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Stem cells from amniotic fluid – Potential for regenerative medicine

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Regenerative medicine has recently been established as an emerging field focussing on repair, replacement or regeneration of cells, tissues and whole organs. The significant recent advances in the field have intensified the search for novel sources of stem cells with potential for therapy. Recently, researchers have identified the amniotic fluid as an untapped source of stem cells that are multipotent, possess immunomodulatory properties and do not have the ethical and legal limitations of embryonic stem cells. Stem cells from the amniotic fluid have been shown to differentiate into cell lineages representing all three embryonic germ layers without generating tumours, which make them an ideal candidate for tissue engineering applications. In addition, their ability to engraft in injured organs and modulate immune and repair responses of host tissues suggest that transplantation of such cells may be useful for the treatment of various degenerative and inflammatory diseases affecting major tissues/organs. This review summarises the evidence on amniotic fluid cells over the past 15 years and explores the potential therapeutic applications of amniotic fluid stem cells and amniotic fluid mesenchymal stem cells.

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Introduction

Regenerative medicine: therapeutic potential and the quest for novel stem cell sources

Regenerative medicine has recently been established as an emerging field focussing on *repair, replacement* or *regeneration* of cells, tissues and whole organs. It involves multiple disciplines devoted to different aspects of the regeneration process, including stem cell biology, gene therapy, bioengineering, material science and pharmacology. After years of basic science research and proof-of-principle experiments on animal models of disease, the first clinical applications of regenerative medicine have recently become a reality [1,2]. The rapid development of regenerative medicine is driven by the unmet clinical needs of patients requiring healthy tissues and organs, but for whom transplantation is not an option mainly due to the limited availability of appropriate grafts of human origin. So far, scientists around the world have been successful in tissue-engineering structurally simple organs with the main functions of allowing passage (e.g., trachea) or storage (e.g., urinary bladder) in the body. However, in the coming few years, more complex structures will likely be prepared in bioreactors before being transplanted into patients. Alternatively, it is possible that regeneration may occur directly in patients by either using their own body as a bioreactor (e.g. cell therapy involving transplantation of stem cells that proliferate, differentiate and replace damaged host cells, or transplantation of a scaffold which is then repopulated/remodelled by host cells) [3] or activating/enhancing innate regenerative processes (e.g., transplantation of stem cells that home to sites of injury and act via a paracrine mechanism to stimulate repair/regeneration of host tissues) [4,5]. Ultimately, regenerative medicine may offer a long-term solution to the problem of shortage of tissue/organs available for therapy.

The significant advances in the field of regenerative medicine have intensified the search for novel sources of stem cells with potential for therapy. Although embryonic and adult tissues can be used for the isolation of pluripotent stem cells, significant limitations, including ethical concerns, complexity of isolation/culture and tumorigenicity, have hindered translation of laboratory findings into clinical practice. In recent years, the amniotic fluid (AF) has been recognised as an alternative underutilised source of stem cells for tissue regeneration. AF cells could be banked and used for either allogeneic or autologous transplantation, the latter being particularly attractive for perinatal applications. Researchers have developed efficient protocols for the isolation of stem cells from the AF, which may be used for regenerative medicine-based treatments against both congenital and adult disorders [6,7].

Amniotic fluid: novel source of stem cells with therapeutic applications in regenerative medicine

The amnion is a sac that contains the developing embryo, surrounded by the chorion and yolk sac in humans and mice, respectively. Along with the enveloping AF, it has protective functions for the foetus, in particular, against trauma, infectious and toxic agents [8]. AF composition and volume fluctuates with gestation, in part due to foetal development. During the first half of gestation, it is dependent on the osmotic gradient developed by sodium and chloride transport across the amniotic membrane and foetal skin. In the second half of gestation, it also contains foetal respiratory secretions, urine and excrement [9].

The AF is composed mainly of water and electrolytes, chemical substances (e.g., lipids, proteins and hormones), suspended materials (e.g., vernix caseosa, lanugo hair and meconium) and cells [10]. The cells present within the AF represent a heterogeneous cell population with varying morphologies, in vitro characteristics and in vivo potential. They are mostly derived from the embryo, in particular the amniotic membrane, respiratory, intestinal and urinary tracts. AF-derived cells steadily increase with gestational age unless a pathological condition alters cellular turnover. For example, cell counts are abnormally low in the presence of intrauterine death and urogenital atresia, whereas they are increased in situations such as anencephaly and spina bifida [11].

Added to the changing cell counts, the AF contains a number of subpopulations that vary in proportion according to gestational age. These subpopulations were initially classified according to their morphology into amniocytes (60.8%), epithelioid (33.7%) and fibroblastic (5.5%) cells [12]. Recently, cells with therapeutic potential have been isolated from the AF: *amniotic fluid stem cells* (AFSCs) and *amniotic fluid mesenchymal stem cells* (AFMSCs). These are selectively cultured from the entirety of AF-derived