Mansilla et al., Hair Ther Transplant 2011, 1:1
DOI: 10.4172/2167-0951.1000e101

Hair : Therapy & Transplantation

Editorial Open Access

Building Small Spheroids/Regenerative Units for Hair Loss Treatment: Just Imitating Nature in an Industrialized Manner

Mansilla E[1]*, Díaz Aquino V[1], Roque G[1], Tau JM[1], Maceira A[1] and Ichim T[2]

[1]Tissue Engineering, Regenerative Medicine and Cell Therapies Laboratory, CUCAIBA, Ministry of Health, Calle 129 e/ 51 y 53- 1925- El Dique-Partido de Ensenada, Province of Buenos Aires, Argentina
[2]Medistem Inc., San Diego, CA 92122, USA

Tissue and organ regenerative capacities have been developed by all living multicellular organisms including men, as an evolutionary advantage mechanism in order to survive [1,2]. The general process of regeneration is a common normal feature observed with different modalities and intensities in all kind of animals, humans and even plants [3,4]. It follows several basic universal rules in all species. Between them, adult stem cells are crucial for all these physiological tissue renewal and regeneration events after injury or disease [5,6]. Also, the idea of spherical structures is important and persistent, from a cell to a colony, and even in the development of an embryo [7,8]. This shape and its elementary forces are seen in equilibrium in all nature, from atoms to planets and stars [9,10]. In this way, amphibians can develop blastemas in their amputated limbs in order to regrowth [11,12], and plants have meristems as self-unique-organizing regenerating systems [13,14]. Meristems and blastemas, seem to be the origin and perpetuation of plants as well as the basic units for rebuilding human and animal body parts respectively [15,16]. These repeating units are structurally and physiologically very similar. They have multiple populations of stem cells surrounded by rapidly dividing cells [17,18]. They work in such a manner in order to maintain stem cells in their niche as a permanent source for new undifferentiated cells throughout life [19,20]. Meristems as well as blastemas basically provide the best microenvironment that allows stem cells to prosper [21]. Hair follicles (HFs) could be functioning as real meristems or blastemas like structures. Embryoid bodies and even laboratory made, stem cells spheroids could also be their close relatives. Basically, all these spherical regenerative units should contain a central zone (CZ) that harbors pluripotent stem cells and a peripheral region (PR), in which cells start to differentiate and organ primordia can initiate [22]. This PR should have artificially added keratinocytes/epithelial cells, in the case of a "lab-made-spheroid" for hair regeneration. Repatterning of these cells during regeneration can be remarkably rapid as seen in trees during spring time [23] or in normal physiological menstrual cycles of normal endometriums of women or female animals in reproductive age [24]. Cycle after cycle, if an embryo has not been implanted, endometrial adult stem cells must regenerate the uterus for years [25]. These regenerative adult stem cells can be isolated and culture-expanded under GMPs for many clinical applications like the treatment of critical limb ischemia [26]. As other mesenchymal stem cells (MSCs), Endometrial Regenerative Cells (ERCs) have a great capacity for regeneration but specially for neoangiogenesis [27,28]. The development of multicellular round-shaped hetero-spheroids comprising bovine endometrial epithelial cells (BEE) and bovine endometrial stromal cells (BES) has been already described [29]. Histological examination found that these hetero-spheroids were covered with BEE on the outer layer while BES were in the core of the spheroids. The spheroids displayed an endometrium-mimic feature being a useful in vitro model of bovine endometrium. Understanding nature in all its expressions and distinguishing triggering factors involved in patterning as well as in the required timing rhythm for a certain repairing process will profoundly change our knowledge of how these mechanisms operate within a living organism and how regenerative strategies should be designed in the near future [30]. We might be thinking of "small-all-purpose regenerative units", like those developed in the extreme of an amputated salamandra limb or in the nude branches of a tree at the end of winter and ready to explode on the first days of spring [31,32]. These units could really be the answer for many clinical applications, from the regrowth of a leg or an arm, even in battle fields, or complete hair regeneration, even in the home setting. They should have a local organizer such as the CZ, composed of stem cells, like those ERCs or other MSCs, a self-organizing system depending on other kinds of local cell interactions and chemical signaling, and a peripheral zone, PR, made of epithelial cells; but always, in the context of spherical structures [33,34] and combining MSCs with epithelial cells like keratinocytes. In any case, beside many of these important pathways related to the fundamental organization of spheroids for optimum repairing are still unknown and need to be discovered, specially in the field of hair loss treatment, they could surely be the beginning of a new conception for tissue and organ regeneration. It is evident that land plants such as trees, which can grow in size and produce new organs for hundreds of years, must have developed robust regulatory systems that enable them to maintain active stem cell populations also under changing or adverse environmental conditions. We are only just beginning to understand how the fate of the stem cell population is regulated in higher plants [35], inside a regenerative endometrium or in a hair follicle. Surely any or all of these principles could be utilized for hair regeneration in the near future. Hair follicle transplant procedures are quite efficient and effective in replacing terminal hair follicles in hair loss areas [36]. Its success clearly shows that whole HFs transplanted to another site will grow and that the donor follicle will behave in the recipient site, as if it were still in the donor site. But this is a laborious procedure that if it fails will need another strategy may be not available or even discovered yet [37]. It is also clear now, that more efficient and smaller HF regenerating units in a whole HF should exist [38] and it could be possible to produce them artificially in the laboratory even in an industrialized manner. Therapeutic applications using adult stem-cells such as MSCs are edging closer to reality in many medical fields including that related to hair loss treatment [39,40]. The understanding of its regulatory mechanisms is of fundamental importance for the

***Corresponding author:** Mansilla E, Tissue Engineering, Regenerative Medicine and Cell Therapies Laboratory, CUCAIBA, Ministry of Health, Province of Buenos Aires, Argentina. Calle 129 e/ 51 y 53- 1925- El Dique-Partido de Ensenada, Buenos Aires, Argentina, E-mail: edmansil@netverk.com.ar

Received October 31, 2011; **Accepted** November 07, 2011; **Published** November 10, 2011

Citation: Mansilla E, Díaz Aquino V, Roque G, Tau JM, Maceira A, et al. (2011) Building Small Spheroids/Regenerative Units for Hair Loss Treatment: Just Imitating Nature in an Industrialized Manner. Hair Ther Transplant 1:e101. doi:10.4172/2167-0951.1000e101

translational application of regenerative medicine. HFs molt and regenerate repetitively in the adult as part of their physiological process as meristems in plants do [41-43]. The kinetics of HFs stem cell´s cycle entry and re-entry differ between different positive and negative stimuli and between species [44]. In animals, HFs are under permanent hormonal regulation due to the importance of coordinating alterations in insulative and color properties of a mammal's coat to the environment or visibility to changes in sexual development. Seasonal changes usually occur twice a year in temperate regions with coordinated waves of growth and moulting to produce a thicker, warmer winter coat and shorter summer pelage. These are linked to day-length, and to a lesser extent to temperature, like seasonal breeding activity; nutrient availability can also affect hair type because of the high metabolic requirements of hair production [45]. These peculiarities of hair growth are less significant in humans but not absent at all, and could be urgently required in some particular scenarios, like those observed during war times or under aggressive weather situations [46]. We can imagine a future of unlimited availability, off-the-shelf, universal, non immunogenic, spheroids, with particular epigenetic properties that will be able to be injected even by the same patient in their homes or in many different places with the required and wanted needs of color, abundance and speed of regrowth between many others for hair regeneration. Then, there is a real need for a cellular isolation, amplification and combination approach to obtain an in vitro human hair follicle regenerative source in an industrial scale in a GMP such as in the morphology of a small spheroid unit [47] like the ones described here. Sphere-forming cells but not two-dimensionally cultured cells seem to possess in vivo hair-inducing capacity. Different data suggests that MSCs including ERCs could attain hair-inducing capacity through the simple process of sphere formation [48]. In this way, very efficient and smaller regenerating units than whole HF could be easily obtained and transplanted. If we could equally manage the fourth dimension of time in hair regeneration while creating the correct interactions between epithelial and dermal cells, as we have described, which are essential for hair follicle morphogenesis and maintenance, then, definitive hair loss treatment could finally be attained. Thus, these regenerating units could increase the number of hairs grown in a transplantated individual in a certain period of time that should be of course, very short. Providing not only a better aesthetical look to that person but also accomplishing maybe, new demands for surviving of the human species during the next decades.

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