A gerophysiology perspective to healthy ageing

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Highlights

- Healthy ageing relies on adequate physiological transverse elements
- Accumulation of defective repair process results in allostatis and frailty
- Stroma/Inflammation and Metabolism directs organ repair and maintenance
- SIM monitoring represents a new avenue to identify predictive biomarkers of decline

Abstract

Improvements in public health and health care have resulted in significant increases in lifespan globally, but also to a significant increase in chronic disease prevalence. This has led to focus on healthy aging bringing a shift from a pathology centered to an intrinsic capacity and function centered view. In parallel, the emerging field of geroscience has promoted the exploration of the biomolecular drivers of ageing towards a transverse vision by proposing an integrated set of molecular hallmarks. In this review, we propose to take a step further in this direction, highlighting a gerophysiological perspective that considers the notion of homeostasis/allostasis to robustness/fragility respectively. While robustness is associated with homeostasis achieved by an optimal structure/function relationship in all organs, successive repair processes occurring after daily injuries and infections result in accumulation of scar healing leading to progressive tissue degeneration, allostasis and frailty. Considering biological aging as the accumulation of scarring at the level of the whole organism emphasizes three body transverse and shared key elements– mesenchymal stroma cells/immunity/metabolism i.e. SIM and play down parenchyma cells. This SIM tryptich drives tissue and organ fate and appears as a shared and common reservoir to regulate the age-related evolution of body functions. It provides the basis of a gerophysiology perspective, possibly representing a better way to decipher healthy ageing, not only by defining a composite biomarker(s) but also by developing new preventive/curative strategies.

Key-words: Healthy aging, homeostasis-allostasis, repair processes, stroma, inflammation, metabolism

Introduction

Progress in medicine and public health has led to a significant increase in life expectancy in almost every country. Unfortunately, there is little evidence that this increase is being accompanied by an equivalent increase in healthy life expectancy. Live longer in good health remains a great advance for both individuals and society, but if these added years are experienced in poor health the benefits are much less clear. Thus, one of the main societal and economic challenges in the twenty-first century is to ensure that increasing lifespan is accompanied by similar or greater increases in health spans (Beard et al., 2016).

In the landmark 2015 *World Report on Ageing and Health*, the World Health Organization outlined a public health framework for action to promote healthy ageing. Rather than focusing on the absence of diseases, the WHO framework was oriented around the functioning of people as they age (Rudnicka et al., 2020). The report proposed a conceptual model that distinguishes between the individual-level and environmental attributes that enable people to build and maintain functional ability. It took a life-course approach, which takes account of the multiple and cumulative changes that accrue with age. The WHO labelled the individual level attributes contributing to healthy ageing as "intrinsic capacity". Subsequent research has suggested this is a measurable construct, which is a powerful predictor of subsequent outcomes (Beard et al., 2016; The Lancet, 2018).

These conceptual advances have been accompanied by other significant advances in our understanding of the complex and dynamic changes that drive human and animal biological ageing. A number of ageing hallmarks have been identified as key drivers of ageing, including the maintenance of DNA integrity, proteostasis and stem cells, as well as intercellular communication (López-Otín et al., 2013). Recent advances within geroscience take this a step further, proposing that ageing biology is the main driver of chronic disease susceptibility and that targeting it will slow the appearance and progression of age-related diseases and disabilities (Kennedy et al., 2014). Bringing these two transformational paradigms together in a holistic framework offers enormous potential in terms of our understanding of the determinants of healthy ageing and possible opportunities for innovative interventions. To allow a fresh understanding of how the complex physiological changes associated with ageing may impact on individual intrinsic capacity, in this review we propose a gerophysiological approach that combines the WHO healthy ageing model with a geroscience view.

Facing the challenge

"Ageing" may be considered as a natural evolutive process resulting from the interactions between internal and external factors occurring throughout life, including some trans-generation elements through the transmissible epigenetic marks on gametes related to the age of the parents (Thuault, 2021; Xie et al., 2018). This inexorably leads to a functional decline of the organism capacities and can, *in time*, result in care dependency - the impossibility for a person to carry out certain activities of daily life on her/his own, in her/his usual environment. This trajectory is not linear and varies greatly between individuals. The occurrence of decline can be accelerated, even transiently, as a consequence of different events, including diseases, infections, injuries and adverse effects associated with the environment, emotional upheavals and health care. Prior to care dependency, individuals may display a period during which they are unable to fully rebound from internal or external stressors – a state known as frailty which can be assessed with grade (Clegg et al., 2013) or clinical index (Dent et al., 2016; Hoogendijk et al., 2019). The functional perspective of research in this area has strongly influenced the evolution of ageing concepts (Rockwood and Mitnitski, 2007) including the WHO "healthy ageing" framework (Beard et al., 2016).

These approaches do not equate healthy ageing with having no pathology, since the presence or absence of disease is only one determinant of functional outcomes. Recent research suggests that intrinsic capacity is a stronger predictor of subsequent deteriorations in health status than the presence or number of morbidities (Beard et al., 2019). Five key sub-domains have been proposed for this construct: locomotor, cognitive, sensory and psychological capacities which correspond to functional capacities that requires the healthy functioning of several organs and tissues. as well as an underlying domain of "vitality" which is a transverse domain that feeds all other sub-domains and participates to individual adaptation (Fig. 1). Functional domain covers different physiological functions thus, locomotion for example, encompasses the skeletal muscle physiology as well as the cardiovascular one, energy homeostasis, osteo-articular and neurophysiology. Each functional domain can be individually assessed using simple and standardized tests. The physiological reserves have to be drawn on in response to a stimulus and this ability to adapt has been termed "resilience" (Kirkland et al., 2016), a generic term used to describe the system response when faced with a challenge. "Functional reserves" define the maximal ability to adequately achieve this response at any given time point (Fig. 2a). These differ, even at an identical chronological age, in a variable way depending on

each individual's life experiences. As long as these functional reserves and their mobilization surpass the adaptive ability necessary to manage the intensity of stimuli, the organism, defined as robust, maintains proper function and avoids declining as a result of the challenge. However, when the adaptive ability conferred by the individual functional reserves is surpassed by the challenges encountered, it results in a progressive impairment of function, which in turn jeopardizes the resilience to future challenges, thus generating a vicious cycle. As soon as this organism enters a zone where it can no longer cope with a daily living stress (depending on nature, duration, yields and iteration), it becomes dependent. However, to date, there has been very limited analysis to guide scientists or physicians on how to practically apply the intrinsic capacity (IC) and reserve concepts so that they can inform the development of effective interventions

This integrative approach requires envisioning the individual as a whole and is far from the current reductive molecular deciphering of biological ageing. The first significant biological discoveries related to biological ageing came from scattered fields: clinical, cell biology, study of the basic mechanisms of life in so-called model organisms such as yeast, *Drosophila melanogaster* or *C. elegans*. Thus, and without this list being exhaustive, the major role of nutrition in mammals, the insulin-like growth (IGF) signalling pathway, and the mechanisms of senescence during cell culture or in vivo for the immune system have been highlighted in biological ageing (Campisi et al., 2019; Desdín-Micó et al., 2020). More recently, a list of ageing hallmarks linked to life expectancy has been proposed as a way of bringing coherence to this diverse body of research. These include genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, chronic inflammation and altered intercellular communication (Kirkwood and Austad, 2000; López-Otín et al., 2013). These hallmarks have been identified from investigations mostly conducted on organ-specific – parenchymal - cells in the frame of organ-related pathologies and for their effects on life span without considering the quality of life (López-Otín et al., 2013). They mainly concern molecular and cell scales without integrated and physiological vision at the level of the whole organism. This also suggests that ageing must be conceived as a sum of major breakdowns at the cellular level. It is noteworthy that slight, infra-visible but general deterioration of several scattered elements, may be sufficient to explain the global phenotype. The recent emergence of the "geroscience field" considerably changes the ageing paradigm considering that ageing is the main risk factor of most diseases, including chronic ones.

Thus, geroscience claims that age-related molecular and cell mechanisms are involved in chronic diseases and ageing decline itself (Kennedy et al., 2014; Sierra and Kohanski, 2017).
However, while comprising the first transverse analysis, the geroscience perspective is not fully aligned with the healthy ageing perspective since it maintains a pathologies-centered vision, particularly regarding chronic diseases and corresponds to a molecular rather than integrative vision (Seals et al., 2016).

A gerophysiology perspective of healthy ageing

The intrinsic capacity (IC) paradigm parallels perfectly the physiological perspective and homeostasis paradigm, as proposed by Claude Bernard in the late 19th century as a way of understanding the functioning of the whole organism (Seals et al., 2016). Homeostasis was defined as the maintenance of a dynamic steady state (set-point) of the vital parameters of the internal environment whatever the environment was. This confers a strong survival advantage for the organism. More recently, the concept of homeostasis has been challenged and the term of allostasis proposed with a main focus on the capability to manage any stress (McEWEN, 1998; Sterling, 2012) (Fig. 3). Allostasis concepts revisit the definition of the "classic" homeostasis set point that is not understood as a fixed parameter but as a changing variable, the value of which results from lifelong development. In two excellent reviews, Ramsay and Woods proposed a compromise for which a revisited homeostasis and allostasis refer to physiological and physio-pathological situations respectively (Ramsay and Woods, 2014; Ramsay and Woods, 2016). Homeostasis sustaining set points are robust and can be achieved under many stimuli and then define the maximal adaptive ability, depending on either i) the tolerance scale of set-point values, or ii) the efficiency of the system to reset to a set-point value compatible with life (Fig. 2b). A set-point value will evolve according to either a change in the intrinsic properties of a tissue structure or function (the elasticity of an organ for instance) or a chronic stimulus, even moderate (chronic hyperglycemia for instance), which will tend to maintain the value of the set point at a new range. In this context, it will induce an adaptive shaping, integrating the changes occurred when facing a challenge in order to stabilize the set-point. Iterative chronic stressors will induce recurrent new critical set-points and a drift to a progressive locking and loss of adaptive ability and the emergence of diseases. This drift would be the consequence of growing “allostatic load” defined as the stress-induced wear and tear on the body that includes the loss over time of the ability to return to the initial

state (McEWEN and Seeman, 1999). Also, if the allostatic load (AL) is higher, the organism is less able to correctly handle a stress or chronic disease when it occurs. It is noteworthy that this progressive drift may be at an infra-clinic level and not detectable by a physician, leading to a silent chronicity for a long time. Furthermore, the correction of the set-point requires the system to reset and drive a re-learning of corrected mechanisms.

If the focus on molecular mechanisms of parenchymal cells is suitable to tackle the issue of diseases and lifespan, systemic physiology clearly appears as the best level (Seals et al., 2016) to address the issue of healthy ageing through the WHO prism. From a gerophysiology perspective, physiological ageing is different from biological ageing and can be understood as the body-wide consequences of AL. This “physiological” reservoir is variable and specific for each individual according to "physiological" (pregnancy, intermittent fasting, day-night rhythm….) and "non physiological" (injury, diseases, infections, therapeutic adverse effects, …) challenges (Li et al., 2015). The allostatic load concept may thus appear as an addition of loss of reserve and the ability to use them (i.e a decrease in IC) (Fig. 2). The increasing weight of this variable physiological reservoir and tear according to the history of the individual results in an increased prevalence of chronic diseases with chronological age and explains the individual variability (Marengoni et al., 2011). The relationship between ageing and chronic disease is complex (Hodes et al., 2016) and, instead of biological ageing, we propose it is the natural process of "physiological ageing" that leads to chronic diseases, the nature of which would reflect the individual specific reservoir and tear on mechanisms occurring with ageing. Chronic diseases, as vicious deleterious cycles (Franceschi et al., 2018), accelerating unbalanced regulations and thus the reservoir of adaptive mechanisms.

Until now, the analysis of the whole organism physiology was built considering both vital internal parameters and classic physiological systems (such as cardiovascular, digestive, immune, respiratory… systems) in a pathology organ-centered view (Khan et al., 2017). This led most of the investigations to be performed on organ-specific cells (parenchyma), i.e. the cardiomyocytes for pressure regulation, the enterocytes for nutrition etc… (Fig. 3). Unfortunately, this vision does not fit in with the IC paradigm. One of the challenges is therefore to propose an alternative physiological understanding of ageing using the identification of transverse and shared key elements among organs and physiological functions independent of their specificities.

Stroma, inflammation/immunity, energy metabolism: three transverse elements for a healthy ageing perspective

Healthy functions is achieved via the maintenance of adequate and optimized relationships between the tissue architecture and function. This interplay is the result of bidirectional and permanent interactions between two cell compartments, parenchyma and stroma. While the parenchyma compartment, composed of differentiated cells and their corresponding precursor/progenitor/stem cells is specific to the physiological functions assumed by the tissue, the supportive stromal compartment, largely composed of immune and mesenchymal stem/stroma cells (MSC), appears as transversal to the whole organism being the ground and the driver for tissue architecture and repair (Stuart J Forbes and Rosenthal, 2014). Among stroma, MSC represent a key element shared by all organs and tissue (Pittenger et al., 2019). These cells are reticular and interconnected with each other through a network present in any tissue and inter-organ connected by fascia (Benias et al., 2018). They largely condition the architecture of tissue and whole organisms through their multipotency towards osteoblast, chondrocytes and adipocytes, as well as fibroblasts and myofibroblasts that secrete and model the extracellular matrix (ECM) giving rise to the mechanical macrostructure of any tissue. Besides this physical contribution, they also display strong supportive features mediated by their pleiotropic paracrine activity among which the secretion of numerous angiogenic and trophic molecules able to regulate both inflammation and immunity(Uccelli et al., 2008; Wang et al., 2014). Via their multiple effects, they contribute to the generation of micro-environments building the whole tissue ecosystem. It is noteworthy that, according to the close dialogue between parenchyma and stroma, the MSC phenotype also reflects parenchyma behavior. Lastly, the fact that a few (or the transient presence of) grafted MSC seem sufficient to induce long lasting effects, even after their disappearance in tissue regeneration (Trounson and McDonald, 2015), is consistent with their putative role as educator cells monitoring tissue integrity and maintenance.

The second transverse element that can be easily identified is energy metabolism, which provides energy for the maintenance of the architecture and the healthy functioning of any cells and tissue whatever the environmental changes (Chapelot and Charlot, 2019). From a bioenergetics point of view, energy homeostasis is synonymous with redox homeostasis (Santolini et al., 2019). It is noteworthy that a phenotype with unbalanced energy regulation has never been evolutionarily selected, demonstrating the basic importance of energy/redox homeostasis, consistent again with the

energy conservation law. The energy management of any living organism is the absolute priority, even to the detriment of maintaining the physical integrity of this organism. Such priority is clearly illustrated in the context of prolonged starvation, where the energetic homeostasis is maintained at the expense of protein stock used as energy fuel (Kerndt et al., 1982). It should be noted that in this situation, protein melting leading to sarcopenia and decline of mobility function is a physiological adaptive mechanism to maintain energy homeostasis in a context of negative energy balance. Similarly, in the case of a strong energy deficit, it is only when the requirement of energy is provided that the protein stock can be reconstituted. As long as the energy requirement is not met, proteins will be used as energy substrates only. At the level of the organism, energy homeostasis is achieved through the metabolic compartmentalization and specialization among the different organs and the intra- and inter-organs metabolic flexibility (Goodpaster and Sparks, 2017). This metabolic flexibility corresponds to the redundant and compensatory biochemical reactions that ensure a satisfactory level of available free electrons with the minimum of associated deleterious oxidative effects compatible with life. The effects of sustained caloric restriction (CR) in many mammal species associated with an extension of lifespan without chronic diseases can be reanalysed in the light of this view (Colman et al., 2014). From an evolutionary viewpoint, CR leads to adapted metabolism that results in energy economy and fitness with the optimisation of the energetic reactions and the limitation of the potentially harmful "misused" electrons escape (Redman et al., 2018; Weindruch and Sohal, 1997).

Beside the first two elements that structure and provide energy for organ functioning, a third transverse element, the immune/inflammatory system can also be proposed since it is systemic, responding and an actor of repair signalling. Patrolling into the circulating system and present into the stroma, immune cells can apprehend and defend the organism integrity against injuries, including infection in order to maintain healthy architecture/function. Immune cells are transiently recruited and activated in order to manage any transition between ante and post-injury/repaired tissue. The orchestration of many innate and adaptive immune cell subsets conditions post-injury outcomes. These cell subsets, as well as the balance between them, evolve with ageing, a phenomenon called immune-senescence, and largely modify the immune system capacity to operate after challenges (Franceschi et al., 2007; Nikolich-Žugich, 2018). Physiologically, the healthy maintenance of the organ architecture is achieved via fine-tuning regenerative processes, leading to the permanent reconstitution of the cells that naturally or accidently disappear following injuries (infection, tissue

destruction…) (Stuart J. Forbes and Rosenthal, 2014; Vriz, 2018). Tissue injury classically leads to an early pro-inflammatory step, characterized by the activation of local innate cells, the influx of myeloid cells followed by lymphoid leukocytes and the production of pro-inflammatory mediators. The resolution of inflammation recruits fibroblasts and myofibroblasts derived from the mesenchymal progenitors that rapidly replenish the destroyed tissue by the accumulation of ECM composed of fibrillar collagens (Stappenbeck and Miyoshi, 2009). Once closure is achieved, the number of activated fibroblasts decreases significantly by apoptosis, and the initial phenotype is restored (Kalluri, 2016). Whereas regenerative capabilities in inferior vertebrates such as salamander axolotl and zebrafish are remarkable, they are strongly limited in mammals, particularly adult mammals, for the benefit of the scar tissue (McCusker and Gardiner, 2011), which is always detrimental for the adequate relationship between tissue architecture and function. Accelerated wound closure that limits hemorrhage and infection spreading and isolates the area of injury from healthy tissue, represents a major evolutionary selective advantage compared to regeneration that requires more time to achieve. In the case where pro-inflammatory signals are not well and timely balanced by counter anti-inflammatory signals, inflammation is only partly solved and is transformed into chronic low-grade inflammation. This induces the persistence of fibroblasts, ECM accumulation, increase of stiffness and inadequate relationship structure/function associated with a vicious cycle resulting in fibrosis then hypertrophic scars or keloids in caricature situations (Hinz, 2016; Wick et al., 2010).

Ageing allostasic load and ageing as a scar

Strikingly, the features of post-injury tissue invaded by ECM are very similar to the features of aged tissue and organs (Dennison et al., 2017; Navarro and Driscoll, 2017; Nikolich-Žugich, 2018). Indeed, with ageing, tissue degeneration is associated with ECM deposition leading to fibrosis and fatty infiltration, inducing a loss of elasticity, increase of stiffness and disorganization of organ anatomy deleterious for proper functioning. This age dependent infiltration of tissue is associated and concomitant with “inflammaging” - defined as chronic low-grade inflammation that could be due to excessive inflammatory stimulation, but also because of les effective anti-inflammatory responses (Franceschi et al., 2007; Franceschi et al., 2018). Thus, the loss of physiological function with ageing is reminiscent of a post-injury chronic fibrotic wound but at different levels of size (organ *vs.* organism) and time (hours or days *vs.* years) and corresponds to an age-dependent “tissue allostatic load” (Fig.

4). The parallel between repair process and biological ageing highlights the importance of repair and the maintenance processes to maintain healthy functioning. This is consistent with an evolutionary perspective of ageing as previously described (Kirkwood, 2005).This striking analogy leads us to propose that physiological ageing could correspond to the accumulation of scar healing processes over time, following multiple and daily aggressions leading to a progressive and silent accumulation of ECM and its reticulation associated with an increase in stiffness, an architecture de-organization and, ultimately, a decrease in function. During youth, this dysregulation would be masked by the growth of organs. When this slight decrease in loss of function cannot be overcome by tissue growth, individuals enter into slow decline leading to a deleterious vicious cycle in which inefficient repair signal, i.e. inflammation, becomes chronic. With time, this chronic inflammation (inflammaging) generates deleterious effects itself. This kinetic is very similar to those of keloid and hypertrophic scars corresponding to a growing mass of ECM resulting in chronic inflammation (Wang et al., 2020). With this in mind, the chronic post-injury inflammation as well as inflammaging can be considered as an un-adapted resolution of inflammation as well as an inefficient adaptive response that promote deficient regenerative mechanisms as proposed for age-related macular degeneration (Rozing et al., 2020). Furthermore, with ageing, the accumulation of undetectable/infra-clinic elements is sufficient to progressively lead to visible deterioration, but often identified too late and which, to date, is often non-reversible. Thus, as an archetype, post-traumatic tissue repair represents a caricature of the processes of ageing but which, by taking place over a short time, are much more accessible to experimentation. This opens an experimental way to generate new hypotheses to target and/or reposition relevant pathways therapeutically to enhance and modulate repair towards combatting frailty and promoting healthy ageing. The similarity between scar healing and phenotype evolution with ageing highlights the three elements (S for structure, stroma, I for inflammation and immunity, M for metabolism, particularly redox metabolism, i.e. SIM) that are relevant transverse elements for a new understanding of physiological ageing, and of healthy ageing.

The three elements of this SIM tryptich are strongly interrelated. Structural cells as MSC, well-known to display immunoregulatory properties, have been recently demonstrated as an integral part of tissue immunity (Krausgruber et al., 2020). The capability of MSC to differentiate towards adipocyte and to manage energy, is an element of the alternate interaction between S and M components. The initial phase of inflammation, crucial for the outcomes of repair processes and the following steps, are

dependent on redox metabolism (Naviaux, 2019; Vriz, 2018) and the close interaction between I and M components are largely illustrated with the growing field of immunometabolism(Hotamisligil, 2017). More particularly, in a recent review, Franceschi drew a parallel between meta-inflammation occurring with obesity and inflammaging (Franceschi et al., 2018). Taken together, this leads to considering SIM as a whole and as a key entity to monitor healthy ageing (Fig. 5). As SIM represents the reservoir of physiological function in close interaction with parenchymal functioning, monitoring the SIM indirectly takes into account the parenchymal component. Because an infinite number of SIM interactions could result in the same physiological age phenotype and homeo/allostasis maintenance, the adaptive ability or resilience would be the ability of each SIM element not only to adapt to a stimulus, but also to be able to be compensated by at least one of the two others. Thus, the assessment of physiological resilience can be achieved only via simultaneous investigations of the three branches of SIM after challenges ("stress test") leading to the definition of a composite index as the reservoir of physiological function and IC that controls the repair processes and tissue homeo/allostasis. Molecular ageing hallmarks can then be declined in such gerophysiology perspective. According to the pleiotropic effects of MSC on the three branches of SIM, MSCs would be a good candidate to focus our investigations on as one of the best replications of SIM at cell level.

Conclusions

A better understanding of healthy ageing requires the integration of physiological conceptual framework to decipher the underlying biological mechanisms that need to be monitored and corrected to achieve this goal. In order to take into account the functional coherence of the architecture/function interaction rather than the specific functions of each organ, we believe the SIM triptych provides a new relevant reading grid to reach this objective. Furthermore, because the robustness of homeostasis/allostasis is ensured by numerous redundant and compensatory regulations, investigations of a single regulation have limited relevance. The multi-scale and multi-level role of the integrated SIM in the repair and maintenance or failure of an organism over its lifespan, will help to highlight new sensible and reliable biomarkers to detect infra-clinic signatures for decline prediction. Overall, the extension of the original computational approaches previously described (Topol, 2019) to assess metabolic dysfunction in aging, to a longitudinal tracking and multiscale assessment of structure-function elements through a health dashboard of SIM biomarkers can be envisioned by

algorithmic pipelines. A first step would be to build such complex biomarker combining redox, MSC and immune cartographies. Another step will be to focus more on dynamic testing following a challenge such as nutrient/inflammatory stimulus to define more precise and predictive criteria, as a glucose tolerance test can be performed to detect early metabolic dysfunction. Indeed, although difficult to implement, the current explosion of applied mathematical and computer science approaches has completely changed our way of understanding problems and should allow to study these issues in all their complexity (van Beek et al., 2016).

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Conflict of interest. None

Figure legends

Fig. 1: Intrinsic capacity (IC) related sub-domains to address healthy ageing issue

To address and promote the issue of healthy ageing, WHO identified five functional sub-domains maintenance, of which for each individual are crucial for the global Intrinsic Capacity (IC). Each of these sub-domains (cognition, sensory, locomotion, psycho-social, vitality in yellow squares) corresponds to functional capacities that requires the healthy functioning of several organs and tissues. For instance, the functional domain locomotion covers the skeletal muscle physiology as well as the cardiovascular one, energy homeostasis, osteo-articular and neurophysiology. Each functional domain can be individually assessed using simple and standardized tests (grey square). Among these domains, vitality is a transverse one that feeds all other sub-domains and participates to individual adaptation.

Fig. 2: Capacities and functional reserve define physiological age, a gerophysiology perspective.

Part A: *Decline in adaptive capacity progressively leads to dependency***.** Adaptive capacity depends on basal or normal part (green box) but also on reserves that might be mobilized (yellow box) in case of challenges (red arrow). When these reserves are able to face a challenge, the person is defined as robust, and the physiological functions are normal. When they start to decrease or exceed slightly in a more drastic manner, this leads to an alteration in physiological functions and the person can be defined as pre-frail or frail. When there are no more reserves and even the normal capacities are decreased, the person is called dependent and the physiological function can be totally lost. These different states can define the physiological age which is different from the chronological one.

Part B: *Homeo-allostatic ageing.* When an individual is robust and the homeostasis is sustained, it is able to respond adequately to challenges and the set-point for a given variable is rapidly coming back to its initial value. This is due to the fact that this individual can adequately mobilize all these adaptive capacities including reserves. As soon as the set point not only decreases slowly but does not come back to its initial value after being challenged and therefore varies, one falls into allostasis. This is the consequence of decreases of adaptive capacities and/or reserves, and corresponds to pre-frail, frail and dependent persons.

Fig. 3: Lifespan vs healthspan

Past and present biomedical investigations are focused on diseases in order to prevent or treat them. The disease management is disease centered on organs and their specific cells, i.e. parenchyma cells, and are the object of all attention to decipher disease related molecular mechanisms. Such an approach is resulting in an increase of lifespan, but not with an equivalent increase of healthspan. To address this issue, WHO is proposing the Intrinsic Capacity paradigm that considers the individual as a whole. Instead of focusing on an organ and their specificities, a new analysis can be developed using the generic framework of the relationship between architecture and function for all organs, their maintenance and repair. This highlights the key role of the general and transverse ground required to achieve healthy organ steady-state through adequate renewal.

Fig. 4: Ageing as a scar

Part A: *Ageing as a scar.* Healthy ageing is ensured as long as tissue homeo-allostasis is achieved. After injury even low grade but daily occurring throughout live, inflammation triggers repair processes. A robust inflammation with a short time inflammation resolution induces regenerative healing leading to tissue architecture and function recoveries. When the burst of inflammation is moderated and long-lasting with poorly resolved inflammation, scar healing takes place with ECM deposition and the progressive impairment of adequate architecture for its function. With time, increasing low-grade inflammation takes place. associated with the reiterated then chronic activation of ECM deposition resulting in chronic infra-clinic fibrosis and inadequate structure/function relationship resulting in progressive dysfunctions. To compensate this impairment, allostasis induced toward a drift in a new optimum set-point/equilibrium but allostatic load takes place progressively leading to frailty.

Part B: *A SIM as transverse supportive ground card for parenchyma to monitor healthy ageing.* Healthy ageing is ensured as long as the optimal architecture function relationship corresponding to close interactions between parenchyma and stroma is renewed and maintained by regenerative processes. Unfortunately, scar healing with ECM deposition is prominent in adult mammals. The analysis of repair processes revealed three key components that control their outcomes. In the stroma, MSCs (S for supportive and structuring cells) act as plastic support cells for the parenchymal compartment and are one of the main actors of the ECM trabeculae that constitutes the skeleton for the emergence and maintenance of optimal organ architecture. The nature of the inflammation (I) in

the early stages and its resolutions, strongly conditions the repair outcomes. Lastly, metabolism (M) and particularly energetic metabolism and its flexibility, are required to ensure cell proliferation, commitment and differentiation. Because these components are strongly interrelated and transverse to all organs and physiological functions, a composite SIM map and index should accurately monitor physiological ageing and putatively predict the evolution of the individual.

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Fig. 1

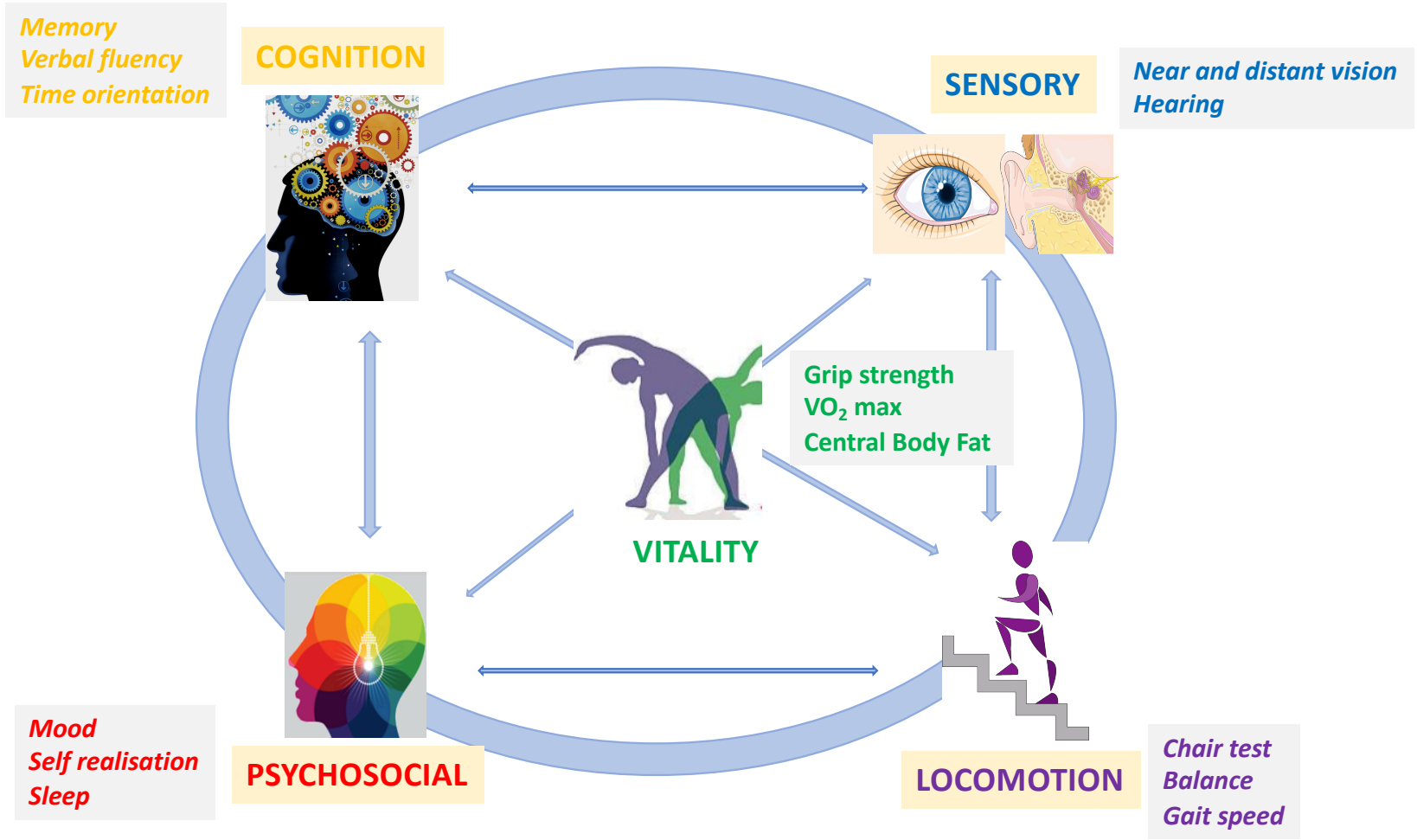
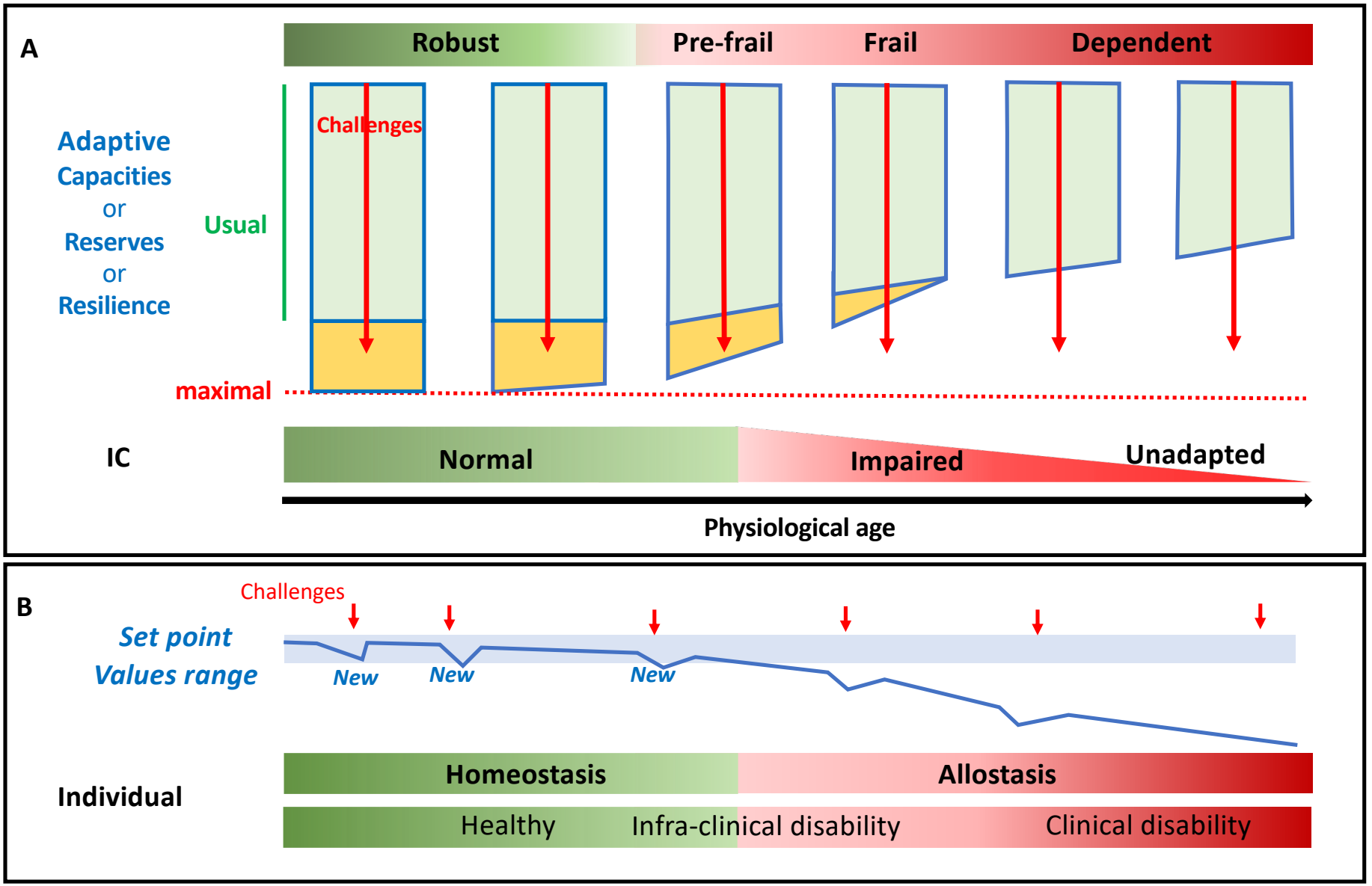


Fig. 2


A
Robust
Pre-frail
Frail
Dependent
Adaptive Capacities or Reserves or Resilience
Usual
Challenges
maximal
IC
Normal
Impaired
Unadapted
Physiological age
B
Challenges
Set point Values range
New
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New
Individual
Homeostasis
Allostasis
Healthy
Infra-clinical disability
Clinical disability

Fig. 3

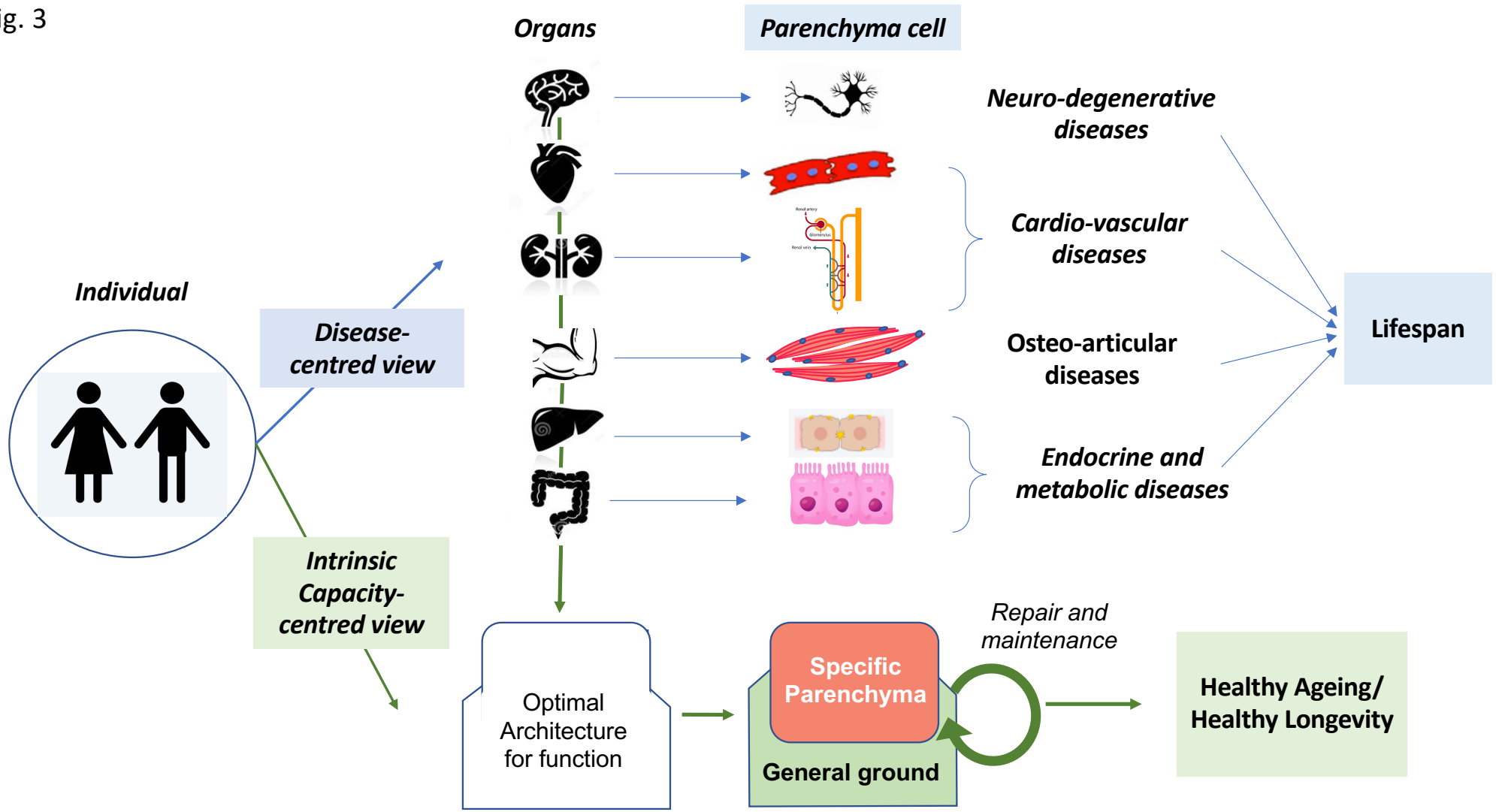
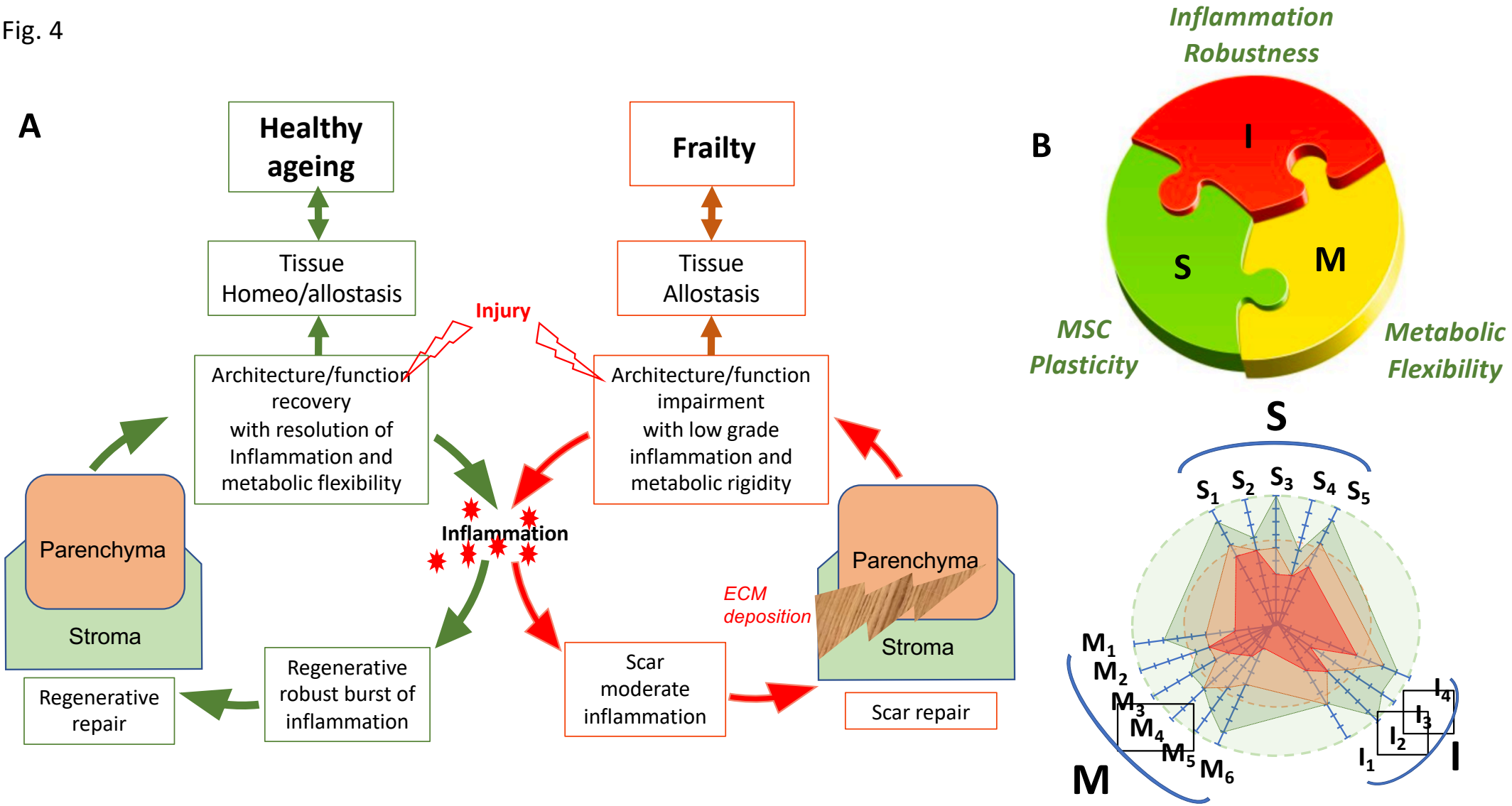

Organs
Parenchyma cell
Individual
Disease-centred view
Intrinsic Capacity-centred view
Neuro-degenerative diseases
Cardio-vascular diseases
Osteo-articular diseases
Endocrine and metabolic diseases
Lifespan
Optimal Architecture for function
Specific Parenchyma
General ground
Repair and maintenance
Healthy Ageing/ Healthy Longevity

Fig. 4


A
Healthy ageing
Tissue Homeo/allostasis
Architecture/function recovery with resolution of Inflammation and metabolic flexibility
Injury
Frailty
Tissue Allostasis
Architecture/function impairment with low grade inflammation and metabolic rigidity
Parenchyma
Stroma
Inflammation
ECM deposition
Parenchyma
Stroma
Regenerative repair
Regenerative robust burst of inflammation
Scar moderate inflammation
Scar repair
B
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MSC Plasticity
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S1 S2 S3 S4 S5
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