Preface

Regenerative medicine in cardiothoracic surgery: do the benefits outweigh the risks?

Aging is a physiologic event caused by a decline in regenerative potential mainly explained by modifications in growth factors, accumulation of DNA damage, and reduced stem cell responsiveness to external and internal stimuli (1).

The activation of aged muscle progenitor cells—that stimulate myoblasts to fuse and form new myotubes—can be restored by forced activation of the Notch signaling pathway, thereby clearly demonstrating that the intrinsic regenerative potential of old stem cells remains intact (2).

Pregnancy has been demonstrated to improve liver regeneration and remyelinate white matter lesions in aged mice, supporting the idea that pregnancy has a rejuvenating effect on the regenerative potential of several organs (3,4).

These initial intriguing experimental results in the field of rejuvenating and regenerative medicine have given rise to a considerable body of research during the last ten years. Much analysis has focused on the clinical perspectives of stem cell technologies in different fields of medicine and surgery, cardiothoracic surgery being one of the most explored but with more controversial results (5).

On the one hand, regenerative medicine applications are already a clinical reality in fields like orthopedics, dentistry and plastic surgery (6-9). On the other, their clinical benefits elsewhere, as in cardiac regeneration, remain unclear and highly debated (10).

In 2001, Orlic *et al.* reported that bone marrow stem cells injected into the infarcted myocardium of rodents dramatically regenerated the cardiac muscle, suggesting that a similar experimental approach could be used in clinical settings to regenerate damaged human hearts (11). Unfortunately, although some randomized clinical trials disclosed a functional improvement due to bone marrow-derived stem cells (12,13), the initial enthusiasm for heart regeneration by stem cell transplantation has since been dampened by the modest clinical benefits observed to date (10). Nowadays, the emerging concept at the basis of cardiac regeneration is that injected stem cells do not persist for long in the myocardium and do not work through a transdifferentiation process into new cardiomyocytes but rather through paracrine effectors (14).

Several critical issues have yet to be resolved in the field of cardiac regeneration by stem cell activity. First, the newly regenerated cardiomyocytes may not couple with the pre-existing cardiac cell population, leading to electric cellular conflicts culminating in arrhythmias (15). Second, the clinical use of embryonic stem cells or induced pluripotent stem cells raises major concerns because of the possibility of cancer tissue developing in the injected host (16).

Similar oncologic concerns exist in the field of airway and lung regeneration, where tumors are much more common than in cardiac surgery, thereby enhancing the risk of cancer cells being boosted by stem cell implantation (17). Following a preliminary experience on a large animal model (18), we performed the first autologous endoscopic bone marrow-derived mesenchymal stromal cell transplant to close a bronchopleural fistula developing after right extrapleural pneumonectomy (19). Some oncologic doubts were subsequently expressed claiming the use of mesenchymal stem cells in tumor excision sites may promote residual tumor growth and metastasis (17). Based on the long-term follow-up, clinical experience and the cell manufacturing techniques, the only clear contraindication to mesenchymal stromal cell topic injection remains local residual tumor (20).

Thanks to the enormous progress made in stem cell technologies and biomaterials, several prototypes of bioengineered tracheal grafts have been described (21-24), but the attractive concept of bioengineered tracheal replacements has not yielded a definitive and reliable solution (25). In fact, scientific papers in the field of stem cell research are retracted 2.4 times more often than the average for biomedicine. Although the proportion of retracted articles is still very low (about 1 out of every 1,900 papers), over half of these retractions are due to fraud (26).

In conclusion, the clinical application of successful regenerative medicine principles and stem cell technologies to daily cardiothoracic practice remains an intriguing and promising field. However, clear warnings are needed against sensational or enthusiastic reports that jeopardize the complex field of regenerative medicine making it even more dangerous and controversial.

In this spirit we invited our most prominent colleagues to contribute to this special issue on regenerative medicine

in cardiothoracic surgery. The aim is to foster high-quality research in this burgeoning field, while shielding it from inappropriate applications.

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