).

Other pathways regulated by the transcriptional stress and damage response network include cell growth and proliferation, apoptosis, metabolism, and regulation of immune modulators (**Figure 3**). The importance of these and other effector functions in the establishment of disease tolerance to infection is further highlighted by **Tables 1** and **2**.

When the transcriptional stress and damage response network fails to sustain the functional output of parenchyma cells, the default pathway becomes programmed cell death (12, 18). Distinct forms of programmed cell death, i.e., apoptosis, necroptosis, pyroptosis, ferroptosis, anoikis, and NETosis, are embedded into specific components of the transcriptional stress and damage response network (**Figure 3**), with diverse pathophysiological consequences (71). Depending on

the relative capacity of different parenchyma tissues to withstand cell loss, programmed cell death can impair the functional output of those tissues and compromise homeostasis (3). While regulation of programmed cell death can contribute to establishing disease tolerance (**Table 1**), its suppression cannot be used as a universal tissue damage control mechanism, at least in part because programmed cell death constitutes a major resistance mechanism against intracellular pathogens.

PROGRAMMED CELL DEATH AS A DEFENSE MECHANISM AGAINST INFECTION

That programmed cell death is an effective means to contain, expel, or kill pathogens is illustrated by the myriad of mechanisms used by pathogenic organisms to manipulate or evade this defense strategy (72). There are different ways in which programmed cell death is used as a resistance mechanism.

In some cases, programmed cell death is triggered via cell-autonomous mechanisms to kill intracellular pathogens (73). This process, however, must be tightly controlled to avoid unfettered cytotoxicity leading to tissue dysfunction. Presumably, the deleterious effects of programmed cell death are countered by tissue damage control mechanisms, in particular in tissues where regenerative capacity is low (3, 12). The reduction of immunopathology and concomitant survival advantage associated with genetic inhibition of specific programmed cell death pathways during influenza virus infection in mice (74) provide an elegant illustration of this balance.

Resistance through programmed cell death also operates at barrier surfaces, where epithelial cells are expelled via anoikis, a form of programmed cell death in which adjacent cells extrude infected cells (75). This defense strategy limits, for example, invasive enteric pathogens such as *S.* Typhimurium from accessing systemic sites (76). Anoikis is also used to shed extracellular pathogens that attach and damage epithelial cells, clearing enteric pathogens such as *Citrobacter rodentium* (77). This is coupled to tissue damage control mechanisms and regenerative responses, restoring and sustaining the functional integrity of epithelial barriers (78, 79).

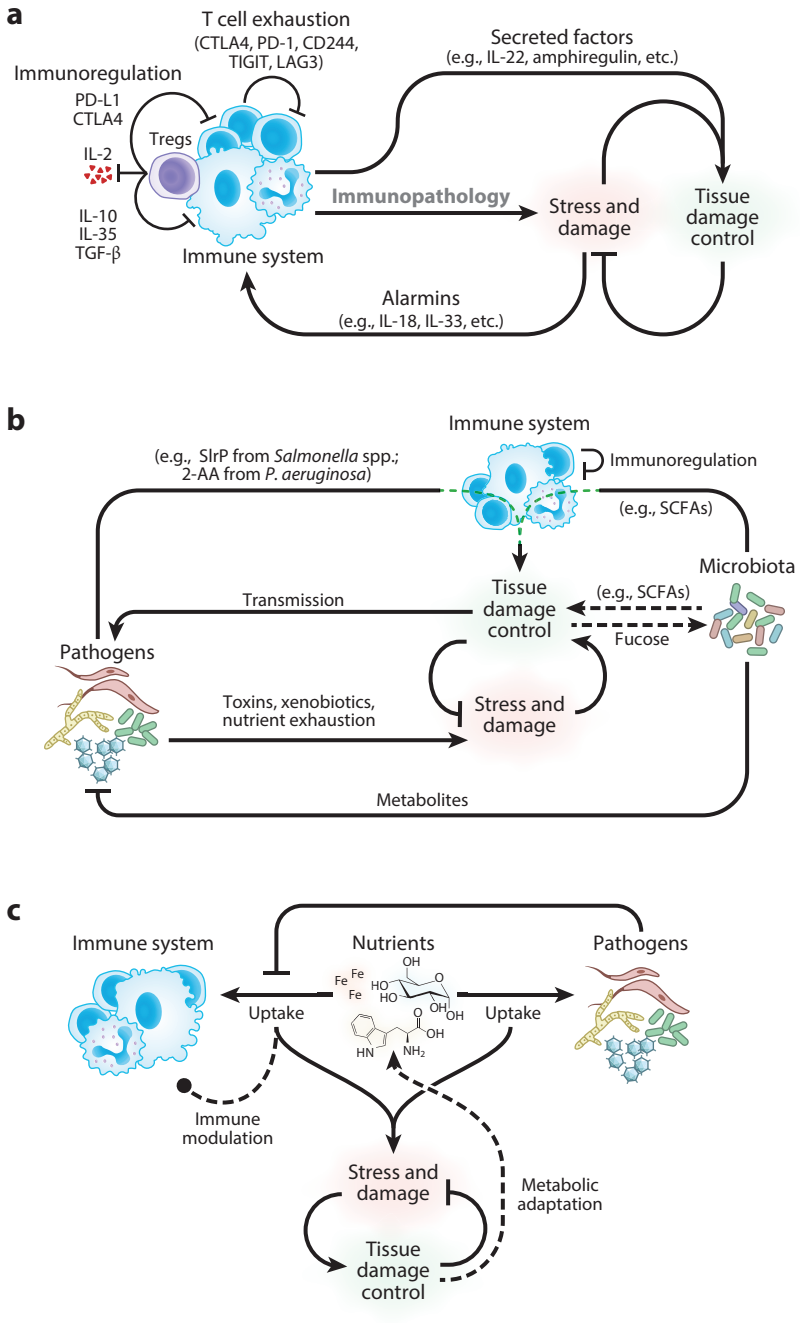
In other cases, components of the immune system such as cytotoxic T cells and natural killer (NK) cells use pore-forming perforin 1 and/or granulysin to deliver cytolytic granzyme B and eliminate intracellular pathogens. While perforin 1 preferentially targets host cell membranes to kill virus-infected cells, the greater affinity of granulysin for cholesterol-poor membranes, which predominate in pathogens, promotes the killing of intracellular bacterial or protozoan parasites (80, 81). While required to kill intracellular pathogens, these resistance mechanisms must be balanced out by cytoprotective responses that minimize tissue damage, such as those that operate during *Plasmodium* infection in mice (17, 56, 57).

In other instances, resistance to infection occurs via mechanisms that involve programmed cell death of immune cells, such as neutrophils, which release an antimicrobial meshwork of chromatin, histones, and various antimicrobial peptides through NETosis (82). These extracellular traps target directly or immobilize microbes for subsequent destruction by phagocytic cell populations (82). They are also, however, pathogenic to the host (83), and NETosis is likely coupled to tissue damage control mechanisms to avoid immunopathology.

IMMUNOREGULATION AS A DISEASE TOLERANCE STRATEGY

Unfettered innate or adaptive immune responses can lead to immunopathology (84) and compromise the establishment of disease tolerance to infection (85–89) (**Table 2**). The relative capacity of the transcriptional stress and damage response network (**Figure 3**) to prevent this pathogenic effect is probably a major limiting factor dictating the robustness of immune-driven resistance

mechanisms. The other critical factor is immunoregulation (**Figure 4**), which restrains innate and adaptive immune responses from operating beyond the thresholds imposed by the transcriptional stress and damage response network. One of the major mechanisms via which this occurs involves regulatory T cells (Tregs), as illustrated by the observation that loss-of-function



(*Caption appears on following page*)

Figure 4 (*Figure appears on preceding page*)

Regulation of tissue damage control. (*a*) Immunoregulatory mechanisms limit the potentially damaging effects of innate and adaptive immunity, i.e., immunopathology. Tregs constrain inflammatory responses via regulatory cytokines, including IL-10, IL-35, and TGF-β (92, 226). Tregs also constrain adaptive immune responses via surface expression of coinhibitory molecules such as PD-L1 and CTLA4 as well as consumption of growth factors such as IL-2, restraining effector T cell activation and proliferation (92). T cell exhaustion also prevents the development of immunopathology via mechanisms involving inhibitory molecules expressed by effector T cells, namely, CTLA4, PD-1, CD244, TIGIT, and LAG3 (103, 104). This negative-feedback loop that constrains effector T cell activation is well described for chronic infections and cancer (104). (*b*) Microbiota-derived metabolites such as SCFAs can act directly on parenchyma tissues to modulate host metabolism and perhaps provide tissue damage control. For example, butyrate, succinate, and propionate act as substrates for intestinal gluconeogenesis (227), regulating organismal bioenergetics (228–230), a critical component of disease tolerance (23, 52, 191). Pathogens can also modulate tissue damage control, as illustrated for *Salmonella* spp., which use the virulence protein SlrP to modulate pattern recognition receptor signaling and inhibit IL-1β secretion (16). This prevents metabolic dysregulation, establishing disease tolerance, while increasing pathogen transmission as a trade-off (16). *Pseudomonas aeruginosa* also promotes disease tolerance through the quorum-sensing signal 2-AA, which regulates population-wide activities including virulence (173). This also activates host histone deacetylase and acetyltransferase, imposing epigenetic modifications that modulate inflammation. (*c*) Pathogens divert micronutrients and other essential factors from their hosts toward their own metabolic pathways. This is countered via innate nutritional immunity, a resistance mechanism that targets and limits the availability of those micronutrients to pathogens (20, 21). This interplay can impose variations in vital homeostatic parameters (13, 28), which are sensed by different components of the transcriptional stress and damage response network, conferring metabolic adaptation and tissue damage control. Moreover, variations in micronutrients such as iron (*light orange*), glucose (*light blue*) or essential amino acids (*light yellow*) exert an immunoregulatory effect of innate and adaptive immune cells. Abbreviations: 2-AA, 2-aminoacetophenone; CTLA4, cytotoxic T lymphocyte–associated protein 4; LAG3, lymphocyte-activation gene 3; PD-L1, programmed death ligand 1; SCFA, short-chain fatty acid; TIGIT, T cell immunoreceptor with immunoglobulin and ITIM domains; Treg, regulatory T cell.

mutations of forkhead box P3, the master regulator of Tregs, are associated with the development of severe and often lethal immunopathology (90, 91).

The immune regulatory effect of Tregs is driven, at least partially, via mechanisms that restrain innate and adaptive immune responses (92, 93) (**Figure 4**). While this is probably sufficient to explain how Tregs suppress autoimmunity (94, 95), these same mechanisms would be expected to impair immune-driven resistance to infection (96). In support of this notion, Tregs can impair resistance and promote the establishment of persistent helminthic and viral infections (97, 98). However, this is not always the case (99, 100) (**Table 2**), suggesting that Tregs can also act in a manner that allows innate and adaptive components of the immune system to provide resistance to infection (95, 101) while limiting their immunopathological effects (99, 100, 102). As described below, this occurs in part via direct or indirect cross talk between Tregs and parenchyma tissues.

Another critical layer of immune regulation is provided by T cell exhaustion, which may serve as a mechanism to prevent the development of tissue damage and promote the establishment of disease tolerance to infection (103) (**Figure 4**). This immune regulatory mechanism is characterized by the expression of inhibitory molecules that modulate signal transduction pathways and downstream transcription factors as well as key metabolic regulators required to support the activation of effector T cells (104). Targeting these immune checkpoints is at the basis of several anticancer therapies as well as therapies against immune-mediated inflammatory diseases and might also be used to treat chronic viral or helminthic infections (104). However, relieving T cell exhaustion to enhance resistance to these types of infections might be associated with the development of immunopathology (85, 105) (**Table 2**).

IMMUNE-PARENCHYMA CROSS TALK IN DISEASE TOLERANCE

The capacity of immune cells to regulate tissue damage control in parenchyma cells is perhaps best illustrated in the context of tissue regeneration. In this setting, immune-driven tissue regeneration and repair provide an additional layer of tissue damage control toward the establishment of disease tolerance to infection (18). This regenerative response relies on local interactions between tissue-resident and circulating leukocytes, producing a spectrum of pro-regenerative cytokines and growth factors acting directly on parenchyma cells (106). Among these, IL-6, IL-22, and TNF appear to have important pro-regenerative effects (107, 108).

IL-6 is a member of a family of cytokines identified originally by its ability to promote cell proliferation and survival (109). This cytokine is also a core effector gene of the transcriptional stress and damage response network (**Figure 3**), which promotes tissue regeneration. This is illustrated, for example, in *Drosophila*, where the unpaired (Upd) proteins (homologous to the IL-6-related cytokines) promote intestinal repair and regeneration (110), as well as in mammals, where IL-6 promotes gut epithelium healing, maintaining barrier function after injury (111).

IL-22 is an acute-phase cytokine of the IL-10 family (112) produced mainly by NK cells, γδ T cells, type 3 innate lymphoid cells (ILC3s), and $CD4^+$ T cells (113). It confers tissue damage control and disease tolerance, as illustrated for *Plasmodium chabaudi* (114), *Leishmania* spp. (115), dengue virus (116), and influenza virus (117) infections in mice (**Table 2**). IL-22 signals via the heterodimeric receptor IL-22Rα1–IL-10Rβ, expressed selectively on nonhematopoietic cells including, but not limited to, epithelial cells (118). The engagement of IL-22Rα1–IL-10Rβ activates a signal-transduction pathway involving the signal transducer and activator of transcription 3 (STAT3), which drives both resistance and tissue damage control mechanisms (118). IL-22 promotes tissue regeneration via mechanisms that rely on stem cell activation, conferring tissue damage control and establishing disease tolerance to infection, as illustrated for cutaneous leishmaniasis in mice (115). Moreover, IL-22 can also induce the expression of effector genes from the transcriptional stress and damage response network (**Figure 3**), including HO-1 (*HMOX1*) (119), which establishes disease tolerance to *Plasmodium* spp. infection in mice (8). While it is likely that IL-22 establishes disease tolerance to malaria (114) via HO-1 induction (8), this remains to be proven.

In addition to its well-recognized proinflammatory effect, TNF is also critical to support tissue integrity via mechanisms that involve the inhibition of programmed cell death via the induction of effector genes of the transcriptional stress and damage response network (**Figure 3**). This occurs most likely via a mechanism involving the activation of NF-κB (nuclear factor kappa B) family transcription factors, which induce the expression of cytoprotective genes such as that encoding the TNF-α-induced protein 3 (TNFAIP3 or A20), constraining inflammation and tissue damage elicited by microbiota sensing via PRRs (120, 121). Moreover, TNF also promotes parenchyma cell proliferation (122) and enhances the production of growth factors (123), promoting tissue regeneration and repair.

TNF secretion is regulated posttranslationally by TNF-α-converting enzyme (TACE or ADAM17) (124). Consistently, loss-of-function mutations in ADAM17 lead to inflammatory disorders and impaired tissue regeneration in humans (125) and mice (126), highlighting the critical function of ADAM17 in tissue damage control (127). ADAM17 is also required for the proteolysis of epidermal growth factor (EGF) family members, such as TGF-α, epiregulin, or amphiregulin (AREG), among others (127), promoting disease tolerance to viral-bacterial coinfections in mice (128). When produced by ILC2s (129, 130) or by Tregs, AREG contributes to tissue damage control (131–133) and to the establishment of disease tolerance, as illustrated for influenza virus infection (131). Presumably, this occurs via a mechanism involving signaling through the EGF receptor (EGFR) to induce epithelial cell proliferation.

AREG production by ILC2s can be induced by IL-33 and neuromedin U (134), a neurotrophic factor that signals via neuromedin U receptor 1, highly expressed by ILC2s (134). AREG production by Tregs is also induced by IL-18 and IL-33, independently of antigen recognition via the T cell receptor (TCR) (131). Consistently, tissue-resident Tregs express high levels of IL-18 and IL-33 receptors, suggesting that they are poised to respond to these alarmins, when released by damaged tissues (131–133). This cross talk between Tregs and parenchyma tissues also operates at steady state, as illustrated for the involvement of Tregs in promoting hair follicle stem cell proliferation (135), neuronal remyelination (136), skeletal muscle cell homeostasis (137), and cardiomyocyte renewal during development (138). These regenerative features of Tregs are evolutionarily conserved, as illustrated in zebrafish (139).

The integration of disease tolerance as a defense strategy against infection is perhaps best illustrated in the context of type 2 immunity, in which tissue damage control is required to mitigate the damaging effects of pathogens such as helminths (140). One of the hallmarks of type 2 immunity is the production of IL-4 and IL-13, which signal via their corresponding receptors expressed in macrophages. The signal transduction pathways triggered by these cytokines synergize with those emanating from receptors recognizing apoptotic cells and soluble molecules such as complement component 1q (C1q) and surfactant protein A (SP-A), to polarize macrophages toward a genetic program promoting tissue repair (141–143). This occurs via a mechanism involving the activation of the phosphatidylserine-dependent AXL tyrosine kinase and MER proto-oncogene tyrosine kinase (MERTK) (142), acting upstream from transcription factors of the NF-κB, SMAD, and NRF2 families, which induce the expression of a number of effector genes in the transcriptional stress and damage response network (144) (**Figure 3**). This macrophage polarization program encompasses a metabolic shift toward oxidative phosphorylation over glycolysis and the induction of genes that promote cell proliferation and repair. These include the gene encoding arginase 1 (*ARG1*), which catabolizes L-arginine to L-ornithine toward the generation of polyamines and collagen (141). Other genes expressed within this macrophage polarization program include *TGFB1* (transforming growth factor beta 1) and vascular endothelial growth factor alpha 1 (*VEGFA1*), as regulated by the transcriptional stress and damage response network (**Figure 3**). A similar macrophage polarization profile is used to encapsulate pathogens, as illustrated for example for *Schistosoma mansoni*, giving rise to granulomas that are maintained by type 2 inflammation (145). Expression of ARG1 by macrophages is critical to fine-tune the T cell response in the granuloma, limiting arginine availability and controlling T cell activation while avoiding excessive inflammation and tissue damage (146). Although these structures fulfill an important protective function limiting pathogen dissemination, as a trade-off they can lead to extensive fibrosis and tissue damage over time (146).

MICROBIAL SHAPING OF DISEASE TOLERANCE

Both commensal and pathogenic microbes can modulate disease tolerance as well as resistance to infection in animals (6, 147, 148). For example, arthropods interact with *Wolbachia*, a bacterial endosymbiont that modulates the establishment of disease tolerance to Flock House virus or insect iridescent virus 6 infections in *Drosophila melanogaster* (6). As discussed in further detail bellow, symbiotic bacteria also promote disease tolerance in mammals (148, 149).

Microbial shaping of disease tolerance is likely to act through several strategies. First, priming of stress responses might subsequently confer tissue damage control and establish disease tolerance to infection. Supporting this notion, *Wolbachia* induces the production of reactive oxygen species in the mosquito vector for dengue virus, *Aedes aegypti*, with coincident induction of an oxidative stress response (150). Some of the effector genes regulated by this stress response, for example the

gene for catalase (CAT), contribute to establishing disease tolerance to enteric bacterial infection in flies (151). Natural members of the mammalian and fly gut microbiota, such as *Lactobacillus* spp., can also trigger the production of reactive oxygen species in flies and mice, inducing the oxidative stress response regulated by NRF2 (CncC in flies). This stress response promotes host survival in the context of sterile injury, namely, irradiation (152). Other components of the stress and damage response network (**Figure 3**), such as the heat shock and the UPRs, as well as ferritin (153), are modulated by *Wolbachia*. Whether this contributes toward the mechanistic basis for *Wolbachia*-induced disease tolerance remains to be shown; it is however, established that these factors promote disease tolerance to infection in other contexts (9, 12, 14, 23).

Cross talk between microbes or their components and the host innate immune system provides another pathway for modulation of disease tolerance. Microbial sensing by host PRRs is critical to regulate host-microbiota interactions and can promote disease tolerance in mammals, perhaps again partially through upregulation of components of the stress and damage response network (**Figure 3**), as proposed for the heat shock response (121). This tissue damage control mechanism is activated via recognition of gram-negative bacterial lipopolysaccharide by TLR4 and MyD88-dependent signaling, after intestinal injury (121). Recognition of gram-positive bacterial peptidoglycan, or other polysaccharides, can also establish disease tolerance, through TLR2-dependent induction of anti-inflammatory responses. Namely, polysaccharide A (PSA) expressed by the gut pathobiont *Bacteroides fragilis* can be delivered to dendritic cells through outer membrane vesicles to trigger IL-10 secretion. This induces Tregs that limit effector T cell responses (154, 155), reducing gut inflammation in response to either *B. fragilis* itself or *Helicobacter hepaticus* infection in mice (155). Two other *Bacteroides* species, *B. vulgatus* and *B. thetaiotaomicron*, can also induce IL-10, as well as TGF-β, conferring protection against colitis (156, 157). As further evidence for a critical role of cytokine signaling in microbial modulation of disease tolerance, antigen-specific recognition of *H. hepaticus* also acts in an IL-10-dependent manner to induce RAR-related orphan receptor gamma t (RORγt)$^+$ Tregs via a mechanism involving the transcription factor c-MAF and restraining RORγt$^+$ T helper 17 (Th17) cell–driven colitis (102). Disease tolerance to *H. hepaticus*–driven colitis may also involve TLR2-dependent sensing of a polysaccharide expressed by certain strains of this bacterium, polarizing gut-resident macrophages toward a tissue damage control response (158).

Carbohydrate metabolism by gut bacteria can also neutralize bacterial virulence behaviors and, in doing so, promote disease tolerance (**Figure 4**). For example, sensing of segmented filamentous bacteria or *B. thetaiotaomicron* via PRRs induces α1,2-fucosylation by intestinal epithelial cells (159, 160), which prevents dissemination of enteric pathogenic bacteria, such as *Alcaligenes* spp. (161), *S.* Typhimurium, or *C. rodentium* (159, 160, 162) (**Figure 4**). This depends upon MyD88 signaling in dendritic cells (159) and consequent IL-23 secretion, targeting ILC3s to secrete IL-22. This latter cytokine induces the expression of fucosyltransferase-2 (*Fut2*) and, consequently, increases fucosylation of gut epithelial cells (159). Fucosidase expression in *Bacteroides* spp. releases fucose from the gut epithelia (163), supporting the growth of commensal bacteria to provide colonization resistance (164). Fucose can also inhibit *ler*-dependent virulence gene expression in enterohemorrhagic *Escherichia coli* (165), and its catabolism into the SCFA propionate, again by *Bacteroides* spp. (159), inhibits the expression of *Salmonella* virulence genes required to invade the epithelium (166) and limits pathogen growth through disruption of intracellular pH homeostasis (167) (**Figure 4**).

SCFAs also modulate immune function, providing another strategy through which microbes can influence disease tolerance. Through production of SCFAs, clostridial members of the gut microbiota promote Treg development (168, 169), while butyrate downregulates proinflammatory macrophage responses (170) (**Figure 4**). Intriguingly, dietary fiber and associated microbiota shifts increase butyrate levels and promote signaling via the free fatty acid receptor FFAR3. This

polarizes macrophages toward a tissue repair program, reducing neutrophil recruitment and immunopathology in the lung and establishing disease tolerance, in the context of influenza virus infection in mice (**Table 1**). This illustrates how both nutritional competition between microbes and signaling through downstream metabolites engage in cross talk with host immune and nonimmune mechanisms to limit disease severity.

Many of the microbial effects supporting the establishment of disease tolerance through immune regulation depend on controlled translocation of either bacteria or their molecules across host epithelial barriers. For example, proteobacteria such as *Alcaligenes* spp. and *Burkholderia* spp. can take residency in dendritic cells of Peyer's patches and mesenteric lymph node dendritic cells (171, 172). Recognition of components of these bacteria by TLR4 induces a MyD88-dependent IL-10 response controlling Th17 responses and IFN-γ production, providing tissue damage control at the level of the intestinal epithelium, as shown in the context of chemical injury (172). Similarly, upon infection the gut pathobiont *E. coli* O21:H+ can translocate to the white adipose tissue, where it is recognized via the NOD-like receptor (NLR) family CARD domain–containing protein 4 (NLRC4) inflammasome (149). This induces IL-18 secretion, which, rather than acting in a pathological manner, provides insulin-like growth factor 1 (IGF1)/PI3K/AKT-dependent inhibition of the muscular atrophy factors muscle RING-finger protein-1 (MuRF1) and F-box protein 32 (FBX032/Atrogin-1), preventing muscle wasting and establishing disease tolerance to *S.* Typhimurium or *Burkholderia thailandensis* infection in mice (149).

Pathogens can also shape disease tolerance to infection, as illustrated for modulation of some components of host sickness behavior by *S.* Typhimurium (16) (**Figure 4**). Briefly, this pathogen inhibits anorexia of infection, which likely contributes to host metabolic deregulation associated with *S.* Typhimurium infection (16). This otherwise salutary effect that limits host disease severity at an individual level is, however, associated with increased *S.* Typhimurium transmission at a population level (16). This trade-off between individual- versus population-level fitness demonstrates that pathogens can modulate host behavior such that their virulence is reduced, perhaps to promote pathogen survival at both the individual and population levels (16).

Reduction of virulence as a pathogen strategy to promote host disease tolerance can also be observed in the context of *P. aeruginosa* infection (173) (**Figure 4**). The overall outcome of this interaction promotes host survival, favoring the establishment of a chronic infection, which in fact features higher bacterial loads (173). Other pathogens likely act in a similar manner; the enteric nematode *Nippostrongylus brasiliensis*, for example, modulates anorexia of infection via the regulation of central nervous system signaling (174), but whether this favors parasite transmission is not clear. In any case, these studies suggest that long-term interactions between a pathogen and its host are contingent on regulation of host disease tolerance. Possibly these are critical steps toward commensalism, and as such they might constitute beneficial host-microbe interactions that could be explored as a means of therapeutic intervention in both dysbiosis- and pathogen-associated diseases.

COUPLING NUTRITIONAL IMMUNITY AND METABOLIC ADAPTATION AS A DISEASE TOLERANCE STRATEGY

Infection is contingent on the capacity of pathogens to divert host nutrients to their own metabolic pathways. The development of anorexia of infection in an infected host is coupled to innate nutritional immunity to prevent pathogens from accessing nutrients, such as iron and zinc, and possibly glucose and amino acids, limiting pathogen growth and conferring resistance to infection. This strategy is perhaps best illustrated for iron, a micronutrient essential to most pathogens and their hosts (21, 22, 175).

Pathogen sensing by PRRs triggers the expression of a variety of heme- and iron-binding molecules that restrict pathogens from accessing iron (21, 22, 175). When targeting intracellular pathogens this defense strategy reduces cellular iron import and induces cellular export, using the opposite strategy against extracellular pathogens (21, 22, 175). Innate nutritional immunity mechanisms targeting intracellular or extracellular pathogens can lead to hyperferremia or hypoferremia, respectively, and in the latter case to tissue iron overload and oxidative tissue dysfunction and damage (21, 22, 175). Anorexia of infection can further promote iron deficiency and anemia of chronic disease (176), a pathological condition that contributes significantly to the global burden imposed by iron-deficiency anemia (177). Some of these trade-offs are limited by core effector genes, regulated by the transcriptional stress and damage response network (**Figure 3**), such as *HMOX1*, which confers disease tolerance to infection (8, 56, 58). Other effector genes regulating iron metabolism and conferring disease tolerance to infection, such as *FTH* (ferritin H chain), are regulated posttranscriptionally, but their expression is synchronized with the transcriptional network (9, 23). Namely, iron released from heme catabolism by HO-1 plays a critical role in posttranscriptional upregulation of ferritin via inhibition of cytosolic RNA-binding iron regulatory proteins (IRPs), which de-repress FTH and FTL (ferritin L chain) mRNA translation and increase mRNA stability and protein expression (178).

After iron, zinc is the most common transition metal used by living organisms, with an estimated 5–6% of prokaryotic proteins binding zinc (179). This divalent metal is essential to regulate key biologic processes, such as transcription, DNA repair, oxidative stress responses, and metabolism (180). Presumably for this reason, innate nutritional immunity mechanisms also target zinc to provide resistance against infection (181). In keeping with this notion, the zinc-chelating protein calprotectin is a component of neutrophil extracellular traps (NETs), which confers resistance to extracellular pathogens, such as illustrated for *Staphylococcus aureus* (182) and *Candida albicans* (183) infections in mice. When expressed by macrophages, the zinc transporters solute carrier family 30 member 4 (SLC30A4) and 7 (SLC30A7) as well as the zinc chelators metallothioneins confer resistance to intracellular pathogens, as illustrated for *Histoplasma capsulatum* infection in mice (184). The trade-offs of these defense strategies include deregulation of host zinc metabolism (185), with zinc deficiency promoting inflammation and tissue damage, and zinc supplementation promoting disease tolerance, as illustrated for HIV infection in humans (186). Consistently, calprotectin (187) as well as metallothioneins 1 and 2 regulate inflammatory responses, with the latter contributing to the establishment of disease tolerance to *Helicobacter pylori* infection in mice (**Table 1**).

Innate nutritional immunity is probably also exerted when targeting glucose or essential amino acids. The same constraints apply: This resistance mechanism must be coupled to tissue damage control so as to limit host metabolic dysfunction and establish disease tolerance. These tissue damage control mechanisms rely on the activation of the transcriptional stress and damage response network (**Figure 3**), regulating the expression of core effector genes that maintain the levels of glucose or amino acids compatible with survival.

Glucose is a major carbon source for most life-forms, including many pathogenic microorganisms. Reducing blood glucose levels, e.g., by anorexia of infection, is most likely aimed at limiting glucose availability to pathogens (23, 52, 188). In keeping with this notion, anorexia of infection is associated with impaired expansion of bacterial pathogens (52), while also promoting disease tolerance, as illustrated for *Listeria monocytogenes* infection in mice (52). Of note, this strategy can be pathogenic, as demonstrated for influenza virus infection in mice (52). This defense strategy is also operational against other pathogens that rely on the uptake of host glucose, such as *Plasmodium* spp. (189), while regulation of host glucose metabolism is also critical to establish disease tolerance to *Plasmodium* spp. infection in mice (190, 191).

The protective effect afforded by host defense strategies reducing blood glucose levels carries, as a trade-off, the development of hypoglycemia (23, 52, 188). This is avoided in part by a host metabolic response where iron neutralization by ferritin promotes hepatic glucose production via a mechanism that induces the transcription of the glucose-6-phosphatase (*G6PC1*) gene, promoting glycogenolysis and gluconeogenesis and establishing disease tolerance to bacterial infections (23, 188). In keeping with the notion of the establishment of cross talk between iron and glucose metabolism contributing toward disease tolerance, increasing dietary iron favors disease tolerance to *Citrobacter rodentium* infection in mice, via a mechanism that promotes insulin resistance (192). This increases blood and intestinal glucose levels, which attenuates the virulence of this enteric bacterial pathogen and favors the establishment of disease tolerance (192).

Limiting pathogen access to essential amino acids is another component of innate nutritional immunity, targeting auxotrophic pathogens that must obtain these amino acids from their hosts. Moreover, immune cells are also auxotrophic for some amino acids, and therefore amino acid availability also affects immune-driven resistance to infection (193). This interplay is perhaps best illustrated for tryptophan, an essential amino acid obtained from the diet.

Pathogen sensing in macrophages is associated with the induction of indoleamine 2,3-dioxygenase (IDO), which catabolizes tryptophan to L-kynurenine, reducing tryptophan levels and conferring protection against intracellular pathogens, as illustrated for *Chlamydia trachomatis* infection (194). IDO also exerts immunoregulatory effects (195) that can contribute to tissue damage control. When generated via tryptophan 2,3-dioxygenase, L-kynurenine acts as a physiologic AHR agonist (37), a component of the transcriptional stress and damage response network (**Figure 3**). AHR senses L-kynurenine and establishes disease tolerance to *S.* Typhimurium or group B *Streptococcus* infection in mice (37).

The overall picture that emerges from these studies is that coupling of anorexia of infection to innate nutritional immunity and the activation of the stress and damage response network is an evolutionarily conserved defense strategy against infection integrating behavioral responses with resistance and disease tolerance. These mechanisms also impact the pathogenesis of noncommunicable diseases associated with high human morbidity and mortality, as highlighted below.

TISSUE DAMAGE CONTROL IN NONCOMMUNICABLE DISEASES

The notion of tissue damage control arose originally from experimental transplantation studies, whereby transplanted organs were shown to prevent their own rejection (196–198). Similar to transplantation, autoimmunity is an immunopathological process affecting different organs, and in which tissue damage control mechanisms might be operational. In support of this notion, some components of the transcriptional stress and damage response network (**Figure 3**) can protect β cells of the pancreas and limit the pathogenesis of autoimmune type 1 diabetes, as illustrated for the UPR (199) or for HO-1 (200). Here we highlight how tissue damage control mechanisms may affect noncommunicable diseases.

A number of chronic conditions such as hypertension, obesity, type 2 diabetes mellitus, and generalized dyslipidemia are associated with metabolic deregulation, referred to as metabolic syndrome (201). This is fueled by chronic low-grade inflammation causing different forms of stress and damage to different tissues, ultimately leading to the development of cardiac failure, stroke, or diabetes (201, 202). The clinical symptoms of these chronic conditions typically manifest years after the onset of metabolic syndrome, suggesting that some level of tissue damage control might operate to limit disease progression. In support of this notion, the stress-responsive program regulated by NRF2 promotes glucose homeostasis and favors energy expenditure by insulin-responsive tissues, inhibiting the onset of type 2 diabetes mellitus in mice (203). This is likely mediated via

effector genes of the transcriptional stress and damage response network (**Figure 3**), acting in β cells of the pancreas (203). Consistently, other components of the network such as HIF1α can also confer tissue damage control in β cells of the pancreas, as illustrated in mice (204). While this shows that components of the transcriptional stress and damage response network (**Figure 3**) can limit the pathogenesis of chronic conditions associated with metabolic dysfunction, this relationship is not straightforward. For example, HO-1 expression in myeloid cells fuels metabolic dysfunction in mice and humans (205), while the stress response regulated by NRF2 promotes diet-induced atherogenesis in mice (206). One possible explanation for this may be that while the transcriptional stress and damage response network (**Figure 3**) evolved as a component of immunity against infection, this response becomes dysfunctional when activated in a sustained manner over time in pathologic conditions associated with chronic inflammation, a common evolutionary trade-off put forward for other genetic networks (207).

Cancer is another pathologic condition where tissue damage control mechanisms are operational and can affect the outcome of this major noncommunicable disease. Cancer cells have an abnormal control of proliferation and programmed cell death, driven by genomic instability and the accumulation of mutations. This is associated with acquisition of a transcriptional and metabolic profile that supports high cellular proliferative capacity, tissue invasiveness, and metastasis (208). It is well established that innate and adaptive components of immunity can affect cancer growth (209), and more recently, disease tolerance was also put forward as a defense mechanism that limits cancer severity without exerting a direct impact on tumor growth (210).

The transcriptional stress and damage response network (**Figure 3**) that sustains tissue damage control probably plays antagonistic roles in the outcome of cancer. When operational in cancer cells, some components of this network can promote tumor progression, as illustrated for NRF2 (211), NFAT5 (212), and mTOR (208), or can act as tumor suppressors, as illustrated for p53 (213). Other core components of the network, such as p21, can have a dual function (68). Little is known, however, regarding the impact of these network components in the establishment of disease tolerance to cancer.

Inflammation is a hallmark of cancer, acting locally but also systemically to disrupt organismal homeostasis (214). This is illustrated by the development of cachexia, a major risk factor of cancer morbidity and mortality (215). Tissue damage control mechanisms that act systemically to prevent cachexia (149) might therefore contribute to establishing disease tolerance to cancer (210). Metabolic deregulation should also affect cancer progression, as cancer cells are highly dependent on glucose supply to fuel glycolysis and generate energy as well as macromolecules, sustaining cell proliferation (216). It is likely, therefore, that components of the transcriptional stress and damage response network controlling glucose metabolism may affect cancer proliferation directly or indirectly, via modulation of innate and adaptive immune responses conferring resistance to cancer (24).

Tissue damage control mechanisms also affect the pathologic outcome of genetic disorders, triggered by gene mutations and/or other genomic abnormalities that impose different forms of cellular stress or damage (217). While polymorphisms associated with the onset of severe diseases are rare and selected against, owing to their fitness costs, balanced polymorphisms are selected upon when their beneficial effects outweigh the fitness cost of the disease (207, 218). Perhaps the best described of such balanced polymorphisms are those in the β globin gene, most commonly Glu6Val (β^S), responsible for sickle cell disease (SCD) (219). While homozygous β^S mutations are pathogenic, hemizygous β^S mutations confer tissue damage control and establish disease tolerance to malaria (17, 220). Presumably, this explains why the β^S mutations are present at such high frequencies in endemic regions of malaria, outweighing the fitness cost of SCD (220).

As is the case for other genetic disorders, SCD has variable penetrance, depending on factors such as the presence of modifier gene variants (217). For example, the oxidative stress response regulated by NRF2 limits SCD severity in mice (221), presumably via HO-1 (222). Interestingly, this stress response is also activated in individuals carrying hemizygous β^S allele (sickle trait), to establish disease tolerance to malaria (17, 220). This illustrates how the same stress-responsive pathway modulates the outcome of an infectious disease, i.e., malaria, as well as a noncommunicable disease.

CONCLUDING REMARKS

Vaccination is perhaps the most successful medical approach ever used against infectious diseases. Likely owing to its overwhelming success, immunologists came to believe that the resistance mechanisms elicited by vaccination are the prevailing if not the only host defense strategy against infectious diseases. However, natural acquisition of protective immunity is contingent on the establishment of infections, which carry health and fitness costs to the host. Therefore, additional defense mechanisms are required to limit these fitness costs, before antigen-specific adaptive immunity becomes operational as well as thereafter to avoid immunopathology. This is achieved via activation of a transcriptional stress and damage response network that confers tissue damage control and establishes disease tolerance to infection. This defense strategy acts as an inherent component of immunity without exerting a direct impact or a selective pressure over pathogens. Further understanding of how disease tolerance operates should provide invaluable information toward our comprehension of immunity and contribute toward the development of novel therapeutic strategies against major diseases.

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