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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.

1. 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 Fig. 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

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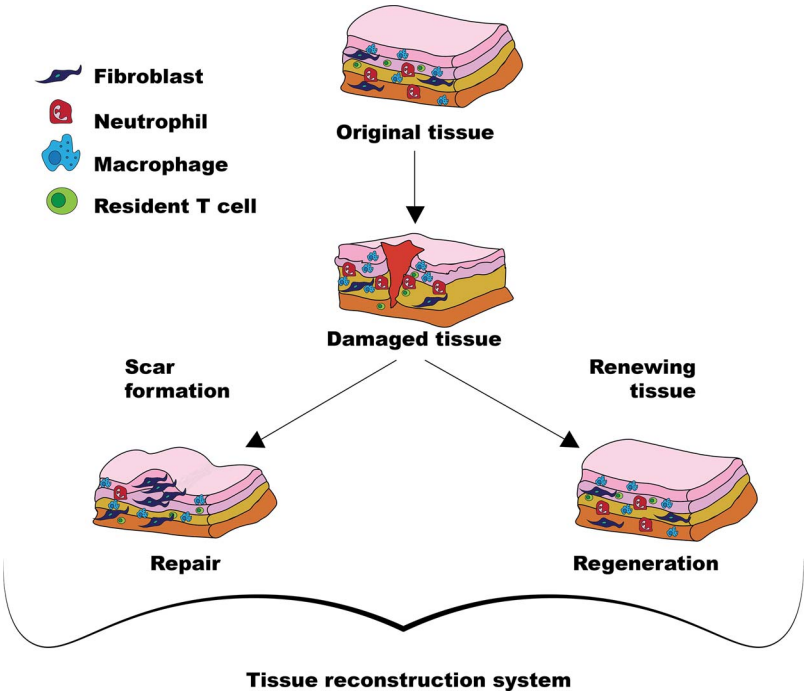

Fig. 1. Overview of the "tissue reconstruction system" (TRS). Many various components and pathways are involved in both tissue repair and tissue regeneration. Crucial components of the TRS include structural (e.g., fibroblasts, extracellular matrix, etc.) and immunological (e.g., neutrophils, macrophages,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

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).

2. 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