Re-thinking our understanding of immunity: Robustness in the tissue reconstruction system

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Abstract

Robustness, understood as the maintenance of specific functionalities of a given system against internal and external perturbations, is pervasive in today's biology. Yet precise applications of this notion to the immune system have been scarce. Here we show that the concept of robustness sheds light on tissue repair, and particularly on the crucial role the immune system plays in this process. We describe the specific mechanisms, including plasticity and redundancy, by which robustness is achieved in the tissue reconstruction

system (TRS). In turn, tissue repair offers a very important test case for assessing the usefulness of the concept of robustness, and identifying different varieties of robustness.

Keywords

Tissue repair; tissue regeneration; robustness; redundancy; plasticity; surveillance.

Introduction

Robustness can be defined as the maintenance of specific functionalities of a given system against internal and external perturbations [1,2]. The term, routinely used in engineering (e.g. [3]), is now pervasive in the life sciences [4]. Systems and processes as diverse as bacterial chemotaxis, biochemical networks, cells, organisms, and ecosystems, among many others, have been described as robust [5–9]. For example, a plane is robust when it continues to fly despite severe turbulence (for example thanks to the flexibility of its wings), and a bacterial cell is robust to modifications in genetic regulation when it tolerates a high number of these modifications [10].

The notion of robustness, however, is very broad, and often elusive. To make it more precise, it has long been emphasized (e.g., [11]) that two crucial questions must systematically be addressed when talking about robustness: first, *what* is robust, and second *to what* is it robust? In other words, a system is not robust in general; rather, it is robust to a certain kind of perturbations that can occur at a given level (or at a limited number of levels). The most stirring applications of the concept of robustness are those where talking about robustness seems directly operative, that is, sheds a new and important light on a given phenomenon, as illustrated by several cases including bacterial chemotaxis [7].

The aim of the present paper is to ask whether the concept of robustness can illuminate the processes of tissue repair and tissue regeneration, and whether, in turn, tissue repair and tissue regeneration offer a promising basis to better define the notion of robustness applied to biological phenomena. We are therefore interested in robustness at a particular level, namely that of tissues, and against a particular set of perturbations, namely damages made on tissues (physical or chemical aggressions, infectious agents, or “internal”

stresses). Our focus on repair and regeneration at the tissue level is justified by the recent wealth of data on this issue [12], and by the obvious clinical interest of this topic, especially in the age of regenerative medicine [13], but it is important to keep in mind that repair occurs also at other levels (including genetic [14] and cellular [15] level) in the organism. The idea that repairing oneself is fundamental to the organism's unity and individuality has been suggested at least since the 19th century, particularly by physiologist Claude Bernard [16]. More recently, the concept of robustness has been commonly associated with repair and regeneration [17–20]. Much remains to be said, however, about how robustness and tissue repair can shed light one on the other.

Tissue repair and regeneration involve a horde of components and pathways, including structural (e.g., fibroblasts, ECM, etc.) and immunological (e.g., neutrophils, macrophages, etc.) ones [12,20–22]. For this reason, we propose the concept of the "tissue reconstruction system" (TRS) to embrace all the different aspects of this phenomenon (see **Figure 1**). Repair is essential for the survival and maintenance of the body [16,21]. Failures in the repair process can lead to various pathological conditions, including fibrotic diseases, ulcers, hypertrophic and keloid scars, as well as cancers [23–25]. Repair is continuously occurring, to some degree, in organisms (e.g., skin renewal), in response to their constant exposure to damages of different types (physical, chemical, radiological, etc.). Even though there exists to a large extent a continuum between repair and regeneration [26], the two phenomena can be considered distinct in several respects. Regeneration describes the capacity to regrow complex organs entirely, generally with the implication of several cell types [18,27–29]. In mammals, for example, the renewal of the epidermis is a form of repair, because it involves a single cell type (keratinocytes), whereas for the liver one can talk about regeneration as it involves several cell types (hepatocytes, sinusoidal endothelial cells,

stellate cells, Kupffer cells, etc.) [30]. Many repair mechanisms have been conserved across different taxa, including Drosophila, zebrafish, chick, and mammals [22,26]. The capacity to regenerate many complex organs such as limbs, however, is found only in a subset of living things [26,27]. One important aim of this paper is to better clarify the similarities and differences between repair and regeneration, thanks to the concept of robustness.

We explain here how robustness can help better characterize the process of tissue reconstruction, through a description of the specific mechanisms, including plasticity and redundancy, by which robustness is achieved in the TRS. We also demonstrate that different repair-associated disorders (such as fibrosis, ulcers, and cancers) can be understood as the result of deregulated robustness. In turn, we show that the TRS offers a remarkable test case to defining the notion of robustness in a more precise and operational way, and more specifically to distinguishing different *forms* of robustness (structural vs. functional; preventive vs. corrective; partial vs. complete; dysfunctional vs. as a dysfunction).

1. What is robustness?

With the increasing attention paid recently to systems biology and complex systems, many living processes or systems have been described as "robust" [1,2,31]. The exact meaning of the word "robustness" often remains, however, elusive. The term originated in physics [11], and engineering [32] (though the engineering-related meaning is itself rooted in the physiology of the 19th and 20th century, including the work of Claude Bernard [33]). (On the relationship between biology and engineering, see [34]). In general, robustness is defined as the maintenance of specific functionalities of the system against internal and external perturbations. Two major requirements for any claim about biological robustness are to

determine what exactly the robust system is, and against which type(s) of perturbations it is said to be robust. Importantly, robustness does not amount to conservation or absence of change. Robustness allows changes in the structure and components of the system owing to perturbations, but the key idea is that robustness leads to the maintenance of specific functions. It is likely that robustness is an evolved trait [9,35,36]. Moreover, there are often trade-offs between robustness and other traits. In particular, systems that are evolved to be robust against certain perturbations can be extremely fragile to unexpected perturbations (see, e.g., [2,4]).

Despite the fact that, historically, the concept of robustness took root to some extent in the concept of homeostasis, the two notions are different. Homeostasis is about maintaining constant (or almost constant, within a certain range) a value (e.g., body temperature in homeothermic animals) [37,38]. Robustness, in contrast, is about maintaining a given function F against given types of perturbations (P1, P2, etc.).

Examples of robust processes or systems in biology abound [4]. These include chemotaxis in bacteria [6,7], cell cycle in budding yeast [39], reliable development despite noise and environmental variations [40], ecosystem reconstruction after a catastrophic event [8], among many others.

As shown by Kitano [2], the four main mechanisms that ensure robustness are: system control, alternative mechanisms, modularity, and decoupling. System control consists in negative and positive feedbacks that enable the system to reach robustness against some perturbations. An example is bacterial chemotaxis, in which negative feedback plays a major role [41]. Robustness can also be realized by alternative (or “fail-safe”) mechanisms, that is, multiple routes to achieve a given function, which is to say that the failure of one of these routes can be compensated by another. This includes redundancy (where identical or nearly

identical components can realize a given function) and diversity (where heterogeneous components can realize a given function). There are now many examples of these phenomena in the immune system (e.g., [42]). Modularity is another important dimension of robustness: robustness is often achieved by modules, that is, flexible sets of components that collectively realize a given function, rather than by individual components [43]. Finally, decoupling is the prevention of undesired connection between low-level variations and high-level functionalities. An example is the buffer mechanisms that decouple genetic variations from phenotypic expression, e.g., HSP chaperones [44].

Here we focus on how the concept of robustness can be applied to the immune system and the TRS across the living world. Robustness has not been widely mentioned in immunology, though some exceptions exist (e.g., [33,45–47]). In particular, Mantovani [47] proposed that robustness provides a conceptual framework to understand intriguing aspects of the chemokine system, most prominently its redundancy (see also Mantovani, this special issue). Germain, Altan-Bonnet, and colleagues have explored theoretically and experimentally the mechanisms through which T cells can be both robust and adaptable to variations in protein expression [45]. Kourilsky has proposed to understand the immune system as conferring robustness to the whole organism via its capacity to systematically detect and respond to internal as well as external perturbations [33]. The question raised here is different and complementary, in so far as robustness is examined at the tissue level, and we ask which exact roles the immune system plays in this tissue-level robustness.

In what follows, we detail how the TRS works, mainly via five processes, namely plasticity, functional redundancy, constant surveillance, restraint, and dynamic adjustment. We then show how pathologies associated with dysfunctions in tissue repair (e.g, fibrosis, ulcers, and cancer) can be understood as resulting from a deregulation of one or several of

these five processes. We propose that the TRS offers a remarkable test case to define the notion robustness in a more precise and operational way, and more specifically to distinguishing different *forms* of robustness (structural vs. functional; preventive vs. corrective; partial vs. complete; dysfunctional vs. as a dysfunction). Importantly, we will consider both "repair" (defined as the partial reconstruction of an organ or tissue) and "regeneration" (defined as the complete reconstruction of a complex organ or tissue) examples, and explain how the concept of robustness helps clarify the differences between repair and regeneration.

2. The mechanisms that mediate tissue reconstruction

Tissue reconstruction is a complex and dynamic process, comprising overlapping, highly orchestrated stages – namely inflammation, tissue formation, and tissue remodeling [21]. Tissue reconstruction involves many molecular and cellular components, which tightly interact. Understanding the interactions between these components and how they are regulated both spatially and temporally is a major aim for anyone interested in tissue repair, regeneration, and repair-associated pathologies. We show here that the TRS exhibits five key features that participate in robustness, and which are shared by many actors involved in the TRS: the TRS is plastic, redundant, under constant surveillance, restrained, and continuously dynamic.

2.1. Plasticity in the TRS

First, a major feature of the TRS is the plasticity of the cells involved in tissue reconstruction. The word “plasticity” is used with different and sometimes confusing meanings in the scientific literature. Here we understand cell plasticity in two different and important senses [20]. The first sense is *intra-lineage cell plasticity*, that is, changes in cell function and phenotype within a given cell lineage – for example, M1 macrophages turning into M2 macrophages. This is sometimes called “functional plasticity” [48]. The second sense is *trans-lineage cell plasticity*, that is, the switch from one lineage to another – e.g., from macrophages to fibroblasts [49]. This can also be called plasticity by “transdifferentiation” [50] or by “reprogramming” – a phenomenon now known to occur in some non-immune cells [51]. Actors of plasticity in tissue reconstruction are diverse, from immune to non-immune cells. In what follows, we describe the main cellular actors in the repair process, with a particular emphasis on how they illustrate the phenomenon of plasticity. We show that this plasticity is central to the functioning of the TRS.

Far from being “one-shot” weapons, long-living neutrophils – which are central players in tissue reconstruction – are remarkably plastic. Indeed, neutrophils can differentially switch phenotypes, and display distinct subpopulations under different microenvironments [52]. At the inflammatory stage of the repair process, neutrophils can play either a pro-resolving or an anti-resolving role. In addition to this intra-lineage plasticity, repair-associated neutrophils are capable of trans-lineage plasticity (plasticity by transdifferentiation) [53–56].

Type 1 macrophages (M1) drive the early inflammatory responses that lead to tissue destruction, whereas type 2 macrophages (“M2” or “alternatively activated reparative macrophages”) exert a central role in wound healing [57–62]. Generation of a pro-type 2 microenvironment gradually leads to the switch from inflammatory to pro-repair

macrophages. These cells promote tissue repair by producing pro-reparative cytokines and participate in a pro-type 2 microenvironment. A wide range of macrophage subtypes exists [50,58,63,64]. Efficient tissue repair requires inflammatory macrophages, tissue repair macrophages, and resolving macrophages (producers of resolvins, IL-10 and TGF-b) [50,60,65]. Beyond intra-lineage plasticity, macrophages might participate actively in the tissue-remodeling phase of repair process by transdifferentiation into other cell types, notably endothelial cells [66].

Innate Lymphoid Cells (ILCs) are a recently discovered family of immune cells that includes three subsets: ILC1, ILC2 and ILC3 [67–69]. ILC2-secreted amphiregulin, a protein shown to orchestrate tissue repair [70], promotes wound healing by acting directly on fibroblasts, leading to ECM deposit. ILC responses to different stimuli allow intra-lineage plasticity between the different subsets [71,72]. This plasticity between different ILC subtypes might allow for rapid innate immune responsiveness in repair [73,74].

Overall, cell plasticity is a pivotal process by which tissue reconstruction is achieved. This is confirmed by the fact that, as detailed below, inappropriate realizations of cellular plasticity (excess or insufficiency) may lead to various disorders.

2.2. Functional redundancy in the TRS

Functional redundancy is another important feature of the TRS. Functional redundancy describes a situation in which different elements have similar functions or similar effects on a trait [4]. Though some forms of functional redundancy occur in every organism as part of normal functioning, this phenomenon has often been observed in pathological contexts, where it appears that an organism deficient in one cell type can “compensate” this

deficiency thanks to other cell types or other molecules or pathways [75]. The TRS often displays “degeneracy”, which refers to the existence of structurally diverse but functionally similar components [75]. Overall, the TRS is characterized by a high level of redundancy, even though some components and pathways seem to be pivotal in the reconstruction process.

ILCs have potent immunological functions in experimental conditions, but their contributions to immunity in natural conditions are unclear. It has been shown that SCID patients with IL2RG and JAK3 mutations and ILC-deficient had no particular susceptibility to disease [42]. Thus, ILCs appear to be dispensable in humans who have a functional adaptive immune system, at least in the context of modern medicine and hygiene conditions [42,76].

Functional redundancy allows the evocation of an overall type 1 or 2 immune response rather than talking more restrictively about type 1 or 2 neutrophils/macrophages/T cells. Those cells often produce the same types of molecules (albeit sometimes with different temporal patterns). This redundancy is not only important to maintain robustness against perturbations; it also creates feedback loops (and thereby a virtuous or vicious circle, depending on the situation), participating in the establishment of a local microenvironment that displays particular features.

Besides immunological redundancy, immune cells participate in the secretion of structural molecules such as matrix metalloproteinases (MMP) altogether with fibroblasts, pericytes, and endothelial cells. The relative importance of macrophage and other immune cell contribution to tissue reconstruction compared to the aforementioned structural cells might depend on the nature of the tissue and the injury.

2.3. Constant surveillance

Tissue reconstruction is an active process where some actors are on constant standby. It is of major importance at the level of DNA repair, as DNA lesions occurring during reprogramming are monitored by a surveillance mechanism called the zygotic checkpoint [77]. At the tissue level, some cells, including various types of immune cells [78], are highly specialized in the surveillance of damages. Of crucial importance are tissue-resident sentinel cells, as they are present and on standby before any damages.

ILCs are found preferentially on epithelial barrier surfaces such as the skin, lungs, and gut, where they protect against infection and maintain the integrity of the barriers. ILCs are tissue-resident sentinels enriched at mucosal surfaces. They exert a constant surveillance on epithelia, and have a complex crosstalk with their microenvironment. They are highly involved in tissue repair through their sentinel position and the cytokines they produce [79,80].

Different tissues often have their preferential sentinels, such as NK cells in the liver, or Langerhans cells in the skin. Cells of the innate but also adaptive immune system are involved in this surveillance. In particular, tissue resident memory T cells (T_{RM}) – which reside in tissues without recirculating through the blood or lymph, and constitute a transcriptionally and phenotypically unique T cell lineage – have been shown to be key guardians against viral infections [81].

Cells traditionally seen as non-immune such as epithelial cells (ECs) play an important role in this collaborative surveillance process. They line body surface tissues and provide a physicochemical barrier to the external environment. This barrier is not a mere passive mechanical protection. Frequent microbial and non-microbial challenges cause activation of ECs, with release of cytokines and chemokines as well as alterations in the expression of cell-

surface ligands. Epithelial stress is rapidly sensed by tissue-resident immune cells, which can directly interact with self-moieties on ECs and initiate both local and systemic immune responses. ECs are thus key drivers of immune surveillance at body surface tissues [82].

2.4. Restraint of the TRS

Detecting and responding to damages is so central for the organism's survival that the TRS is always on alert, ready to be triggered. But at the same time this system also constitutes a potential threat for the organism (inflammation, tissue formation, and tissue remodeling can all go awry, with potentially dramatic consequences), and must therefore be constantly kept under control. Numerous cells restrain the TRS through negative feedback, active production of pro-resolving molecules, and other dynamic mechanisms. These cells are important at all stages but they are particularly crucial for the pro-resolving phase after inflammation.

Pro-resolving neutrophils demonstrate the ability to: (i) produce several pro-resolving mediators (as lipoxins), (ii) form NETs and aggregated NETs, according to a cell-density dependent sensing mechanism, which dismantles the pro-inflammatory gradient by degrading the inflammatory cytokines and chemokines, (iii) store and release the pro-resolving protein annexin A1 [83].

Inflammation resolution is partly mediated by the clearance of apoptotic neutrophils by macrophages through efferocytosis [84]. Non-apoptotic neutrophils can leave the injury site by reverse transmigration. Recently described resolving macrophages (producers of resolvins, IL-10 and TGF-b) are important actors of repair regulation.

In mice, some regulatory T cells (Tregs) are able to produce amphiregulin, favoring the resolving phase of the inflammation process [85]. Depletion of muscle Tregs has

profound impact on muscle regeneration with loss of regenerative fibers, collagen deposition and fibrosis, leading to a disorganized tissue structure. In the absence of Tregs, effector T cell infiltrate increases in the injured muscle and the switch from inflammatory to anti-inflammatory macrophage diminishes.

2.5. Dynamic adjustment of the TRS

TRS is a highly dynamic process implying a large recruitment of various cells, with movements in a tri-dimensional matrix, and with many back and forth between different steps that are not fixed and can often overlap. The dynamic character of the TRS is visible at the level of the recruited cells, but also of the resident cells.

Standby periods are not to be considered totally at rest. Resident cells are never completely motionless. Moreover, cells are constantly replaced in a dynamic process. Tissues are continuously exposed to potentially hazardous environmental challenges in the form of inert material and microbes. In the epidermis, for example, Langerhans cells (LC) form a dense network of cells capable of capturing antigens and migrating to the lymph node after crossing the basement membrane into the dermis, and they are able to promote tolerance or immune responses [86]. Velocity of migration is partly regulated by the microenvironment, and skin Tregs display a much slower migration compared to effector CD4+ T cells, although acute inflammation results in a rapid increase in their motility [87].

Gradients of chemokines largely participate in cell recruitment when damages occur. CD14+ monocytes and neutrophils are very mobile cells, highly and promptly recruited in case of injury [88]. The recruitment of neutrophils during the inflammatory phase is linked to a sharply regulated communication system based on the CXC chemokine/CXC receptors

balance [89]. The injury triggers the production of G-CSF that converts the CXCR4 dominant signaling to that of CXCR2 in the bone marrow microenvironment, leading to the release of more mature neutrophils into the peripheral blood stream [90]. Functional aberrancy in these systems leads to impaired wound healing [91]. In a collaborative pathway, the release of chemoattractant factors by neutrophils, such as lactoferrin, attracts monocytes and activates macrophages [92]. A counterpart to recruitment is obviously needed to ensure robustness of a tissue, or else an overabundance of cells could lead to tissue destruction. Efferocytocis, transmigration, and specific apoptosis allow recruited cells to be cleaned up after damages.

As the rest of the paper will show, two kinds of consequences follow from this analysis of the five key features of the TRS. First, it offers an important basis to re-think some tissue reconstruction-associated pathologies as dysfunctions of robustness. Second, it offers a test case to assess the usefulness of the notion of robustness in physiological and pathological conditions, and leads to distinguishing different forms of robustness.

3. Dysfunctions of the tissue reconstruction system

It has been suggested by Kitano and others that the concept of robustness can shed light on certain pathological processes [2]. Pathologies could result from robustness as a dysfunction (the process under consideration is robust, but this robustness is detrimental to the organism, as happens for example in AIDS or some cancers, where the robustness of a system is “hijacked” [2,93,94]) or a dysfunctional robustness, which is to say a rupture of

robustness (i.e., the process should be robust, but is not). This approach applies very well to the dysfunctions of the TRS.

Mechanisms that mediate tissue reconstruction to ensure robustness are constantly challenged. These mechanisms are sometimes overwhelmed, leading to various consequences depending on the situation, from the rupture of robustness to the promotion of the disease thanks to robustness-associated mechanisms, and to an excess of robustness. The final consequence of each situation is a pathological process. Through concrete examples (ulcers, fibrosis, and cancers), we will illustrate these different threats to the TRS to ensure robustness, emphasizing in each case exactly which mechanisms are challenged (see **Table 1**, which present several additional examples).

3.1. Ulcers, or rupture of robustness

Pathological situations of insufficient repair such as ulcers underlie that the TRS mechanisms ensuring robustness are overwhelmed. Since the robustness of the tissue can be jeopardized, it is important to analyze the various components listed earlier. The value of a more detailed analysis of component robustness is dual. This makes it possible to precisely identify vulnerabilities, which vary depending on the clinical situation, but also to work out innovative therapeutic strategies. As we saw, cell plasticity is a crucial dimension of the TRS and it is especially true for neutrophils. This is confirmed by the fact that incapacity of neutrophils to switch plastically from one state to the other can contribute to ulcers, e.g., skin or gastric ulcers. Impossibility of tuning the response toward a pro-resolving phase by experimentally blocking neutrophils in a pro-inflammatory state directly leads to chronic inflammation and deregulation of the TRS [95], while the reintroduction of very plastic cells

in damaged tissues can overcome this defect. Understanding that in this case the ulcer is a rupture of the robustness due to insufficient cellular plasticity allows to consider completely new therapeutic options. Several studies in animal models showed that adipose tissue-derived stem cell sheet application to mucosal or skin wounds accelerates wound healing and decreases the degree of fibrosis [96,97].

While inflammation has to be regulated to ensure the completion of the TRS, a failure in that process can lead to a rupture of robustness. A deficiency of efferocytosis has been identified as a causative agent of sterile chronic granulomatous disease in mice [98]. In chronic ulcers, favoring the resolving phase (e.g., through efferocytosis, pro-Treg therapeutics, or resolving compounds) could be an innovative strategy [99–101]. Even though defects of inflammatory regulation are clearly involved in the deregulation of the TRS, therapeutic avenues to counteract these defects are still in their infancy, and mostly limited to animal models. A better understanding of the crucial place of that mechanism in the global robustness of the TRS will tend to raise the interest for therapeutics targeting regulation.

In ulcers, the loss of epithelial cells disturbs the ongoing surveillance of the TRS. In the eye, the inflammation of the cornea leads to damages of this protective barrier. Given that the cornea is an avascular tissue and contains few immune cells, corneal resident cells function as sentinel cells as well as immune modulators during corneal inflammation. They are able to sense bacterial infection through toll like receptor (TLR)-mediated detection. As a consequence, a loss of substance (i.e., a very significant injury) could lead to the disappearance of key first-line sentinel cells, normally responsible for the recruitment of other crucial cells in the repair process [102,103]. Other resident cells are involved in this

mechanism (see **Table 1**). Targeting sentinels could constitute a new therapeutic avenue in the treatment of chronic ulcers.

Finally, due to the reduction of the dynamic flow to the damage site, new cells cannot come from the upstream and revitalize the system in an ulcer. Promoting the migration and proliferation of cells could accelerate wound healing [104,105].

Each of the five components of robustness can be compromised depending on the type of ulcer. For clinicians, thinking according to our classification and identifying which mechanism is deficient can therefore change very concretely their therapeutic management.

3.2. Fibrosis or excess of robustness

Keloid and hypertrophic scars can also be seen as the result of a dysfunction in the fundamental mechanisms of the TRS. One could consider fibrosis as a kind of hypertophic scar, and as such fibrosis could follow from a deregulated TRS as well. In a normal repair cycle, the resolution of damage-induced inflammation allows the system to rebuild itself efficiently. In contrast, the absence of resolution means the persistence of inflammation and also, especially in fibrosis, a disconnection between the levels of resolution and remodeling.

An excess of plasticity can also be pathological. For example, epithelial-mesenchymal transition (EMT) reflects a high level of cell plasticity essential during embryogenesis and wound healing, but EMT can be aberrantly regulated in fibrosis [106,107]. Cell plasticity could also be a hurdle for achieving some cell therapy. A pro-fibrotic microenvironment results in systematic M2 polarization even if macrophages of another type are injected. In contrast, the infusion of stabilized pro-resolving macrophages is associated with reduced

kidney interstitial fibrosis and inflammation, as well as preservation of the phenotype and functions of macrophages [108]. Thus, a precise knowledge of the proper physiopathology of the studied condition is crucial to understanding whether a higher or a lower plasticity is needed.

The cause of fibrosis is sometimes attributed to the persistence of damage triggers such as chronic infection. Nevertheless, in hepatitis C, it is the inadequacy of the TRS response rather than the persistence of the infection that is at stake [109]. Tregs or pro-resolving cells have also been suspected to be involved in more general fibrotic processes, such as systemic sclerosis (SSc) [110,111]. From this point of view, promoting the resolution of inflammation could be considered as a key aim to reverse fibrosis [112,113].

A constant monitoring is an essential element of the TRS responsiveness. The fact that it is provided by resident cells guarantees this prompt response when damages occur. However, in some cases, including fibrosis, this surveillance can be over-stimulated and associated with an overly sustained response. As described before, innate immune signaling via TLRs is a key driver of persistent fibrotic response. Chronic signaling on resident mesenchymal cells underlies the switch from a self-limited repair response to non-resolving pathological fibrosis characteristic of systemic sclerosis. Limiting the responsiveness of resident cells to innate stimulation could be of interest to prevent fibrotic processes [111]. Resident cells themselves can also be responsible for the excessive stimulation without any clear external trigger [114–116].

A static TRS cannot result in normal repair. Indeed, different but more or less intricate phases must follow one another. Nonetheless, an excess of migration of pro-fibrotic cells into the tissue can be detrimental in a normal repair process. This happens, for example, in the lungs with fibrocytes. These cells enter the lungs in response to their

chemoattractant CXCL12, and differentiate into fibroblasts or myofibroblasts, leading to excessive deposition of collagen-rich extracellular matrix. It has been shown that inhibiting the flow of fibrocytes to the lungs by a peptide called R1R2 attenuates pulmonary fibrosis by reducing the invasion of fibrocytes through basement membrane-like proteins [117].

3.3. Cancer or hijacking of robustness

Cancerous tumors have been related to deregulated repair by Dvorak, who describes them as “wounds that do not heal” [118]. It is now well established that an inflammatory microenvironment promotes cancer [119]. It has also been suggested that the formation and maintenance of a cancerous tumor could be seen as a robust process [120]. Here we consider cancer as evolving from a damaged tissue, where the TRS could act to prevent the expansion of the injury and promote repair. The cancerous tumor, to drive its own development, hijacks some properties of the TRS that normally ensure robustness in physiological conditions.

Epithelial-mesenchymal transition (EMT) is an important process in embryonic development, fibrosis, but also in cancer metastasis. The activation of EMT in cancer allows cells to acquire migratory, invasive, and stem-like properties. SCAI is characterized as a tumor suppressor inhibiting metastasis in different human cancer cells, and which is thought to be reduced in some tumors. SCAI expression decreases in a model of endothelial-mesenchymal transition, which suggests that it could be important for cell plasticity. Nevertheless, its role in cancer remains to be further investigated, as its expression could be associated with high or low progression of the tumor depending on the type of cancer [107]. Macrophage polarization could influence immune checkpoint therapy resistance. The

plasticity of macrophages is used by cancerous tumors, and targeting this plasticity could be of interest to increase the response to immunotherapy such as ipilimumab [121].

Redundancy may explain cancer resistance to certain treatments. Recently developed immunotherapies do not target the tumor cells as such; instead, they promote the local immune responses in the tumor microenvironment, which has some important consequences on key immunological actors of the TRS. Redundancy of the TRS becomes central in these conditions [122]. For example, IL-6 belongs to a family of cytokines with highly redundant functions, which use the glycoprotein 130 chain for signal transduction. It has an important role in the pathophysiology of multiple myeloma, where it supports the growth and survival of the malignant plasma cells in the bone marrow. Because of this redundancy, targeting IL-6 is highly difficult. Antibodies against glycoprotein 130 constitute a better option, as they can overcome this redundancy [123].

Insofar as cancer may be seen as both a cause and consequence of tissue damages, cancer cells could activate the TRS. In particular, cancerous tumors can use the above described restrain mechanisms of the TRS to induce a type of immune tolerance that will be at their own advantage. Tumor associated macrophages (TAMs) are one of the main actors of this phenomenon. Different therapeutic strategies have been proposed to address this problem, such as the suppression of TAM recruitment, their depletion, the switch of M2 TAMs into antitumor M1 macrophages, and the inhibition of TAM-associated molecules [124].

Immune surveillance could be considered as insufficient in cancer. The TRS lets cancer cells grow and develop as if it were incapable of “seeing” them. Resident memory CD8+T cells (TRMs) represent a recently described subset of long-lived memory T cells that remain in the tissues, do not recirculate, and are therefore very important actors in

immunosurveillance. It has been shown that TRMs were present in human non-small cell lung tumor tissues, and their frequency was correlated with better overall survival than other infiltrating immune cells. In that case, the cancer misleads the immunosurveillance system, which suggests that strategies increasing the number of TRMs or activating them such as vaccines could be developed following this concept [125].

Prior to metastatic cell arrival, a premetastatic niche in distant organs could be an important step in the metastatic cascade. This phenomenon suggesting highly dynamic process from cancer cells could be preceded by neutrophil migration and recruitment. As such the dynamic property of the TRS is used to prepare the basis for tumor cell engraftment in parenchyma [126].

Overall, the concept of robustness helps better understand TRS-associated pathologies, either as a deficiency in the fundamental processes by which robustness is normally realized (plasticity, etc.), or as an emerging, local form of robustness that is detrimental to the organism.

4. Conclusion: the virtues of thinking about tissue reconstruction in terms of robustness

In light of the various physiological and pathological examples examined in this paper, we propose that it is extremely fruitful to conceive of the tissue reconstruction system in terms of robustness, for three main reasons.

First, the recognition by Kitano and others [2] of different robustness-promoting mechanisms (system control, alternative mechanisms, modularity, decoupling) constitutes a

useful conceptual framework to better describe the TRS and its dysfunctions in pathological situations. For example, plasticity and redundancy of immune components within the TRS have been described by scientists who were supportive of the concept of robustness [47,58], and it seems likely that continuing to apply this concept will reveal even more plasticity and redundancy. Moreover, thinking in terms of robustness helps understanding that even a situation that could seem static, such as skin renewal for example, is in fact the outcome of a highly dynamic, continuously ongoing, process, and that it is pivotal to study in detail the mechanisms ensuring this process. It also suggests that the "default state" of the TRS is to be on alert, which means that tissue reconstruction is always active, though under constant restraint. As soon as the brake is lifted, the whole process of tissue repair (i.e., inflammation, tissue formation, and tissue remodeling) is triggered, which guarantees a higher capacity to react to various and often inevitable damages. Of course, this constant activation is energetically costly, but one should keep in mind that it is a low-level activation, and that it is probably essential for survival.

From a pathological point of view, the emphasis on the redundancy of the TRS, for example, is of the utmost importance. It shows that it is often entirely inadequate to hope for important benefits by intervening on just one actor or pathway. Indeed, in many cases, although some cells or pathways seemed crucial in a pathological process *in vitro*, their inhibition *in vivo* does not lead systematically to the pathological phenotype, because of the redundancy of some components and pathways. In other words, some pathological conditions reveal the role of certain cells or pathways, which are not normally indispensable, but become central when other components are missing. For example, alarmins IL-25, IL-33, and TSLP have a high level of redundancy, which makes anti-fibrotic treatments very difficult to develop. Blocking a single pathway is most often ineffective, so it is more promising to

consider modulation of the response at a very early stage, or to identify common pathways that could be targeted. Moreover, acting on one of the mechanisms of robustness while others play a more significant role is not effective in achieving repair. This is probably what happens when one treats fibrosis with immunosuppressive therapy in cases where restoring cellular plasticity would in fact be more adequate. As a general rule, then, one should never draw hasty conclusions about whether or not some actors have an important role in the TRS before having tested them in real-life pathological conditions.

Second, the example of the TRS can, in turn, help us make some crucial conceptual distinctions about robustness. On the basis of the examples explored here, one can indeed distinguish functional vs. structural robustness, partial vs. complete robustness, and corrective vs. preventive robustness (**Figure 2**). Functional robustness in the case of the TRS means that tissue function (or, at least, one tissue function) is restored, but not tissue structure. For example, after significant skin injury, a scar will form, which will restore the protective function of the skin, but the initial structure of the skin will not be restored. In contrast, regeneration often leads to the restoration of both the structure and the function of the tissue. For example, adult zebrafish fins, including their complex skeleton, regenerate exactly to their original form within two weeks after an amputation. Importantly, some forms of complete tissue regeneration can also be observed in mammalian embryos, but this capacity is subsequently lost for most tissues (the most significant exception in humans is the liver, which can indeed regenerate, though it does not always recover its initial structure). Along similar lines, it is important to emphasize that robustness to a given challenge and at a certain level can be more or less effective. Robustness is partial when tissue function and/or structure is not completely restored, as illustrated by most cases of tissue repair in mammals, for example. Robustness is said to be complete when tissue

function and/or structure is entirely restored, as illustrated by cases such as fin regeneration in zebrafish already mentioned, limb regeneration in many amphibians [127], or tissue regeneration in many echinoderms [128]. Furthermore, robustness can be corrective or preventive. It is corrective when it consists in the active restoration of a strongly disturbed state. For example, tissue repair or regeneration after significant damages is a form of corrective robustness, because it follows a major perturbation (damages), and it involves, as we saw, a complex, dynamic, and regulated interplay of many different components. In contrast, robustness is preventive when it occurs in the absence of a major perturbation while minimizing the risk of a major perturbation and its detrimental consequence. For example, epithelial repair occurs continuously in the body, which requires an extremely rich orchestration of events [129]. This preventive robustness helps insure that the skin is always sufficiently "sealed off" and at the same time sufficiently smooth to achieve its functions. When this process is interrupted, for example in ulcers, the organism is at a high risk of being damaged and invaded by pathogens or toxic substances. Of course, there will be a grey zone here, because it is not always clear whether a perturbation is major or not, and different tissues are likely to perceive perturbations differently. For example, the liver is constantly exposed to toxic chemicals that could endanger the rest of the body, and its regenerative capacities are certainly evolutionarily related to this particular exposition [30]. **Figure 2** sumps up the three distinctions proposed here (structural vs. functional; partial vs. complete; corrective vs. preventive. It is likely that these distinctions could be useful in other biological and engineering contexts, beyond the example of tissue repair and regeneration examined in the present paper.

An additional distinction seems important to better grasp the role of robustness in pathological contexts. Dysfunctions in robustness of the TRS can indeed be understood along

two different lines. In some cases, the tissue fails to be robust, presumably because one or several important components or pathways of the TRS are not working properly. This is what we call a dysfunction of robustness. For example, we saw that the incapacity to realize cell plasticity can sometimes lead to the failure of tissue reconstruction. Yet, in other cases, the tissue is robust, but this robustness is, in this specific context, detrimental to the organism. This is what we call robustness as a dysfunction. For example, a tumor can constitute a robust tissue, which is well vascularized, nourished, and constantly repaired, often via the co-optation of classical physiological mechanisms to the benefit of the tumor itself. Here again, this distinction between a dysfunction of robustness and dysfunctional robustness might prove useful in other contexts, beyond the case of the TRS.

A third and final consequence concerns the very understanding of immunity. Since the beginnings of immunology, immunity has been conceived primarily as a form of defense – most often against pathogens. Yet, if the perspective offered in this paper is correct, then immunity needs to be re-defined within a much wider context. Immune processes, we submit, concern not only defense, but also the construction (development) and reconstruction (constant repair; occasional repair after a significant damage; regeneration) of the organism,. Indeed, a typical immune system in nature is constantly busy surveying, renewing, and repairing the body,. This is not to say, obviously, that immune defense is not important, and has not been a major selective pressure in the evolution of immune systems. Our suggestion is that immune systems have evolved under a multidimensional complex selective pressure, which includes a capacity to develop and repair as well as a capacity to defend against different sorts of threats. The way scientists traditionally delineate the immune system reflects an intellectual decision. This does not mean, of course, that the immune system is not “real”, but rather that there exist many different ways to divide up

living entities into different “systems”. In the present paper, we have argued in favor of another intellectual decision by suggesting that it is more appropriate to focus on a functionally defined “system” of interest (namely the tissue reconstruction system) than on traditionally defined systems (such as the immune system). Repair and defense are probably just two sides of the same coin – a lesson that thinking immunity in terms of robustness might help us keep in mind.

Figures and Tables

TRS robustness	Dysfunctions in TRS robustness		
	Ulcer (rupture of TRS robustness)	Fibrosis (excess of TRS robustness)	Cancer (hijacking of TRS robustness)
Plasticity	- Adipose tissue-derived stem cells accelerate wound healing [96,97] - N1 polarization by *H. pylori* in gastric ulcers [95]	EMT and SCAI in renal fibrosis [107]	- MET/EMT with the tumor-initiating ability required for metastatic colonization [130] - Plasticity between the epithelial and the mesenchymal states rather than a fixed phenotype [131] - UPR in macrophage polarization and plasticity with shift to M1-like profile [121]
Functional redundancy	ILC redundancy [42]	- IL-25, IL-33, and TSLP redundancy and fibrosis [132,133] - Targeting porcupine in kidney fibrosis and Wnt O-acylation [134]	- IL-6 and glycoprotein 130 in the pathophysiology of multiple myeloma [123]
Constant surveillance	- Loss of substance (i.e., a very significant injury) and disappearance of sentinel cells in ulcers [103] - Langerhans cells and hypoxia [135]	- Fibronectin-EDA and tenascin-C sensed by TLR4 on resident cells and fibrotic processes [111] - ILC2s in pulmonary fibrosis [114,115] - CD8+CD28- T cells and profibrotic cytokine IL-13 in the skin of systemic sclerosis (SSc) patients [116]	- TRMs in human non-small cell lung tumor tissue [125] - Role of amphiregulin in orchestrating responses to tumors [136]
Restraint	- Resolution deficiency and sterile chronic granulomatous disease [98–101] - Imbalance Treg/Th17 in pyoderma gangrenosum [137]	- Chronic hepatitis C and hepatic fibrosis with the Th17/Treg balance [109] - Role of TRegs in SSc [110] - SSc and TLRs with persistence of the response [111] - Resolving inflammation against fibrosis and specialized pro-resolving lipid mediators [112] - Macrophages and efferocytosis [113]	- TAMs recruitment in triple negative breast cancer [124] - Tregs in tumor progression [138] - Tregs and cancer cell clearance [139] - Tregs and cancer immunotherapies with IL-2 [140] - To target immune checkpoints such as CTLA4, PD1 or TIGIT to both interfere with Treg function and enhance effector responses at the same time [141]
Dynamic adjustment	- Electrical stimulation and migration [105] - Selective migration and wound healing [104]	Fibrocyte migration to the lungs inhibited by R1R2 attenuates pulmonary fibrosis [117]	- Cancer cells and use of the dynamic potential of neutrophils [126] - CCL26 in colorectal cancer cells invasion by inducing TAM infiltration [142] - Inhibitors of the receptor tyrosine kinase c-MET and impairment of the mobilization and recruitment of neutrophils into tumors [143]

Table 1. Main mechanisms involved in the robustness of the tissue reconstruction system (TRS), and its dysfunctions in major pathological situations (ulcer, fibrosis, and cancer).

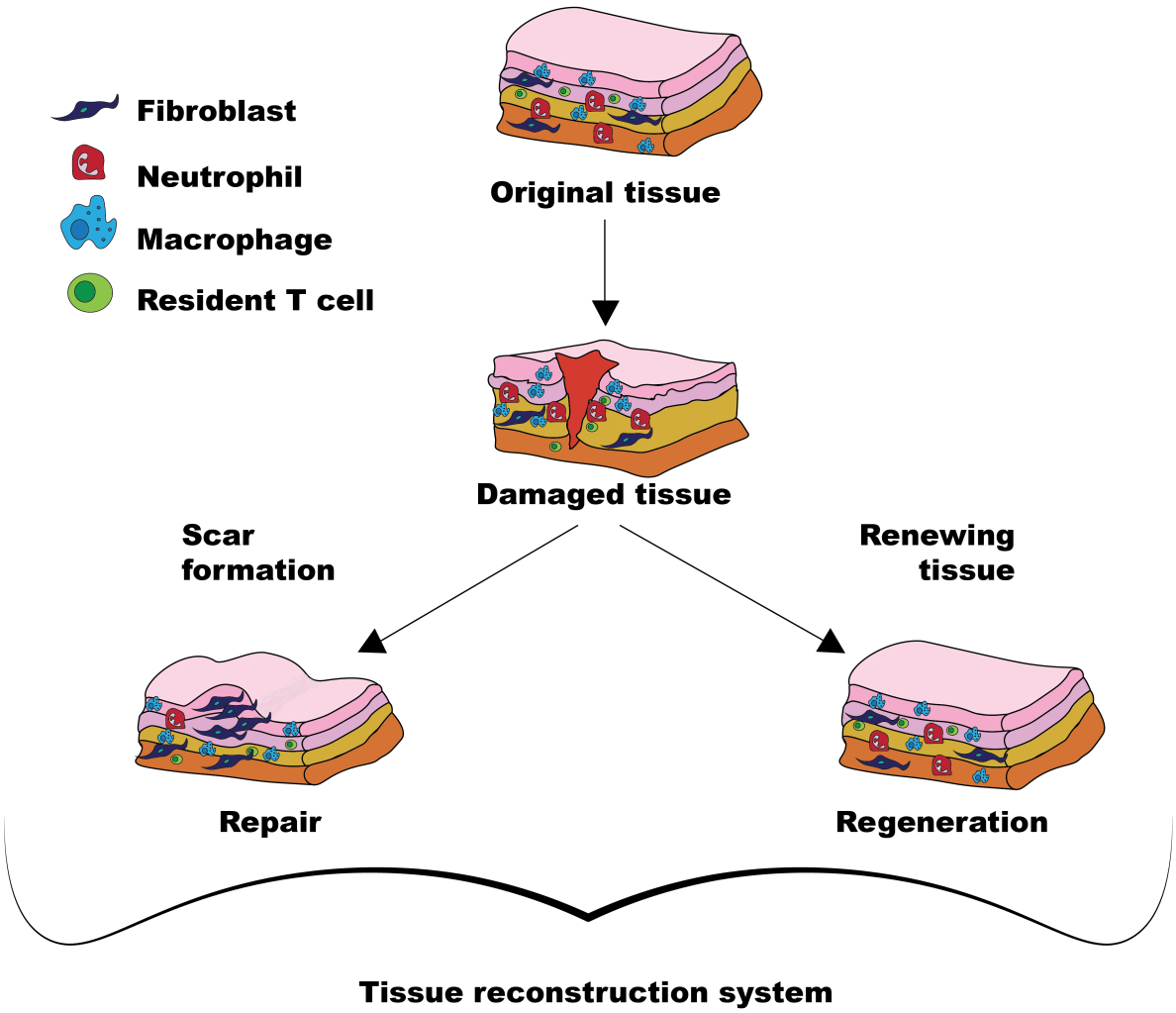

Figure 1. Overview of the "tissue reconstruction system" (TRS). Many various components and pathways are involved in both tissue repair and tissue regeneration. Crucial components of the TRS include structural (e.g., fibroblasts, extracellular matrix, etc.) and immunological (e.g., neutrophils, macrophages, etc.) components. The concept of TRS is intended to embrace all the main entities and mechanisms responsible for tissue repair and tissue regeneration.

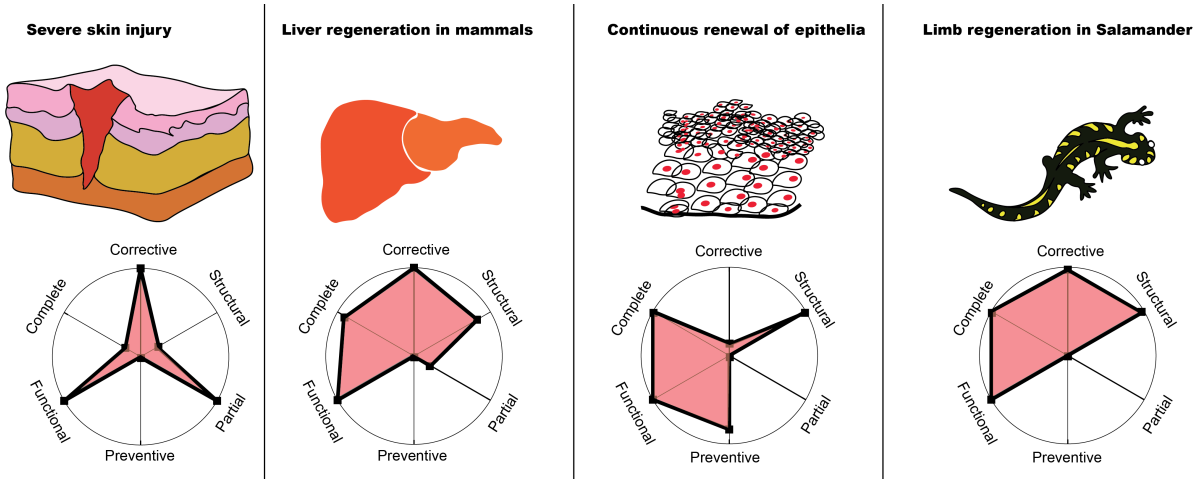

Figure 2. The exploration of the tissue reconstruction system (TRS) leads to distinguishing different types of robustness, namely structural vs. functional robustness, partial vs. complete robustness, and corrective vs. preventive robustness. The four cases presented here are merely illustrations, among others, showing how these distinctions can be applied to real-life cases. In severe skin injury, robustness is corrective, partial, and functional. In liver regeneration in mammals, robustness is corrective, almost complete, and functional. In the continuous renewal of epithelia, robustness is preventive, complete, and functional. Finally, in limb regeneration in salamander, robustness is corrective, complete, and functional.

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