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FUTURE PROSPECTIVES OF STEM CELL TRANSPLANTATION

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Stem cells are defined biologically by their functional properties; such as self-renewal capacity and multi-lineage differentiation. These cells are tissue generators through coordinated and programmed divisions, but are also implicated in the maintenance of this tissue during life. Originally, stem cells contributed to create tissues and organs with precise locations, morphologies and integrated functions, from a fertilised ovocyte. Then, once formed, tissue maintenance depends on the existence of tissue-specific stem cells that generate new functional cells in normal conditions (replacement), but also after specific stress as increasing activity requirements or injuries (rebuilding). These cells are thought to reside in these organs where they are tightly controlled within specific niches, after appropriate signals that cells are mobilised and attracted to places where cell regeneration is required.

Stem cells were first demonstrated in the model of bone marrow transplantation. So, haematopoietic stem cells were generically identified as stem cells for years. In adult voluntary related or unrelated donors, stem cells are obtained from harvesting bone marrow or by the use of GCSF to mobilise them by PBMSC. Recently, another important source of stem cells are those obtained from cord blood. There is the possibility that there are some subtle differences between these stem cells in terms of its potential for differentiation and engraftment.

Transplantation of cellular concentrates from bone marrow to a myeloblated individual, allows the generation of a long-term lympho-haematopoietic chimera that maintains production of all haematopoietic lineages throughout life. Using DNA markers, it is possible to demonstrate that this repopulation comes from a very narrow group of cells. For instance, CD34 or CD133 selection has demonstrated in humans an ability to repopulate the bone marrow, both in a short and long-term period. Moreover, in animal models, some groups have demonstrated that a single cell is able to regenerate multiple tissues in one particular individual, so this is used as a surrogate in the presence of stem cells. Recently, other types of stem cells have been recognised in nearly all tissues. In the community, there is a scientific debate on stem cell definition and classification, according to their plasticity across embryonic layer boundaries. Nevertheless, several authors using either stem cells or progenitor cells have shown potential therapeutic benefits both in animals and humans.

However, stem cells for therapy require a different analysis. Stem cells are not judged now by their “stem-cellness” rather than by how they can contribute to reverting degenerative processes or, even, trigger regenerative responses in the context of injuries. Therefore, they have been implicated in two different capacities. First, they can differentiate into distinctive end-stage cell types. Hence, these cells can be used for reforming these tissues through the principles and practices of tissue engineering. Second, stem cells themselves secrete a broad spectrum of bioactive macromolecules that are both immunoregulatory and serve to structure regenerative microenvironments in fields of tissue injury (Caplan, J Cell Physiol, 2007).

Under this perspective, stem cells become a tool for cell therapy. If we consider cell therapy as the usage of cells as therapeutic agents, we can differentiate two big areas. One, involving regeneration, substitution or replacement of functional cells (stem cell therapy) and a second area, related to the use of immune cells to exploit their specific types of responses in the effector and suppressor directions (cellular immunotherapy). In the context of allogeneic stem cell transplantation this means GVHD, GVL and GVI and in solid organ transplantation this could mean rejection and tolerance. Other potential applications outside these areas are regenerative medicine in the context of degenerative diseases and/or autoimmunity.

One of the most difficult steps in clinical scaling-up, is the definition of a homogeneous population capable of producing predictable in-vivo responses. This results in a particular need in many applications to produce cells after a very comprehensive ex-vivo manipulation, or the use of heterogeneous sources of cells which makes a product containing different proportions of targeted cells them or even having different functional stages.

Recently, our group has focussed its attention on cord blood, trying to define cell subpopulations useful for therapy in the context of a better defined product (same age, same physiology, same environment) but also approaching them with minimally manipulated procedures. This could make possible the generation of “off-the-shelf” products to be tested clinically for application in regenerative medicine (using cord blood stem cells after CD133+ selection) and tolerance (using natural naïve T regulatory cells after CD25+ selection). Obviously, this approach will require understanding and controlling of the potential immunoreactions produced by infusing allogeneic cells from one or multiple donors to a particular patient. Altogether, knowledge acquired by basic research studies on stem cells and immunomodulatory cells contained in cord blood, would help with the translational challenges before application of cord blood cells in adoptive cell therapy.

Finally, it is important to consider that in the stem cell graft that is used to rescue patients after chemotherapy or radiotherapy, there are other “contaminant cells” that play important roles in the outcome of stem cell transplantation. These cells, mainly memory T cells, can be responsible for mediating GvHD, GvI or GVL. We have been working during the last years to characterise the properties of each one of these cells and. in addition, through international collaborative projects such as AlloStem (AlloStem.org), we are using “educated” T-cells to mediate either GvL and GvI, or to modulate GvHD and tolerance.