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Forum

Metabolic Disease Epidemics: Emerging Challenges in Regenerative Medicine

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The interplay between cell/tissue damage caused by metabolic dysfunction and regenerative potential remains elusive. The tissue engineering and regenerative medicine (TERM) field is now facing a worldwide epidemic of obesity. This Forum article uncovers prospective questions to be addressed in TERM toward the development of effective regenerative therapies adjusted to these new demands.

At the Dawn of Metabolic Disease Epidemics

The field of TERM envisions the generation of therapeutic strategies for restoration of normal tissue function after damage. Over the past decades, advances in TERM have been leading to the development of new therapies, particularly targeting the modulation of cellular behavior. Several approaches are proposed, which can be roughly divided into two groups: (i) cellular strategies based on cell transplantation (either alone or embedded in biomaterials/*in vitro* engineered tissues); and (ii) acellular strategies targeting *in situ* cell modulation (through the use of smart biomaterials or biomolecules). Given that cells are in general the main targets, such therapies rely on knowing/predicting to some extent how cells will respond. TERM scientists often face the challenge of patient variability, but this frequently disregards patients with metabolic alterations as a result of overweight, obesity, and metabolic diseases. Notwithstanding, the worldwide epidemic of obesity is a serious public health problem as it is increasing the incidence of metabolic diseases (onset of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular disease) and associated complications, including in young people [1,2] at an alarming rate, being a major driving force for research on metabolism-associated pathologies.

It is well known that metabolic dysfunctions, particularly diabetes, lead to non-healing conditions and chronic wounding as a result of exacerbated local inflammatory responses. Therefore, alterations in wound healing and tissue regeneration in patients with metabolic disorders are often extrapolated as a consequence of immune/inflammatory dysregulation. Nonetheless, metabolic effects at the cellular level, as well as the regenerative capacity of other cells, rather than on the immunobiological microenvironment, are frequently neglected.

Here, the interplay between metabolic dysfunction and tissue regeneration is discussed along with novel questions arising in the field of TERM.

Inflammation and Tissue Repair: Uncovered Paradigms in TERM

Obesity and the metabolic syndrome are characterized by a subclinical form of chronic inflammation. In turn, inflammation is a strategic partner of tissue repair and regeneration [3]. The immune system/inflammation comes into play in virtually all systems of the human body; thus, the inflammatory dysregulation may have an impact not only locally but also systemically. The metabolic dysfunction and associated oxidative stress affects the pro-/anti-inflammatory balance of signaling molecules, resulting in a feed-forward loop of macrophage activation and altered polarization toward the proinflammatory phenotype as an adaptive physiological immune response. Hence, it is intriguing to speculate whether this subclinical/low-level chronic inflammation of obesity alters immune-sensing and infiltrating compartments in metabolism-associated pathologies, particularly those that are themselves triggered by inflammatory processes [e.g., osteoarthritis (OA), tendinopathies; Box 1]. Furthermore, the link between metabolism and cellular functions is not limited to immune cells and metabolic tissues, prospectively impacting the role of other cells orchestrating tissue repair. Diet-induced obesity triggers a proinflammatory state as the first-line response of adipose tissue to overnutrition, including an increase of proinflammatory cytokines and relative deficiency of anti-inflammatory ones, accumulation of advanced glycation end products (AGEs), a switch on macrophage phenotype, and increased production of reactive oxygen species (ROS), promoting a profibrotic program [1,2]. Altogether, these immunometabolic shifts challenge tissue regeneration. Nonetheless, there is a lack of understanding regarding the biological mechanisms underlying the differential repair processes between healthy/lean and metabolically altered tissues. Therefore,

Box 1. Musculoskeletal Complications of Metabolic Dysfunctions

Excess adipose tissue is strongly connected to poor musculoskeletal health mainly as a result of intramuscular fat infiltration and joint-compressive forces, together with the altered environment coordinated by fat endocrine function. Dietary changes and physical activity are the first-line indication for overweight and obesity management. This results in a vicious cycle, exposing the musculoskeletal system to increasing forces besides other musculoskeletal complications. Thus, consequent musculoskeletal degenerative alterations impact patient compliance to clinical indications for increased physical activity, while physical activity can have beneficial outcomes in counteracting several other metabolism-associated complications and comorbidities (type 2 diabetes, fatty liver disease, cardiovascular diseases). Such degenerative changes can affect different tissues of the musculoskeletal system. For instance, although no causal relationship has yet been proved, metabolic factors have been associated with the development and poor prognosis of chronic tendinopathies and poorer outcomes on repair of tendon injuries [9,10]; obesity and diabetes have been referred to as risk factors for tendon degeneration [11,12]. Downregulation of tenogenic genes was observed in tenocytes on *in vitro* high-glucose culture [13]. Also, tendons from diabetic mice displayed significant alterations, particularly in terms of matrix organization through an increased interfibrillar space [13]. Furthermore, the obese population is exposed to an increased risk of OA development and severe progression, leading to articular cartilage and bone degeneration. The association between OA and obesity is well established. In the particular case of severe cases of OA of the knee, total knee replacement, a demanding surgical procedure with unsatisfactory recovery outcomes, may be required. Stem cell therapy is proposed as an alternative aiming at cartilage regeneration. In this regard, clinical studies on the intra-articular injection of ASCs for OA treatment have supported the safety and role of ASCs in hyaline-like cartilage regeneration (NCT01300598 [14,15]) and even the application of autologous microfragmented adipose tissue (Lipogems®) injection is currently under clinical study (NCT03379168). However, published reports on the outcomes of such procedures in obese patients with OA are missing. Overall, further attention should be invested to unravel the molecular pathways involved in these degenerative processes and the interlinked conditions to develop more efficient therapies.

TERM strategies are facing provocative questions. How do healthy/lean cells respond to an immunometabolic dysfunctional environment on transplantation? Can healthy/lean cells locally contribute to the recovery of an injured tissue and effectively promote regeneration in a patient with a metabolic disorder? How do cells from patients with metabolic disorders respond in a healthy environment? Are nonadipose cellular changes induced by immunometabolic dysfunction reversible or do they have obesogenic memory as adipocytes? Are there any differential responses being orchestrated by cells derived from overweight, obese, or metabolically diseased patients?

Adipose Tissue Biology: Connecting to Regeneration

The adipose tissue, as an active endocrine organ, releases hormones, adipokines, and inflammatory cytokines that act both locally and at the systemic level, controlling metabolism and inflammation. Adipose tissue biology is known to vary with the anatomic location of fat depots and to strongly depend on sex differences, which are reflected in differences in adipocyte function owing to sex hormone effects. Male and females deposit fat differently: men predominantly have visceral white adipose tissue (VWAT), whereas premenopausal women deposit fat distributed as subcutaneous white adipose tissue (SWAT). Sex dimorphism of adipose tissue distribution has a role in the onset of metabolic dysfunctions and complications. VWAT deposition is correlated with higher susceptibility to metabolic complications. Contrarily, SWAT accumulation may have a protective function (improved plasma lipid profile, insulin sensitivity, blood pressure, and atherosclerosis). Recent findings have demonstrated sex-specific patterns of adipogenesis in response to high-fat diet (HFD) feeding [4]. Obesogenic adipogenesis (adipocyte hyperplasia) has been shown to occur in a sex hormone-dependent manner given that HFD induced adipogenesis mainly in VWAT in male mice, while in females adipogenesis was induced in both VWAT and SWAT [4]. Strikingly, activation and proliferation of adipocyte precursors has been reported in transplantation studies as being determined by cell-extrinsic factors in the depot microenvironment rather than by cell-intrinsic differences [4]. Hence, although it is expected that stem cells [particularly adipose-derived stem cells (ASCs)] obtained from obese donors exhibit cellular behavior different to those obtained from healthy/lean donors and that these cells will function differently even when transplanted to healthy/lean recipients, potentially affecting therapeutic outcomes, this needs to be further exploited given the lack of knowledge in this field.

Additionally, intradermal adipocytes have been shown to play a critical role in skin wound healing through repopulation within skin wounds on injury through both adipogenesis and migration from non-wounded areas, as well as by promoting fibroblast production and migration [5]. Furthermore, *Drosophila* fat-body cells, equivalent to vertebrate adipocytes, have been recently described to actively participate in wound healing once they are rapidly attracted to the injury site, helping the clearance of cell debris, wound closure, and fighting of wound infection [6]. It is clear that adipose tissue-derived cells have a role in the orchestration of repair and, eventually, regenerative processes. In this sense, adipose tissue is frequently used as a self-renewable source of stem cells for TERM strategies and clinical therapies. Nevertheless, adipose stem cells have been shown to differ between healthy/lean (nonobese) and obese donors in terms of metabolic characteristics and adipogenic differentiation capacity, but not in osteogenic and chondrogenic differentiation potential [7]. Strikingly, phenotypic alterations in obese-derived ASCs could be rescued by delivering subcellular fractions from normal cells [7] or even partially recovered by weight loss [8]. Overall, these findings demand a more in-depth comprehension of biological mechanisms to better clarify

the regenerative potential of ASCs from metabolically challenged donors. Furthermore, uncovering whether stem cells from nonmetabolic tissues are affected in the same manner would be of great interest to better establish clinical therapy protocols based on TERM approaches.

Concluding Remarks and Perspectives

At the dawn of a precision and personalized medicine era, the regenerative medicine field must awaken to these unexplored connections between immunometabolism, inflammation, metabolic diseases, and tissue regeneration. Thus, important questions arise that must be taken into consideration. How is the regenerative potential of tissue-specific cells modified in light of metabolic diseases? Do metabolic diseases condition the use of autologous stem and progenitor cells in regenerative therapies? Can the proregenerative role of 'healthy/lean' adipose tissue be rescued in metabolic diseases?

Only when targeting the needs of an increasing generation of patients with metabolic disorders will ingenious therapies be translated to clinical applications.

Acknowledgments

The authors acknowledge financial support from the ERC Grant CoG MagTendon nr 772817; Project NORTE-01-0145-FEDER-000021; and HORIZON 2020 under the TEAMING Grant Agreement No 739572 – The Discoveries CTR.

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https://doi.org/10.1016/j.tem.2019.01.001

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