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Editorial

Mesenchymal Stem Cells and Regenerative Quantum Medicine: The Novel A, B and C of Burns Treatment

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Large burns are extensive soft tissue injuries with severe deep skin damage associated with high mortality [1-2]. This type of lesions can also lead to mental distress and chronic ilness but specially to scars, contractures, limitation of motion and bad quality of life [3-5]. Treatment of large burns as well as chronic nonhealing wounds have always been difficult medical problems and many different methods have been used to treat such injuries [6-7]. Current wound treatments are ineffective in many cases, so alternative novel types of therapy are needed and should urgently be understood and correctly explored. Abnormal damaged body environments can promote wound healing and tissue regeneration by local biochemical "alarm signals", but usually these innate mechanisms are not enough to reach complete restoration of normal skin, specially in an acceptable time [8-12].When these impairments in wound healing arise, it is also often followed by an increased susceptibility to infection, further complications, failure of other organs and death [13-14]. In these circumstances, time management should be a crucial fundamental issue to be considered. In the near future we will not only ask for better novel therapeutic approaches but also for those that could lead to complete skin healing, restoration of function and acceptable aesthetics in the shortest period of time [15-16]. The development of tissue engineering and living skin substitutes started more than 40 years ago with the in vitro culture of keratinocytes as established by Howard Green in 1975 [17-18]. His outstanding discoveries led to the possibility of replacing the epidermis of extensively burned patients by using cultured keratinocytes autografts [19].

In this way and by this novel procedure, living cells expanded in vitro were used to regenerate the skin [20-21]. Since then, there have been many cases of severely burned patients in which this technique has been used [22-23]. Many interesting advances during the past years allowed an increase in the quantity and quality of cell therapies and biological wound dressings in order to treat severe large burns [24-26]. Then, it was possible to reproduce in the laboratory and in a rudimentary way, the two layers of skin, epidermis and dermis, co-culturing adult fibroblast and keratinocytes in collagen or other biopolymer supporting scaffoldsin order to deliver them, into the patients to heal their wounds [27-28]. Many types of these skin substitutes with living cells have been used clinically with different results. They were usually designed to easily integrate with host tissue providing a strong stimulus for cell growth and differentiation. The cells themselves further encouraged the progression of tissue formation. Most of these cell-based substitutes were built using scaffolds upon which cells were seeded. The type and origin of the scaffold material and cells varied between products [29-31]. Many years of research in cell biology, growth factors and extracelular matrix permitted a progressively increased understanding of wound healing and skin regeneration in different clinical scenarios like those of large burns and chronic ulcers. The slowly uncovering of some not very well known or understood mechanisms started to show us the possible benefits of these cell based therapies including the modulation of chronic inflammation, the promotion of angiogenesis and several paracrine signaling effects that could stimulate and attract healthy cells to the wounded bed as well as the transdifferentiation into effector cells that could orchestrate a faster and more organized wound closure [32]. Concomitant advances in the field of Regenerative Medicine and Stem Cells led to many novel wound treatment options [33-34]. It was demostrated that Mesenchymal Stem Cells (MSCs) are involved in the regeneration of many injured tissues, including lung, kidney and spinal cord between many others [35-36]They have also been shown to accelerate burn wound healing in animals and humans and may revolutionize burn care in the near future [37-40]. MSCs derive from stroma and can be isolated from multiple human tissues, such as bone marrow, fat, skeletal muscle, synovium, gingiva, amniotic fluid, endometrial blood, umbilical cord and peripheral blood between many others [41-42]. One of the most exciting developments in the field of MSCs and wound treatment is the concept of healing without scarring or contractured as has been demonstrated in early fetal life [43]. MSCs could have the unique ability to initiate different wound-healing programs including those for "neo-matrix" formation in the context of dermal repair

and regeneration of skin in severe burns as well as other types of wounds [39-44]. Compared to other skin repairing cells, MSCs have the advantages to be cultured and multiplied in very short periods of time, have a high proliferation rate, very low or non immunogenicity at all, higher safety, abundance, and convenience [45-46]. It has also been reported that MSCs could promote the functional recovery of patients with radiation-induced burns [47-49]. However, little is known today in which way these cells could better be used and applied in the treatment of severe thermal burns, beside there are relevant clinical and pre-clinical studies illustrating the therapeutic impact of autologous as well as allogeneic sources of MSCs, including those from cadaver donors as we have first published [44-50].

There is an urgent need for further insight into the properties of MSCs and the dramatic host-to-MSC interactions within these pathological states that could lead to the development of more effective strategies and clinical protocols for improving outcomes in impaired wounds as well as a better understanding of their therapeutic potential. We have called all this available knowledge the: "A, B and C of burns treatment with MSCs". In this way, there could be two mayor possible mechanisms to be used to regenerate skin in a short period of time with MSCs: [1] MSCs mobilization from "central or peripheral body pools" such as the bone marrow and/or fat tissue respectively [51-54]. A major goal should be the development of an endogenous non expensive system that could vigorously mobilize and recruit at the same time the patient's MSCs, circumventing in this way all the ex vivo laboratory steps generally used in cell therapies [9-55]. It is important to highlight that endogenous mobilization has been studied in some animal models and we have shown for the first time that large amounts of MSCs circulate in peripheral blood under the influence of large burns [10]. Therefore, they may represent a previously unrecognized circulatory component to the process of skin regeneration [56]. As the translational settings toward humans for such a treatment might represent a long leap specially when the available products with these possible effects could be extremely expensive for the general patients with burns, then the most followed and second approach for exploiting the therapeutic action of stem cells in wound healing has been: 2] Autologous or allogeneic MSCs transplantation after *ex-vivo* culture and expansion [44-46]. The application of exogenous MSCs at the wound site and their potential has been reviewed by several authors [57-61]. MSCs gently moderate the wound inflammatory response by the secretion of anti-inflammatory factors [62-63]. MSCs could then play a fundamental role in committing the wound healing process to the next stage of repair avoiding the possibility to fall in a chronic nonhealing lesion [64].

Alarm signals generated from injured tissues including chemotactic molecules that make MSCs to migrate from bone marrow and probably other cell pools to these sites are needed [52-53-65]. At their arrival MSCs may improve wound healing in several ways [66]. MSCs possibly stimulate angiogenesis secreting signaling/growth factors like Vascular Endothelial Growth Factor [VEGF] and hypoxia inducible factor 1a [HIF1a] [67], and by cell-to-cell interactions [68]. Angiogenesis is very important process occurring during wound healing in which there is an explosive surge of neovascularization and angiogenesis developing in a microvascular network within the granulation tissue in the wound site. Failure to maintain angiogenesis during wound repair is known to lead to chronic wound development [69]. Also, if it turns impossible to correctly exit the inflammatory phase after burns, it can then result in excessive scar production [70]. MSCs have antimicrobial properties and could help to prevent infections in the wound beds as we have seen. MSCs can secrete bactericidal factors and increase the amount of phagocytosis [44-71]. When MSCs are delivered in a fibrin matrix and a transparent polymeric film is used to cover the treated wound bed, a yellowish creamy material is always observed under it and beside its appearance never associates with superinfection. This material could be an interesting promoter of wound healing with great potential as a future pharmaceutical regenerative product to be used for the treatment of burns, as it is supposed to be full of stem cells and growth factors [44]. In the regenerative milieu of MSCs and fibrin treated wounds a rapid development of neo-angiogenesis is seen usually by the fifth day as well as the simultaneous growth and full development of a "Simil-Like Granulation Tissue". We call it in this way as we think, by the preliminary observation of their biopsies, that denominating it as only granulation tissue, is an under estimation of its importance in the wound healing process. Patients treated in this way have a fast and significant improvement of their clinical condition specially pain in the burned areas, which rapidly decreases in intensity. Also, a surprisingly early and not very well adherent thin epithelial growth is always seen advancing from the wound edges. This "Simil Like Granulation Tissue" induced by topical application of MSCs during large burns treatment is a convenient niche and source of adult stem cells that could be maintained in culture and used to repair and regenerate injured tissues [44]. At the same time, granulation tissue formation warrants arrival, proliferation and differentiation of MSCs and specially wound healing. Granulation tissue could be an important potential source of dermal MSCs, and stem cells derived from it could improve the rapid recovery of burned patients and could have many other therapeutic clinical appications [70,72,73]. This "Simil like Granulation Tissue" is probably a very early vascularized "neo-dermal-like matrix" under an active growth and differentiation natural program, and not just simply a "granulation tissue". Almost a growing novel scaffold that allows for a rapid take of skin grafts, the growth of keratinocytes and probably the development of a complete epidermis. The needed time for the complete regeneration of any wound, beyond the therapeutic strategy employed, is always related to the speed of development and maturation of this "Simil Like Granulation Tissue" or "Universal Matrix ", as it could be the fundamental primary reparative material that appears prior to the closure of any wound [44]. It can develope spontaneously or by the effects of many diverse treatments in all kind of skin injuries, specially if the patient has the necessary time to do so. In the case of large deep burns treated with MSCs and Fibrin, its formation time usually only takes less than a week. When other available treatments or skin substitutes are used the median time to reach this level of healing is around 50 or 60 days. Our future challenge in the treatment of severe burns when using MSCs will surely be a more precise management and understanding of the variable of time. For this purpose we have suggested to: (1) Early apply Meshed Skin Grafts as soon as the granulation-like tissue induced by MSCs is seen [around the fifth day after the application of MSCs]. (2) Put together immediately after escarecthomy the MSCs with fibrin and the Meshed Skin Grafts specially one made of very wide meshes. (3) Early and simultaneous use of cultured keratinocytes/epidermal grafts with MSCs and fibrin toghether. (4) Deliver MSCs in novel different ways

like in the shape of "spheroids" as we have previously described, in which their cores should be loaded with fibrin and MSCs and their Shell with keratinocytes [74]. (5) Use of "intelligent matrices" with biodegradable nanoparticles and stem cells to accelerate the time for healing as it was said before [75-76]. (6) Use of another type of metal nanoparticles that could also have some Quantum advantages as has been explained from which Photons could be irradiated into the tissue engineering device and the wound [77]. (7) Use of external sources of Photons like those provided by LED lamps [78-81]. Physics or Quantum Mechanics refers to the behavior of matter when its dimensions are very small [82]. The Quantum Mechanisms, especially those of certain Elementary Particles such as photons, could explain the transfer of unique and fundamental regenerative or healing signals to the cells or to the whole body of patients that could be treated in the near future by this modality [83]. in quantum physics, we begin to notice strange effects such as the impossibility of knowing exactly the position of an elementary particle or simultaneously its position and speed, without affecting the particle itself [83]. Quantum Dots, for example, are very small semiconductor particles of only a few nanometers in diameter, so small that their optical and electronic properties differ from other larger particles. They are a central issue in nanotechnology [77-82]. Particles exchange energy in whole multiples of a minimum possible quantity, the so-called "quantum of energy" [82]. The theoretical position of the particles is given by a probabilistic function, that is to say that it is not a certainty but rather a possibility. Thanks to the Pauli Exclusion Principle, a particle could be in two places at once [84-85]. These QDs can emit light of specific frequencies if electricity or light is applied to them, and these frequencies can be changed only by modifying their measurements, form or materials used in their construction, giving rise to many applications. In this way electrons and holes are kept separated for tenths to hundredths of nanoseconds and then they can recombine, producing the emission of a photon [77-86]. Also, "LEDs", acronym for the english expression light-emitting diodes, are a type of diodes used in computers, numerical panels, digital clocks, pocket calculators, etc, could be an interesting source of photons to be used. Its operation is based on the effect of Electro-Luminescence, in which through a direct polarization stimulation allows this device to release energy in the form of a Photon, whose color is determined by the band of energy that has been stimulated [78]. We think of a completely new possible therapeutic system: "Quantum Regenerative Medicine". It could be applied to cure almost any disease in patients of any age and regenerate tissues and organs at our will in exceptional times. The question of greater importance in this novel system would be if unique photons could trigger a chain of macroscopic phenomena in complex organic systems, for example the skin [78-79]. Modern Biology, Pharmacology and Medicine are embarking on a growing attempt to understand molecular interactions and the processing of organic information through quantum phenomena [87-90]. The trans-cis photoinduced state of transition of the retina is a famous example where a single photon can cause considerable conformational changes [91-92]. Heliotropism is, in reality, a response to blue light. In fact, if during the night a heliotropic specie is covered with a transparent cover for red but blocks the blue light, the plant will not move at all when the sun rises. In contrast, if covered with a transparent cover for blue, the plant can be oriented towards the sun [93-94]. Geotropism is a type of tropism, typical of plants, which is reflected in a growth in response to the acceleration of gravity. It allows the basípeto growth of the roots, that must sink in the soil for its correct functioning, and the growth of the stems towards the air environment. It is of special importance during the germination of the seeds [95]. Numerous animals can obtain directional information from geo-magnetic fields [96]. Some mammals perceive the field of the earth as a compass of polarity, distinguishing north and south, while birds and reptiles depend on a compass of inclination that discriminates between the poles and the equators that can exploit both the intensity and the gradients of the fields. The orientation in the magnetic field requires the presence of visible light beyond a certain photon energy, in this way an oscillating magnetic field [0.1-10 MHz] can disturb the senses of birds [95-96]. Photosynthesis is carried out in different ways in plants, algae or bacteria. But all convert light into chemical energy. Photosynthesis includes a plethora of complex processes such as long-range excitation transfer, redox reactions, hydrolysis, proton transport or phosphorylation. The conversion of energy begins with the absorption of an incident Photon by a molecule of pigment, chlorophyll, porphyrin or carotenoid, embedded in a protein structure, the complex antenna. The large number of these pigment units ensures a very high probability of photo-absorption, and their structuring ensures an efficient excitation transfer from the primary absorbent to the reaction center [98-99]. Quantum Molecular Resonance (QMR) stimulation on MSCs cultures affected a lot of different biofunctions, including the transcriptionally modulation of several genes related to development processes, regulation of phosphorylation, regulation of cellular pathways such as metabolism, kinase activity and cellular organization. Gene by gene analysis also revealed that 40 up- and down-regulated genes were involved in cellular and tissue development processes such as ECM remodelling, angiogenesis, cellular migration and regulation of actin filaments [100]. Finally, certain facts that we will see under all these newburns treatments with MSCs and Quantum Regenerative Medicine, could probably not be accounted for by any of the laws of wound healing and tissue regeneration, at least those that we know up to date. The rate of tissue reconstruction that we think about will probably greatly exceed that which has ever been observed in the healing of wounds under optimum conditions. There is a real possibility for science to achieve these capacities sometime soon, especially those related to the management of time during regeneration. In this way the future of large burns treatment and regenerative medicine as a whole will probably bring a new and outstanding repertoire of novel techniques that should be important to start talking about including the correct use of MSCs probably in the form of spheroids or artificial blastemas, the possibility of understanding the clues of morphogenesis including those of the extracellular matrix [101], and probably incorporating quantum mechanisms by the use of Quantum Dots and external photon stimulation [102-103].

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