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Tissue Homeostasis and Inflammation

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Abstract

There is a growing interest in understanding tissue organization, homeostasis, and inflammation. However, despite an abundance of data, the organizing principles of tissue biology remain poorly defined. Here, we present a perspective on tissue organization based on the relationships between cell types and the functions that they perform. We provide a formal definition of tissue homeostasis as a collection of circuits that regulate specific variables within the tissue environment, and we describe how the functional organization of tissues allows for the maintenance of both tissue and systemic homeostasis. This leads to a natural definition of inflammation as a response to deviations from homeostasis that cannot be reversed by homeostatic mechanisms alone. We describe how inflammatory signals act on the same cellular functions involved in normal tissue organization and homeostasis in order to coordinate emergency responses to perturbations and ultimately return the system to a homeostatic state. Finally, we consider the hierarchy of homeostatic and inflammatory circuits and the implications for the development of inflammatory diseases.

INTRODUCTION

Homeostasis and inflammation are conventionally described as opposing states of biological systems that are typically associated with health and disease, respectively. This understanding has deep historical roots that can be traced to a debate between Rudolf Virchow and Elie Metchnikoff, two founding figures in the study of inflammation. Virchow viewed inflammation as a pathological phenomenon, giving rise to the perspective that prevails to this day. Metchnikoff, on the other hand, had the insight that the vascular changes responsible for the cardinal signs of inflammation were not a pathological accident of biology but rather were induced on purpose, in order to deliver phagocytes to the site of infection (1). Moreover, Metchnikoff conceived of a spectrum of biological states, from homeostasis to physiological inflammation to—only at the extreme—pathological inflammation and immunity (2). To refer to homeostasis, Metchnikoff used the term harmony-disharmony balance; the term homeostasis was not coined until decades later, in 1929, when Walter Cannon published his seminal paper defining homeostasis and its mechanisms (3). However, Metchnikoff's insights, identifying a spectrum from homeostasis to inflammation, did not gain much traction. (Perhaps his disagreement on this issue with the undeniable authority of Virchow did not help.) One unfortunate consequence was that for the next century inflammation was studied primarily in the context of pathology, largely disconnected from physiology.

The concept of homeostasis plays a central role in our understanding of mammalian physiology. Many aspects of systemic homeostasis are now understood in great detail. The picture is much less clear when it comes to homeostasis at the tissue level, where a lack of formal definitions has led to ambiguity and obscured important biological mechanisms. This problem is amplified by the largely descriptive knowledge of tissue organization. In this review, we discuss a functional perspective on tissue organization and its relationship to tissue homeostasis and inflammation. Based on that framework, we revisit Metchnikoff's idea of a homeostasis-inflammation spectrum and discuss the hierarchy of cellular, tissue, and organismal levels of homeostasis and inflammation.

BASIC PRINCIPLES OF TISSUE ORGANIZATION

At first glance, mammalian tissues appear very different from one another. The skin, lungs, liver, and bone have distinct gross anatomy, cellular composition, and organization. Yet, each of these tissues is organized according to the same principles. We can understand this fundamental organization by considering the primordial design of multicellular tissues. The earliest metazoan tissues, like those of common ancestors of humans, Ctenophora, and Cnidaria, consisted of epithelial and mesenchymal cells. The layer of epithelial cells created a barrier that separated the internal environment of the organism from the external environment, in order to defend against external threats and maintain internal homeostasis. This was the primary function of these primordial tissues. The mesenchymal cells provided the tissue with structural integrity and organization, through the production of extracellular matrix (ECM) and soluble signals to the epithelial cells. These were supportive functions that allowed the epithelial cells to perform the primary barrier function (4–6). This primordial epithelial-mesenchymal tissue unit illustrates an important design principle that is conserved in modern multicellular organisms: Cells within a given tissue fall into two functional categories, (*a*) primary cells, responsible for performing the primary function of the tissue, and (*b*) supportive cells, responsible for performing supportive functions, which facilitate the performance of the primary function.

As numerous specialized cell and tissue types appeared over the course of evolution, the basic tissue design composed of primary and supportive cell types was preserved and elaborated. Each tissue or organ is specialized to perform one or more essential functions for the organism. The

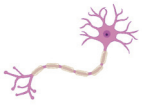
skin, for instance, serves primarily as a barrier, the lung functions to exchange oxygen and carbon dioxide, the liver regulates systemic metabolism, and bone provides structural integrity and organization for the body. As in primordial tissues, each of these tissues contains a cell type dedicated to performing the primary function of the organ. These include specialized epithelial cells in the skin, lung, intestines, kidney, and liver; neurons in the brain; and cardiomyocytes in the heart. All of the other cells within the tissue are supportive cells, which serve to optimize the performance of the primary function by creating the appropriate conditions within the tissue. Examples of these supportive components include endothelial cells, pericytes, and smooth muscle cells, which form vasculature to deliver oxygen and nutrients to the primary cell; fibroblasts, which (as in primordial tissues) produce growth factors and ECM to position the primary cells and provide the necessary mechanical properties to facilitate the particular function of the organ; stem cells, which replenish the primary cell type; neurons innervating the tissue, which transmit critical information to and from other parts of the organism; and tissue-resident macrophages, which sense and respond to changing conditions within the tissue to maintain an optimal environment (7) (**Table 1**). While these cell types play supportive roles in most organs, they can also serve the primary function in other specialized organs. For instance, endothelial cells are the primary cell type in large blood vessels like the aorta, osteoblasts (a specialized type of fibroblast) are the primary cell type in bone and cartilage, hematopoietic stem cells are the primary cell type in the bone marrow, and neurons are the primary cell type in the central nervous system. We can think of these organs as elaborations of the supportive functions that those cells normally serve. In these cases, the supportive functions (such as nutrient transport) are outsourced to whole organs (such as the aorta), in order to adequately supply multiple tissues or the organism as a whole.

These examples highlight an important principle: The distinction between primary and supportive cell types does not describe intrinsic characteristics of cells but rather the relationship between cells (**Figure 1**). To illustrate this point, we can consider a blood vessel within an organ, such as the gut. In the blood vessel, endothelial cells serve the primary function, creating a barrier between the systemic circulation and the tissue and regulating the transport of specific contents. Smooth muscle cells and pericytes are supportive cells that optimize those functions. If we zoom out to the whole tissue, though, those same vascular endothelial cells are playing a supportive role, delivering oxygen to the intestinal epithelial cells, which serve the primary function of nutrient absorption. If we further zoom out to the organismal level, intestinal epithelial cells are playing a supportive role, supplying nutrients for the organism as a whole. We can see from this example that the terms primary and supportive are relational rather than absolute and also that the relationship of supportive to primary components exists along a hierarchical axis. Each biological component supports the functions of a higher-order unit (**Figure 1**). This hierarchy of functions is not unique to biological systems and can be seen, for instance, in the structure of large companies. Each department has supportive personnel that optimize the performance of that department, and the department in turn supports the overall function of the company. The departments are analogous to tissues, and the company is analogous to an organism. This hierarchical support structure allows for the multiscale organization of biological systems, beginning from subcellular units and building up to cells, tissues, organ systems, and organisms.

CORE FUNCTIONALITIES OF CELL TYPES

Most tissues in complex metazoans are composed of multiple cell types, each specialized for one or more core functionalities (**Table 1**). For instance, the core functionalities of epithelial cells are barrier, transport (absorption and/or secretion), and environmental sensing, while the core functionalities of smooth muscle cells are contraction and relaxation. The diverse array of vertebrate cell types, with their distinct core functions, provides a biological tool kit for building tissues.

Table 1 Core functions of different cell types

Cell type	Core functions	Characteristic examples
 Epithelial cells	Barrier	Skin epithelial cells: external environment Intestinal epithelial cells: intestinal contents
	Transport: absorption	Small intestinal epithelial cells: nutrients Type 1 alveolar epithelial cells: gases Kidney epithelial cells: electrolytes
	Transport: secretion	Goblet cells: mucus Hepatocytes: plasma proteins Paneth cells: antimicrobial peptides Type 2 alveolar epithelial cells: surfactants
	Sensing	Enterochromaffin cells: metabolites and noxious stimuli
 Stromal cells	Extracellular matrix production	Osteoblasts: bone matrix
	Growth factor production	Niche cells: stem cell survival factors
 Endothelial cells	Barrier	Vascular endothelial cells: fluids, plasma proteins, and solutes
	Transport	Pulmonary capillary cells: gases
 Smooth muscle cells	Contraction and relaxation	Vascular smooth muscle cells: blood flow Intestinal smooth muscle cells: peristalsis
 Macrophages	Phagocytosis	All macrophages: microbes and apoptotic cells Alveolar macrophages: surfactants Microglia: cellular debris and unnecessary neuronal structures Splenic red pulp macrophages: red blood cells
	Sensing	Intestinal macrophages: microbes Splenic red pulp macrophages: heme
 Adipocytes	Lipid storage and release	White adipocytes
	Thermogenesis	Brown adipocytes
 Neurons	Sensing	Sensory neurons
	Computation	Interneurons
	Control of target tissues	Motor neurons
 Stem cells	Self-renewal and differentiation	Hematopoietic stem cells Intestinal stem cells

Each tissue uses a unique complement of these same fundamental building blocks to achieve the particular function of that organ and to optimize its performance.

Comparing two barrier tissues, those of the lung and the gut, exemplifies how these same basic cellular units are utilized across different tissues, as well as the variations in how they can be

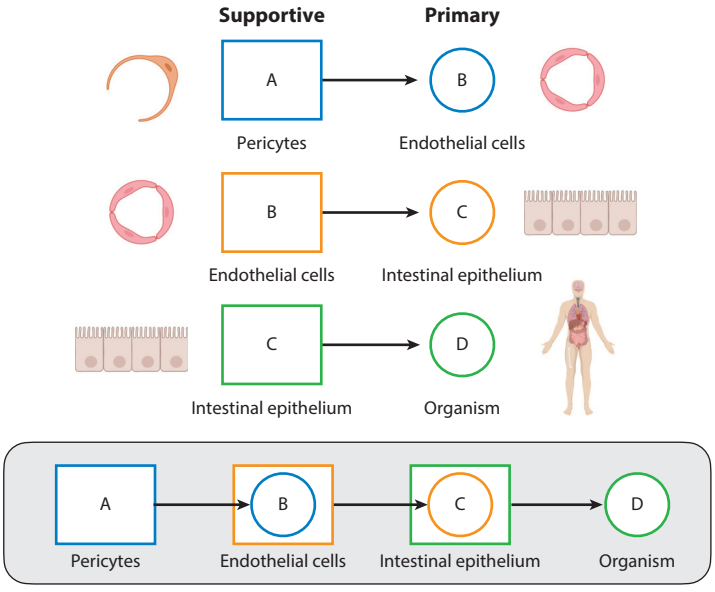


Figure 1

Hierarchy of supportive and primary cellular functions. Using the hierarchy of blood vessels, intestine, and organism, the relationships between supportive and primary functions are illustrated. Within the blood vessel, pericytes (A) are supportive for the primary barrier and transport functions performed by endothelial cells (B). At the level of the intestine, endothelial cells play a supportive role for the primary function of nutrient absorption performed by intestinal epithelial cells (C). At the organismal level, the intestinal epithelium supports primary functions of the organism as a whole (D). Rectangles represent supportive functions, and circles represent primary functions. Colors denote primary-supportive relationships.

deployed. The primary functions of both the lung and the gut are transport and barrier functions. However, they perform these functions in different contexts and for different purposes, which has driven specialization of the basic epithelial unit for each organ in several ways. First, both epithelia are specialized for transport, but of entirely different kinds of substances. Intestinal epithelial cells must absorb nutrients, for which they express specific enzymes and transporters (8). Alveolar epithelial cells must exchange gases (oxygen and carbon dioxide), so they have a flattened morphology to minimize the distance for diffusion (9). Second, both epithelia are adapted for a barrier function, separating the internal from the external environment and defending against pathogens. This function is supported by further specialized subsets of epithelial cells that have a dedicated secretory function: Goblet cells in both organs secrete mucus that lines the epithelial barrier and helps prevent the penetration of microbes. In the lung, type 2 alveolar epithelial cells solve the lung-specific problem of surface tension by secreting surfactants, and in the gut, Paneth cells secrete antimicrobial peptides to deal with ubiquitous exposure to microbes (10, 11). Third, both epithelia have distinct, specialized sensory cells. For example, the intestinal epithelium contains enteroendocrine, enterochromaffin, and tuft cells that detect nutrients and noxious substances and produce hormones, neurotransmitters, and cytokines to coordinate appropriate responses to the luminal contents of the gut (12, 13).

Supportive cells are also deployed in each tissue to facilitate those unique primary functions and to help address the particular challenges faced by each organ. To help regulate the large microbial community in the intestines, there is an extensive and highly organized population of

gut-resident immune cells (11). In the lung, alveolar macrophages support the critical surfactant biology described above by sensing surfactant levels and appropriately clearing surfactant from the alveoli, balancing surfactant production by epithelial cells (14). The fibroblasts in each tissue produce ECM that confers distinct mechanical properties, optimized for cycles of inspiration and expiration in the lung and distention and motility in the gut (15–17). Endothelial cells supply oxygen and nutrients from blood to both tissues, but in the lung they also have the special function of absorbing oxygen from the air and off-loading carbon dioxide. To achieve this, the endothelial cells of pulmonary capillaries are closely apposed to the alveolar epithelial cells, sharing a single basement membrane to minimize the distance for gas diffusion (18).

Both organs pair smooth muscle with endothelium (with the exception of capillaries and post-capillary venules) to regulate the diameter of blood vessels. However, this partnership follows tissue-specific rules. In the gut, like elsewhere in the body, hypoxia stimulates smooth muscle relaxation and thus vasodilation to increase blood flow and oxygen delivery to the tissue, correcting the hypoxia (19). In contrast, in the lung, hypoxia stimulates smooth muscle contraction and thus vasoconstriction to prevent blood flow to regions of the lung that are not being well-ventilated. The failure to match oxygenated air with blood flow in the lung is called ventilation/perfusion mismatch and is a major cause of hypoxemia (20). Each organ also deploys smooth muscle in other contexts. The lung pairs smooth muscle with bronchial epithelial cells to regulate the caliber of the airways, similar to the role of smooth muscle in blood vessels. Smooth muscle in the gut uses the same core functionalities of contraction and relaxation to a very different end, generating coordinated waves of peristalsis that cause directional movement of the intestinal contents. Neurons in both organs, in turn, have the function of controlling smooth muscle contraction. They also relay local information, from sensory enteroendocrine cells in the gut, for instance, to other parts of the organism (21, 22). Finally, each tissue has stem cells that are located within the organ's basic units of organization, the villi in the intestine and the alveoli in the lungs, which allows them to regenerate regularly and in response to damage (11, 23).

Like the tissues that make up the lung and gut, each tissue in an organism can be described as an assembly of complementary core functions. We elaborate on some additional examples below, as we detail how these core functions are modified in the context of homeostasis and inflammation. For now, we can make two important generalizations based on the discussion above. First, there is intimate coordination between the primary and supportive components of tissues because the supportive functions exist to facilitate and optimize the primary functions. As a consequence, certain supportive and primary cell types are typically paired together. Cell types specialized in transport (like epithelium or endothelium) are typically paired with smooth muscle to control the flow of luminal contents, as well as neurons to control the contraction of the smooth muscle. Pericytes also regulate endothelial transport, in some cases together with other stromal cells; for example, astrocytes in the brain maintain the blood-brain barrier, and podocytes in the kidney control the filtration of blood into urine (24–27). Epithelial cells that serve a barrier function are paired with immune cells to prevent infection. Primary cells specialized in sensing are often paired with afferent neurons to integrate and communicate that information to other parts of the organism. Second, the role of the supportive cells within a tissue is often to maintain the internal environment of the tissue—such as the composition of ECM and the concentrations of oxygen, nutrients, and waste products—in an appropriate and stable state. In a similar fashion, primary cells of each organ regulate internal conditions of the whole organism, like blood pressure and the concentrations of ions and metabolites. Thus, supportive cells are responsible for maintaining homeostasis on the tissue level, while primary cells are responsible for maintaining homeostasis on the organismal level.

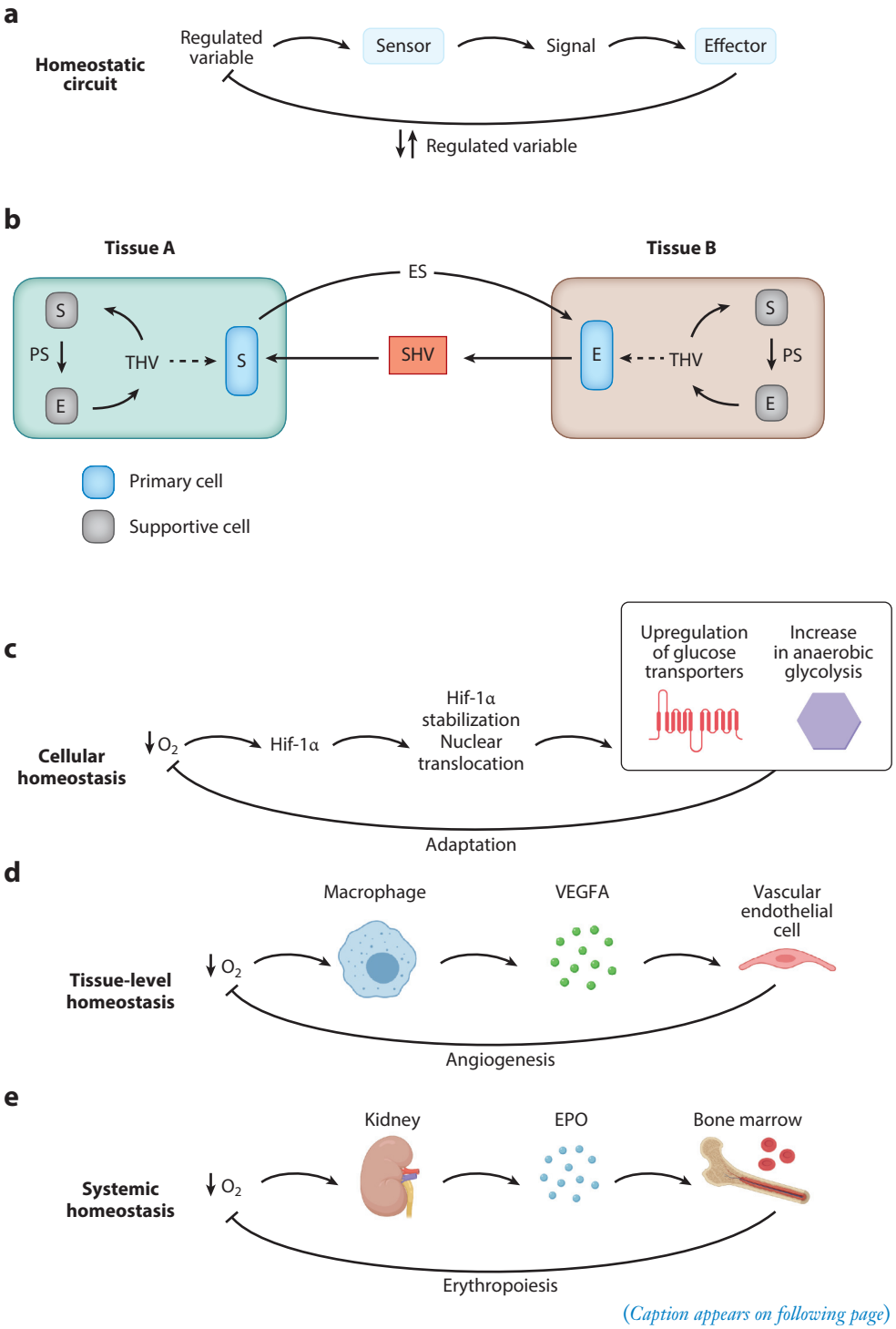
TISSUE HOMEOSTASIS

Tissue homeostasis is a term that is often used to describe a normal, steady-state, or uninflamed condition of a tissue. However, this loose definition obscures important features of tissue biology. To arrive at a more precise definition of tissue homeostasis, we first discuss the components of a homeostatic circuit and examples of systemic and cellular homeostasis, which are better understood, and then examine these concepts on the tissue level.

Homeostasis describes the active maintenance of certain quantitative characteristics of the system, known as regulated variables, within a desired range. The homeostatic circuit is structured to maintain them at a stable level, close to a target value known as the set point. In order to be maintained, the values of regulated variables have to be monitored by specialized sensors and corrected by effectors. Sensors must be able to communicate with effectors through dedicated signals that report on changes in the regulated variable. Together, regulated variables, sensors, signals, and effectors make up a homeostatic circuit (**Figure 2*a***). In the case of systemic homeostasis, the components of homeostatic circuits are typically well-defined. For instance, to regulate blood glucose (regulated variable), pancreatic alpha and beta cells serve as sensors; glucagon and insulin are signals that reflect the glucose concentration; and liver, skeletal muscle, and adipose tissue are effectors that can correct any deviations of blood glucose levels from a set point value (28).

Cellular homeostasis is not yet understood as completely as systemic homeostasis, since most of the knowledge comes from studies of cellular stress responses (discussed below). The known regulated variables of cellular homeostasis include concentrations of various metabolites and macromolecules, like oxygen, ATP, and proteins, as well as membrane potential and the number and size of various organelles, like mitochondria, lysosomes, and endoplasmic reticulum (ER) (29). The known sensors of these variables are HIF-1α (for oxygen) (30), AMPK (for ATP) (31), HSF1 and IRE1 (for cytosolic and ER proteins) (32), mTOR and GCN2 (for amino acids) (33, 34), and TFEB (for lysosomes) (35). Each of these sensors activates a set of effectors that can correct deviations in the regulated variables. AMPK activates catabolic metabolism to increase ATP production, the IRE1-XBP1 pathway regulates ER size (in part through control of lipid synthesis), and TFEB controls lysosome size and number by inducing expression of lysosome-resident proteins. The signals that connect sensors and effectors in cellular homeostasis are either signaling pathways that control activity of effectors or transcription factors that control their expression.

Tissue homeostasis should be similarly defined in terms of regulated variables, sensors, signals, and effectors (7). Regulated variables at the tissue level include local concentrations of oxygen and nutrients, ECM density and stiffness, osmolarity and pH of interstitial fluid, and cell numbers and composition (29). The sensors for these variables include tissue-resident macrophages and sensory neurons (36, 37). Sensing mechanisms of some of the regulated variables are well understood, particularly when the molecular sensors are the same as in cellular homeostasis, such as HIF-1α for oxygen (38) and NFAT5 (39) for osmolarity. In tissue homeostasis, however, activation of these sensors results in the production of paracrine signals that engage effectors on the tissue level: HIF-1α stabilization leads to vascular endothelial growth factor A (VEGFA) production to induce angiogenesis, which increases oxygen delivery (40), while NFAT5 activation leads to VEGFC production to induce lymphangiogenesis and lymphatic drainage, which reduces osmolarity (41). Interstitial fluid pH can be sensed by GPR4, GPR65, and GPR68 expressed by endothelial cells, macrophages, and sensory neurons (42). The mechanisms for sensing many other tissue homeostatic variables, such as cell number and ECM composition and stiffness, are unknown. It can be predicted, however, that sensing a deviation in any of these variables will result in production of a paracrine signal that acts on the appropriate effector cell types to correct the deviation (except when a single cell type serves as both the sensor and effector for the same variable). In most cases, the specific homeostatic circuits that control tissue-level variables remain to be defined.



(*Caption appears on following page*)

Figure 2 (*Figure appears on preceding page*)

Homeostasis at the levels of the cell, tissue, and organism. (*a*) The homeostatic circuit illustrates how regulated variables are maintained within an appropriate physiological range. Deviations in regulated variables are detected by sensors, which then signal to effectors to correct the deviation. (*b*) The interplay between tissue-level and systemic homeostatic circuits is shown. Supportive cell types within tissues are the sensors and effectors for tissue-level homeostatic variables. Maintaining these variables in the proper range allows for effective function of the primary cells within the tissue. Thus, tissue homeostasis is maintained by supportive cells. Conversely, at the systemic level, primary cells are the sensors and effectors for systemic homeostatic variables. Therefore, organismal-level homeostasis is maintained by primary cells, which may also be influenced by the local state of the tissue homeostatic variables (*dashed arrows*). (*c–e*) The regulated variable of oxygen level is sensed and maintained at the cellular, tissue, and organismal levels. These pathways are depicted using the logic of the homeostatic circuit. Abbreviations: E, effector; EPO, erythropoietin; ES, endocrine signal; PS, paracrine signal; S, sensor; SHV, systemic homeostatic variable; THV, tissue homeostatic variable; VEGFA, vascular endothelial growth factor A.

It is important to note that the sensors and effectors in tissue homeostatic circuits are the supportive cells within tissues. In fact, their supportive functions are largely defined by their roles in tissue homeostasis. These core functions can be quantitatively dialed up and down by the homeostatic signals that communicate between sensors and effectors, allowing supportive cells that serve as effectors to respond dynamically to the needs of the tissue. The cell types that perform primary functions within tissues, on the other hand, are the sensors and effectors of systemic homeostasis. Thus, pancreatic alpha and beta cells have the primary function of sensing blood glucose, a systemic homeostatic variable, and skeletal muscle cells, hepatocytes, and adipocytes are primary cells in their respective organs that function as effectors to correct blood glucose concentration. This example illustrates a principle that connects tissue organization with homeostatic circuits: Systemic homeostasis is maintained by primary cells, while tissue homeostasis is maintained by supportive cells within tissues (**Figure 2*b***).

STRESS RESPONSES

Each homeostatic variable is characterized by a normal range of variation—the maximum deviation from the set point that can be tolerated. When values of regulated variables change within that range, homeostatic mechanisms correct them through negative feedback, as discussed above. Deviations that approach the limits of this homeostatic range put more strain on the system, resulting in what is commonly referred to as a stress response (43). These larger changes in regulated variables are detected and corrected by the same homeostatic sensors and effectors. In fact, what we know about cellular homeostasis was learned primarily by studying extreme perturbations to regulated variables, such as hyperosmolarity, hypoxia, and nutrient deprivation, or by manipulations that indirectly affect regulated variables, such as treatment with tunicamycin (glycosylation inhibitor), thapsigargin (calcium ATPase inhibitor), or proteasome inhibitors. Accordingly, the pathways involved in correcting these cellular perturbations are traditionally referred to as stress pathways, rather than homeostatic pathways (44). It is important to emphasize, however, that cellular stress is just a large deviation of a homeostatic variable nearing the limits of what can be addressed through homeostatic effector mechanisms. Stress responses are part of a continuum of homeostatic responses. Yet, the outcomes of stress responses can be qualitatively different from those of homeostatic responses. In addition to engaging homeostatic effectors to correct the deviations in regulated variables, stress responses may also suppress processes that either contribute to these deviations or are incompatible with correcting the deviations. For example, most cell stress responses inhibit cell proliferation, while homeostatic responses to normal variations in the regulated variable do not.

Consistent with the hierarchy of homeostatic circuits, stress responses can be engaged at the levels of the cell, tissue, and organism. All individual cells can detect and respond to stress. These cell-autonomous stress responses allow individual cells to adapt and survive in changing environments. For example, the cellular response to hypoxia is initiated by the hypoxia sensor HIF-1α, which activates transcription of the genes for the glucose transporter GLUT1 and glycolytic enzymes to promote anaerobic glycolysis (45) (**Figure 2*c***). This response occurs in all nucleated cells and is an example of the cellular stress response. However, cell-intrinsic adaptations to stress provide only short-term solutions, as they do not correct the problem itself. In this example, the cellular stress response does not eliminate local hypoxia. In multicellular organisms, cells can also coordinate with one another to perform tissue-level stress responses. Although all cells can sense stressors such as hypoxia, tissue-level responses generally rely on cells that have specialized sensory functions, such as tissue-resident myeloid cells and sensory neurons. In the case of hypoxia, tissue-resident macrophages detect low oxygen levels and secrete VEGFs and other angiogenic signals to endothelial cells, which act as effectors (46) (**Figure 2*d***). The outcome of this tissue-level response is local angiogenesis and increased oxygenation of the tissue, thus correcting the low oxygen levels directly. This response, however, may not be adequate when blood oxygen levels are low (i.e., systemic hypoxia or hypoxemia), which requires a stress response on the level of the whole organism. The sensors of systemic hypoxia are peritubular interstitial fibroblasts in the kidney, as well as hepatocytes, which detect hypoxia through HIF-1α and HIF-2α and induce expression of erythropoietin (EPO) (47, 48). EPO acts on erythroid progenitors in the bone marrow to promote erythropoiesis and increase oxygen delivery by red blood cells (**Figure 2*e***). The example of the stress response to hypoxia illustrates two points: First, even for the same homeostatic variable, sensors, signals, and effectors can differ at the cellular, tissue, and organismal levels. Second, it highlights again that supportive cell types in tissues serve as sensors and effectors to maintain tissue homeostasis, while the primary cells of tissues function as sensors and effectors to maintain systemic homeostasis.

TISSUE MICROENVIRONMENT

The framework for tissue homeostasis described above allows us to better define the tissue microenvironment. Individual cells within tissues are surrounded by a milieu that includes nutrients, oxygen, metabolic waste products, and the composition and mechanical properties of neighboring cells and ECM. From the perspective of the individual cell, these are features of their environment. From a tissue-level perspective, however, these are regulated variables: They are actively monitored by homeostatic sensors and corrected by effectors. When these variables deviate to the limits of the homeostatic range, stress responses are mobilized at the cellular and tissue levels. When these variables are within a normal range, close to the homeostatic set point, individual cells enjoy an optimal environment.

The notion of a tissue microenvironment became particularly popular in reference to tumors, which have characteristically altered homeostatic variables. Unrestrained proliferation of cancer cells within tumors results in oxygen and nutrient depletion (49) and alteration of cell composition and tissue architecture (50). These changes tend to limit proliferation of cells. The deviations in these regulated variables are sensed by tissue homeostatic sensors, such as tissue-resident macrophages (in this context referred to as tumor-associated macrophages) (51). Various effectors, like endothelial cells and stromal cells, attempt to correct them, just as they would in normal tissues. By maintaining tissue homeostasis, the supportive cell types (macrophages, endothelial cells, and stromal fibroblasts) enable tumor growth, which makes them essential components of most solid tumors. However, in fast-growing tumors, the homeostatic capacity is eventually

overwhelmed by uncontrolled proliferation of cancer cells, leading to the formation of a necrotic core at the center of the tumors, where homeostatic alterations are most severe (52, 53). The extreme deviations and ultimately the loss of tissue homeostasis observed in tumors can also occur in normal tissues in response to severe perturbations of homeostatic variables that exceed homeostatic capacity. This can result in cell death and the loss of normal tissue architecture and function. When this happens, tissues engage in the next line of defense—the inflammatory response.

TISSUE INFLAMMATION

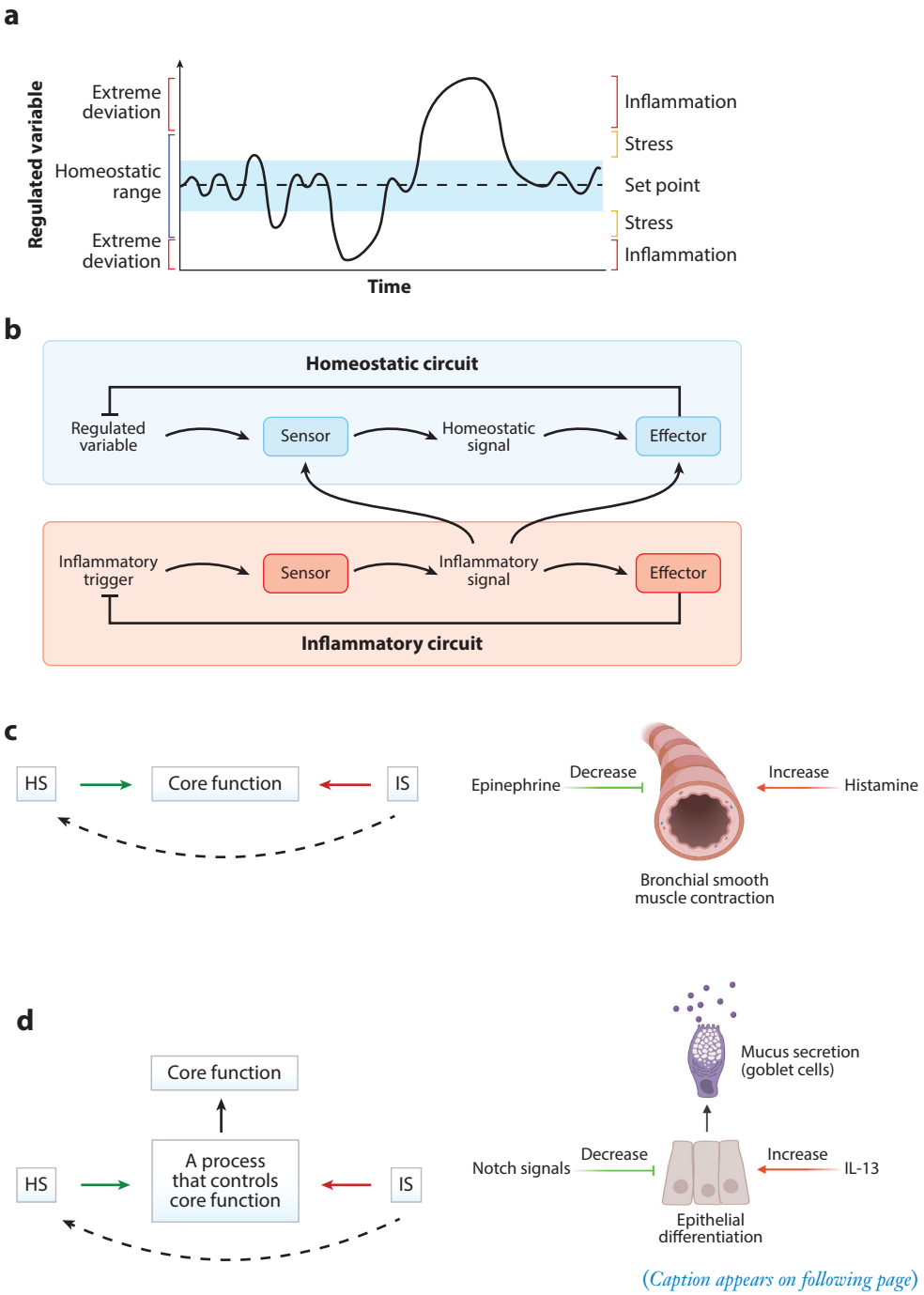
Inflammation is usually defined as a response to infection or injury. While this view is certainly correct, it does not capture the essence of the inflammatory response or explain its role in a wide range of physiological and pathological conditions. Infection and injury are extreme perturbations. As a result, they cause inflammatory responses of a magnitude that is readily observable. However, it is now well appreciated that inflammation can occur without infection or overt tissue damage. A common theme of conditions that initiate inflammation is the disruption of cellular and tissue homeostasis (54–57). There are several well-known examples of this. (*a*) Cells with disrupted homeostasis that undergo senescence can release inflammatory mediators known as the senescence-associated secretory phenotype (SASP) (58). (*b*) Excessive cell stress, such as ER, mitochondrial, or osmotic stress, that cannot be handled by effector mechanisms within the homeostatic regime activates the NLRP3 inflammasome (43). This leads to production of IL-1 family cytokines (55, 59, 60), as well as ligand-independent activation of tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL) receptors (61). In obesity, lipid overload in adipocytes and hepatocytes causes ER stress and production of inflammatory signals (62). This type of inflammation, called metaflammation (63), is caused by a disruption of metabolic homeostasis.

The pathological roles of these inflammatory responses are well appreciated and are exemplified by the contribution of ER stress–induced inflammation to metabolic disease (64) and the contribution of SASP to tumor progression (65) and aging (66). However, they also have important physiological roles that are becoming clear. For instance, endurance exercise increases production of proinflammatory cytokines, such as IL-13 and IL-6. IL-13 induces the expression of mitochondrial and fatty acid oxidation genes in myocytes, which leads to a transition to slow-twitch oxidative muscle fibers and enhanced mitochondrial biogenesis in order to optimize energy utilization and adapt to high-endurance exercise (67). IL-6 is produced by myocytes based on the duration and intensity of physical activity and acts on liver and adipose tissues to regulate glucose and lipid metabolism in order to meet long-lasting energy demands (68, 69). IL-6 is also produced by brown adipocytes under conditions of acute psychological stress, in response to adrenergic stimulation by the sympathetic nervous system, and promotes hepatic gluconeogenesis to support fight-or-flight responses (70). In these cases, inflammatory cytokines regulate both tissue-level and systemic adaptations to anticipated physical activity that exceeds homeostatic demands. Research to shed further light on the roles that inflammatory signals play in these exercise-induced physiological responses is ongoing (71).

The examples above illustrate the common principle that extreme perturbations of tissue homeostasis induce inflammation. While deviations of regulated variables within a normal range are corrected by the homeostatic circuit (including stress responses), extreme deviations of regulated variables beyond the homeostatic range trigger the inflammatory response (**Figure 3*a***). Here, homeostatic, stress, and inflammatory responses are activated based on the degree of deviation in the regulated variable, rather than qualitatively different types of challenges. Thus, homeostasis, stress, and inflammation represent a continuum of responses to tissue perturbations. The cellular sensors that trigger these different responses can be either distinct—as in the case of the NLRP3 inflammasome, which responds to the most extreme deviations to activate inflammation (43)—or

the same, such as IRE1, which coordinates the cell-intrinsic ER stress response and can induce inflammatory signals such as IL-6 and TNF (44, 72).

Similarly, although the homeostatic and inflammatory signals released by these sensors are traditionally thought to be distinct, accumulating evidence indicates that many inflammatory



(*Caption appears on following page*)

Figure 3 (*Figure appears on preceding page*)

Regulation of core functionality by homeostatic and inflammatory signals. (*a*) The value of a regulated variable fluctuates as a function of time, but homeostatic mechanisms maintain it within a homeostatic range around a set point. When the regulated variable experiences more significant deviations within the homeostatic range, the stress response acts to restore the regulated variable to the set point. When the regulated variable deviates beyond the homeostatic range, this extreme deviation triggers an inflammatory response to return it to the homeostatic range. (*b*) The inflammatory circuit has a parallel structure to that of the homeostatic circuit, consisting of an inflammatory trigger, sensor, signal, and effector. The effectors of inflammatory responses eliminate inflammatory triggers (e.g., bacteria) or resolve the tissue disruption caused by the inflammatory triggers. In addition to regulating effector functions specific to inflammation, inflammatory signals also act on sensors and effectors of homeostatic circuits to control homeostatic effector functions. (*c*) Homeostatic signals (*green arrow*) and inflammatory signals (*red arrow*) can directly control the core functionality of cells. Inflammatory signals can also operate by changing the levels of homeostatic signals (*dashed arrow*). These signals quantitatively increase or decrease the core functions and can operate in the same or opposite directions. For example, epinephrine decreases bronchial smooth muscle contraction (or causes relaxation) by acting on β-adrenergic receptors. During allergic responses, histamine released by mast cells and basophils increases smooth muscle contraction, antagonizing homeostatic control to cause bronchial constriction. (*d*) Homeostatic signals (*green arrow*) and inflammatory signals (*red arrow*) can act indirectly by regulating a cellular process, such as cell differentiation or migration, that in turn controls the core function of cells. For example, Notch signals inhibit goblet cell differentiation, which limits the quantity of mucus secreted by goblet cells during homeostasis. Parasitic infection increases IL-13 production, which increases goblet cell differentiation and enhances mucus production. In addition, inflammatory signals can alter the levels of homeostatic signals (*dashed arrow*). Abbreviations: HS, homeostatic signal; IS, inflammatory signal.

mediators can also function as homeostatic signals. For instance, TNF promotes epithelial cell proliferation (73), and IL-6 maintains self-renewal of hematopoietic, mesenchymal, and epithelial stem cells (74–77). Prostaglandins have both inflammatory and homeostatic functions, including their role in maintaining epithelial barrier integrity (78). Histamine is a potent inflammatory mediator produced by mast cells and basophils (79), but it also plays an important role in controlling intestinal peristalsis (80) and gastric acid secretion (81) and functions as a neurotransmitter in the brain (82). Whether these signals perform homeostatic or inflammatory functions may depend on their expression range and the source and target cell types.

In addition to sensing extreme perturbations in homeostatic variables, cells can sense the loss of tissue homeostasis retrospectively by monitoring its consequences, such as cell death. Cells undergoing several forms of unscheduled cell death, including necrosis, necroptosis, pyroptosis, and ferroptosis, are known to release signals that initiate inflammatory responses (83–88). These signals include ATP (89), HMGB1 (90), histones (91), some amino acid–tRNA synthetases (92), succinate (93), and the IL-1 family members (55). Finally, the inflammatory response can be induced prospectively when inflammatory sensors detect stimuli that are anticipated to result in the loss of tissue homeostasis (29). These stimuli include microbial agents and foreign bodies (57). Their detection initiates the inflammatory response even before there is any loss of tissue homeostasis. For instance, detection of LPS by TLR4 on macrophages leads to an inflammatory response not because LPS causes disruption of homeostasis, but because it is associated with bacterial pathogens that do. The inflammatory response to LPS is therefore induced preemptively, in anticipation of the loss of homeostasis. The sensors involved in initiating preemptive inflammatory responses are various pattern recognition receptors, typically on innate immune cells (94), and the resulting signals are well-known inflammatory mediators, including cytokines and chemokines.

In summary, inflammatory responses are induced either as a result or in anticipation of the loss of tissue homeostasis. In the former case, inflammation is induced either by extreme deviations of homeostatic variables or by tissue damage that results from the loss of homeostasis. In the latter case, inflammation is induced when conserved microbial products (pathogen-associated

molecular patterns) or allergens are detected, before tissue damage takes place (29, 79). In all cases, the inflammatory response follows the same general design as the homeostatic circuit, with the same four universal components (**Figure 3*b***). Inflammatory triggers are monitored by a sensor that produces inflammatory signals that act on various effectors, either locally within the tissue or systemically. The ultimate goal of the inflammatory response is to restore the system to a homeostatic state and its regulated variables to their set points.

EFFECT OF INFLAMMATION ON CORE FUNCTIONALITIES IN TISSUES

In previous sections, we describe how primary and supportive cells within tissues act as the effectors within homeostatic circuits. Homeostatic and stress signals tune the core functions of those cell types in order to maintain regulated variables at the appropriate levels, both systemically and within the tissue environment. Similarly, inflammatory signals increase or decrease those same core cellular functions in order to achieve their effects. To understand how inflammation alters cellular functions within tissues, we can consider the well-studied example of microbial infection. Sensing of microbes within tissues triggers the production of inflammatory cytokines and chemokines that cause vasodilation and increase vascular permeability, allowing for the recruitment of neutrophils into the tissue. At the infection site, neutrophils become activated and release neutrophil extracellular traps (NETs), proteases, and other antimicrobial agents to contain the pathogens and prevent them from spreading systemically (95, 96). In the short term, these inflammatory responses alter cellular functions (like endothelial permeability) and tissue composition (for example, through neutrophil recruitment) in the service of inflammation. However, in the long term, this is necessary to prevent more severe damage by the spread of microbes and ultimately to restore tissue homeostasis.

To achieve these ends, the inflammatory response follows three important principles. First, inflammatory signals alter tissues by making quantitative changes to the performance of their core functionalities. Second, inflammatory functions take priority over homeostatic functions: The inflammatory signals must override incompatible homeostatic signals to change the performance of cells' core functions. Third, similar to the hierarchy that exists in tissue-level and systemic homeostasis, changes in the core functionalities of supportive cell types enable inflammation at the tissue level while changes in the core functionalities of primary cell types support inflammation at the systemic level. Below, we discuss each of these generalizations and their implications.

Most commonly, inflammatory signals act directly on a given cell type to enhance or suppress certain core functions that it performs (**Figure 3*c***). For example, core functions of fibroblasts are production of ECM and production of growth factors. These functions can be modulated by inflammatory cytokines such as TNF and IL-13 (97, 98). The core functions of adipocytes are lipid uptake from circulation for storage and lipid release when there is a demand for fatty acids in other organs. Inflammatory cytokines (TNF, IL-1, and IL-6) suppress lipid storage by inhibiting lipoprotein lipase and at the same time promote lipolysis to increase fatty acid release (99). A core function of endothelial cells is to form an internal barrier to separate the tissue environment from the systemic environment while allowing selective exchange of oxygen and metabolites (100). They are often the first target of inflammatory signals and provide a good example of how these signals change core functionalities. Endothelial barrier function is modified to either increase or decrease endothelial permeability. Histamines released from mast cells during allergic inflammation or prostaglandins produced during microbial infections can activate specific G protein–coupled receptors (GPCRs) on endothelial cells, leading to an increase in intracellular calcium and activation of Rho signaling through the Gαq subunit (101–103). Elevated calcium

activates myosin light chain (MLC) kinase, and Rho signaling inhibits the MLC phosphatase. Synergistically, these two signaling pathways increase phosphorylated MLC, which initiates actin filament contraction to increase permeability (104). In contrast, activation of GPCRs through the Gαs subunit increases cyclic AMP synthesis, which strengthens tight junctions, reduces actomyosin contraction, and decreases barrier permeability (105, 106). Ligands such as adenosine, when signaling through adenosine A2 receptors, activate Gαs proteins to change endothelial permeability in the opposite direction of inflammatory signals (107). These GPCR-mediated inflammatory and anti-inflammatory effects take place within minutes of stimulation (108). In addition to GPCR signaling, cytokines such as TNF and IL-1β activate downstream transcription factors NF-κB and AP-1 in endothelial cells and drive vascular permeability and leukocyte adhesiveness in a manner that is dependent on new protein synthesis (103, 109). This process takes a few hours and thus follows GPCR activation to regulate permeability on a longer timescale. Although different types of inflammation elicit different inflammatory mediators, these signals generally converge to dial up or down the core functions of particular cell types.

To enable inflammatory responses within tissues, inflammatory signals must act on multiple cell types and change their core functionalities in a coordinated fashion. For example, the core function of vascular smooth muscle is to control blood flow through contraction and relaxation, and the core functions of vascular endothelial cells include barrier and transport functions. During inflammation, cytokines, prostaglandins, and nitric oxide promote relaxation of vascular smooth muscle, causing increased blood flow to the site of inflammation (110, 111). This is coupled with the activation of endothelial cells, which secrete chemokines, increase surface expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin, P-selectin) for circulating neutrophils, and increase barrier permeability for fluids rich in plasma proteins (103). Extensive signaling between endothelial and smooth muscle cells ensures coordinated actions to recruit immune cells from circulation into the tissues (an extension of the transport function of the endothelium).

In the examples cited above, the inflammatory signals change the core functions by acting directly on the cell types that perform these functions. However, in some cases, the effects of inflammatory signals can be indirect, through processes that contribute to or control the core functions (**Figure 3*d***). These indirect effects are often mediated through control of differentiation of cells performing a given function, particularly when these cell types are short-lived. For example, IL-13 indirectly promotes epithelial barrier function by stimulating differentiation of goblet cells, which in turn secrete mucus to reinforce the epithelial barrier (112). Similarly, TNF and granulocyte colony-stimulating factor (G-CSF) produced during bacterial or fungal infection act on hematopoietic progenitors to increase neutrophil differentiation (113), while IL-5 produced during helminth infection promotes generation and migration of eosinophils (114). This theme applies not only to inflammatory signals but also to the homeostatic signals discussed above, which can affect core functions either directly or indirectly (**Figure 3*d***). EPO acts indirectly, for example, because it increases the differentiation of red blood cells to increase oxygen-carrying capacity (115), rather than directly enhancing their oxygen-carrying function. Finally, inflammatory signals can also modulate core functionalities through their effects on homeostatic signals (**Figure 3*c*,*d***).

This leads us to the second generalization, which is that inflammatory signals take precedence over homeostatic signals, in order to coordinate emergency functions. This can occur in a few ways. Inflammatory signals can act on the same effector that participates in the homeostatic circuit, overriding the effect of the homeostatic signal and changing the quantitative performance of the effector's core functionalities. Alternatively, inflammatory signals can act on the homeostatic sensor, changing its gain (input-output function) (**Figure 3*b–d***). To illustrate this, consider the bone, the primary function of which is to provide mechanical support for the organism. To perform this function, osteoblasts (primary cells) and osteoclasts (supportive cells) work as a complementary

Table 2 Effects of homeostatic and inflammatory signals on core functionalities of cell types within tissues

Tissue	Cell types	Core function	Homeostatic signals	Inflammatory signals
Vasculature	Smooth muscle cells	Contraction	↑ Endothelin-1, thromboxanes (138); norepinephrine (α receptors) (139)	↑ Leukotrienes (140), histamine (H_1 receptor) (101)
		Relaxation	↑ NO (110), norepinephrine (β_2 receptor) (141)	↑ TNF, IL-1β (111); histamine (H_2 receptor) (101)
	Endothelial cells	Vessel permeability	↑ NO and PG (100)	↑ TNF and IL-1β (103), histamine (142)
Bone	Osteoblasts	Matrix deposition	↑ BMPs, IGF-1, FGFs (116)	↑ IL-22 (118), IL-23 (134)
	Osteoclasts	Matrix resorption	↑ M-CSF (143), RANKL (144) ↓ OPG (145)	↑ TNF, IL-1, IL-6, IL-17 (118); histamine (146) ↓ IL-4 (147); IL-12, IL-18, IL-33 (118); IFN-β (148)
Adipose	Adipocytes	Lipid storage	↑ Insulin (149)	↑ IL-6 (150)
		Lipid release	↑ Catecholamines (149)	↑ TNF (121), IL-1 (122), IL-6 (64)
Small intestine	Enterocytes	Nutrient and mineral absorption	?	↓ IL-22 (151, 152, 159)
	Goblet cells	Mucus secretion	↑ Acetylcholine (153) ↓ Notch (154)	↑ IL-13 (112)
	Smooth muscle cells	Peristalsis	↑ Acetylcholine, serotonin[a], histamine[a] (21, 80)	↑ Serotonin[a], histamine[a] (80)
Hematopoietic system	Stem cells	Self-renewal and differentiation	Wnt (155); PG (156); IL-7, EPO (115); M-CSF, GM-CSF (157)	↑ TNF, IL-1β, IL-6 (neutrophils, monocytes) (113), IL-5 (eosinophils) (114), TSLP (basophils) (158)

Abbreviations: BMP, bone morphogenetic protein; FGF, fibroblast growth factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; IGF-1, insulin-like growth factor 1; M-CSF, macrophage colony-stimulating factor; NO, nitric oxide; OPG, osteoprotegerin; PG, prostaglandin; RANKL, receptor activator of NF-κB ligand; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

[a]These signals can be both homeostatic and inflammatory. In these contexts, the quantity of the signal determines whether it has homeostatic or inflammatory functions.

unit. The core function of osteoblasts is to deposit ECM, and the core function of osteoclasts is to degrade or resorb ECM (these are essentially specialized fibroblasts and macrophages, respectively, which also regulate ECM in their roles as supportive cells in other tissues). Homeostatic control of this system operates through the production of growth factors for each cell type (**Table 2**). The main growth factors for osteoclasts are macrophage colony-stimulating factor (M-CSF) and receptor activator of NF-κB ligand (RANKL), both of which are produced by osteoblasts. Under normal conditions, therefore, osteoblasts regulate the numbers of the supportive osteoclasts to maintain control of bone homeostasis (116). Inflammatory signals like TNF, however, override this homeostatic circuit in one of two ways: (*a*) They act directly on osteoclasts to promote osteoclast differentiation and activity or (*b*) they act on osteoblasts to increase the level of RANKL, which in turn controls osteoclast numbers. The cytokine IL-4 can oppose the activity of TNF by preventing both its direct effects on osteoclasts and its effect on osteoblast expression of RANKL (117, 118).

Most of the examples that we discuss above describe changes in supportive functions that control tissue-level biology during inflammation. However, recall that, under homeostatic conditions, primary cell types within tissues perform supportive functions at the organismal level to maintain

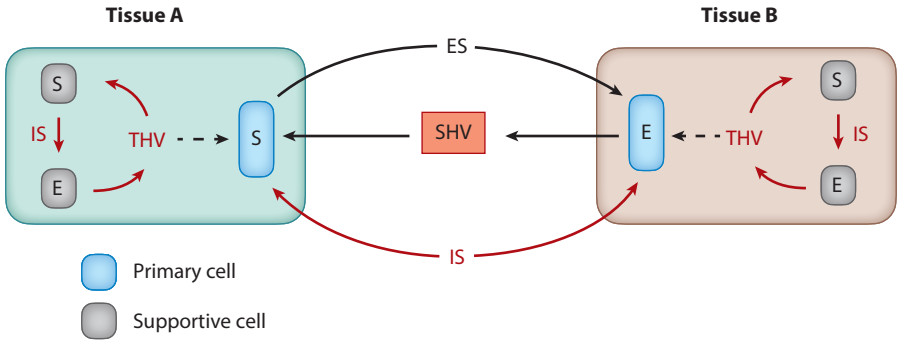


Figure 4

Local and systemic effects of inflammatory signals. At the tissue level, supportive cell types act as inflammatory sensors and effectors. Inflammatory signals (*red arrows*) act on effectors to change tissue homeostatic variables, such as cell composition and endothelial permeability. These changes are often required to facilitate inflammatory responses at the tissue level. At the systemic level, inflammatory signals act on primary cell types to change systemic homeostatic variables and coordinate the systemic inflammatory response. As is the case with homeostatic circuits, primary cell types can also be influenced by the local state of the tissue homeostatic variables (*dashed arrows*). Abbreviations: E, effector; ES, endocrine signal; IS, inflammatory signal; S, sensor; SHV, systemic homeostatic variable; THV, tissue homeostatic variable.

regulated variables of the entire organism. Similarly, in the context of inflammation, we can make the final generalization that changing core functionalities of primary cells supports inflammatory responses at the organismal level (**Figure 4**). In the case of systemic infections, for instance, adjustments in the primary function of different organs are coordinated to enable systemic inflammatory responses against pathogens and promote tissue-level tolerance to those responses (119, 120). In systemic inflammation, cytokines TNF, IL-1, and IL-6 act on many primary cell types to tune their core functionalities. For example, as noted earlier, these cytokines act on adipocytes to suppress lipid uptake from the circulation and promote lipolysis (64, 121, 122), on skeletal muscle cells to release amino acids (123), and on hepatocytes in the liver to optimize the production of ketone bodies (124). These signals also act on pancreatic beta cells to inhibit insulin production and on hepatocytes, skeletal muscle cells, and adipocytes to reduce responsiveness to insulin (125, 126). They dramatically increase the secretory function of hepatocytes, inducing secretion of large quantities of acute phase proteins into circulation (127), which in turn further propagate the inflammatory response. In addition, they change the activity of hypothalamic neurons to induce fever and anorexia (128, 129). These changes both support the metabolic demands of the immune response and render the host more tolerant to the damage caused by inflammation (119, 130–132). The primary functions of different tissues are thus adjusted and coordinated by systemic inflammatory signals to optimize the systemic inflammatory response.

INFLAMMATORY DISEASES

The goal of the inflammatory response is ultimately to restore homeostasis. This is obvious in the case of infection-induced inflammation, where a successful inflammatory response results in elimination of the pathogen. However, in the process of achieving that goal, the inflammatory response leads to temporary disruption of homeostasis. This occurs in part because collateral tissue damage is an unavoidable consequence of antimicrobial immune responses, but also because inflammation deliberately alters many aspects of tissue homeostasis. Recruitment of monocytes and granulocytes changes cell numbers and composition within tissue compartments, and

the inflammatory exudate changes the interstitial fluid volume and protein concentration (57). Proteases produced by neutrophils degrade ECM proteins, and the functions of most cell types within an inflamed tissue are altered by inflammatory cytokines (96). Similarly, inflammation alters many aspects of systemic homeostasis, such as body temperature, metabolism, and endocrine functions (119). These changes, which are clearly a departure from a homeostatic state, are necessary to eliminate the inflammatory trigger (such as a pathogen) and ultimately restore homeostasis.

As described in the previous section, a general theme of inflammation is that inflammatory signals override homeostatic pathways that are incompatible with inflammatory processes. For example, maintaining stable cell composition within the tissue compartment (133) is clearly incompatible with recruitment of inflammatory cells necessary to combat an infection. Therefore, the mechanisms that maintain cell numbers within tissues have to be overridden by inflammatory signals to allow for neutrophil and monocyte recruitment. Inflammation has higher biological priority than many homeostatic functions because the benefits of the inflammatory response generally outweigh the costs of temporary loss of homeostasis. This very property of inflammatory signals, however, also creates a vulnerability for pathologic disruption of homeostasis by dysregulated or chronic inflammation. To illustrate this, we can return to the example of how inflammatory signals regulate core functions in bone. In rheumatoid arthritis, which is characterized by erosion of bone tissue within joints, sustained type 1 inflammation (including increased levels of TNF, IL-1, and IL-6) drives increased RANKL expression in osteoblasts, which in turn causes increased osteoclast activity (118). Another set of chronic inflammatory disorders known as spondyloarthropathies (such as ankylosing spondylitis and psoriatic arthritis) are characterized by the opposite process—new bone formation at specific anatomical sites. These diseases are driven by a distinct set of cytokines that have the opposite effect on core cellular functions: IL-23 (together with IL-22 and IL-17) acts to increase osteoblast deposition of ECM, again both directly and by increasing levels of normal, homeostatic growth factors (118, 134). The same principle applies to type 2 (allergic) inflammation. For instance, patients with chronic asthma often have prominent infiltrates of type 2 inflammatory cells in the airways, such as eosinophils, mast cells, basophils, type 2 T helper cells, and group 2 innate lymphoid cells (135). These cells produce type 2 cytokines, like IL-13, which are responsible for changing the core functions of local cell types, including increased goblet cell differentiation and mucus production, fibroblast ECM deposition, and bronchial smooth muscle contractility. These changes, when they are persistent, lead to the pathologic setting of airway remodeling in asthma (135, 136). Sepsis is a common and often fatal example of sustained inflammatory signaling. One of the hallmarks and dangers of sepsis is hypotension. As described above, inflammatory cytokines (like TNF, IL-1, and IFN-γ) and prostaglandins induce relaxation of vascular smooth muscle, both directly and through induction of nitric oxide production by macrophages and smooth muscle itself (110, 111, 137). This inflammatory regulation of smooth muscle function is typically adaptive, allowing for increased blood flow to the site of inflammation. But because these signals override normal homeostatic regulation, it makes the system susceptible to disease and even death in the case of sustained inflammatory signaling, which can cause systemic hypotension and decreased blood flow to vital organs (137).

CONCLUDING REMARKS

Here we present a perspective on tissue homeostasis and inflammation based on a framework for understanding the functional organization of tissues. We describe how the core functions of supportive and primary cell types are assembled in tissues that are optimized to perform particular functions for the organism, how these core functionalities are tuned up and down to

maintain tissue and systemic homeostasis, and how inflammation overrides homeostatic control to coordinate emergency functions and ultimately defend homeostasis.

Homeostasis is a powerful concept that, if carefully defined, can be applied to understand tissue biology and inflammation. The homeostatic and inflammatory circuits are composed of the same components, including sensors, which monitor variables of interest, and effectors, which can change the values of these variables in the desired direction. Inflammation is induced by one of three possible indicators of the loss of homeostasis. First, inflammation can be induced by extreme deviations of regulated variables beyond their normal range—a direct indication of the loss of homeostasis. This form of inflammation relates to what Metchnikoff called physiological inflammation and, if the inflammatory response is successful, likely does not manifest in clinical symptoms. Second, inflammation can be induced retrospectively by the consequences of the loss of homeostasis, such as nonapoptotic cell death or the disruption of tissue architecture. This type of inflammation may fall into Metchnikoff's pathological inflammation category (where pathological refers to the cause rather than the consequence). Finally, inflammation can be induced prospectively, when inflammatory sensors detect pathogens or allergens as indicators of forthcoming loss of homeostasis. The ensuing inflammatory response would match what Metchnikoff referred to as immunity—the highest end of the inflammatory spectrum. While we can now appreciate that Metchnikoff had a deep intuition about the homeostasis-inflammation spectrum, much work is still required to fully elucidate its underlying principles and mechanisms.

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