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Review

Highly potent stem cells from full-term amniotic fluid: A realistic perspective

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ABSTRACT

Amniotic fluid (AF) is now known to harbor highly potent stem cells, making it an excellent source for cell therapy. However, most of the stem cells isolated are from AF of mid-term pregnancies in which the collection procedure involves an invasive technique termed amniocentesis. This has limited the access in getting the fluid as the technique imposes certain level of risks to the mother as well as to the fetus. Alternatively, getting AF from full-term pregnancies or during deliveries would be a better resolution. Unfortunately, very few studies have isolated stem cells from AF at this stage of gestation, the fluid that is merely discarded during delivery. The question remains whether full-term AF harbors stem cells of similar potency as of the stem cells of mid-term AF. Here, we aim to review the prospect of having this type of stem cells by first looking at the origin and contents of AF particularly during different gestation period. We will then discuss the possibility that the AF, at full term, contains a population of highly potent stem cells. These stem cells are distinct from, and probably more potent than the AF mesenchymal stem cells (AF-MSCs) isolated from full-term AF. By comparing the studies on stem cells isolated from mid-term versus full-term AF from various species, we intend to address the prospect of having highly potent amniotic fluid stem cells from AF of full-term pregnancies in human and animals.

Contents

Abbreviations: AF, amniotic fluid; AFCs, amniotic fluid cells; AFSCs, amniotic fluid stem cells; AF-MSCs, amniotic fluid mesenchymal stem cells; ESCs, embryonic stem cells; iPSCs, induced pluripotent stem cells.

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1. Introduction

An increasing number of studies have reported AF as the alternative source for highly potent stem cells. To a greater extent, a report was once made that pluripotent stem cells could be isolated and cultured from mid-term AF collected through an invasive procedure, amniocentesis [1]. The term was then not accepted as the isolated stem cells known as amniotic fluid stem cells (AFSCs) were unable to form tumours upon transplantation, excluding them from the classification of the standard pluripotent stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) [2]. Most groups now categorize mid-term AFSCs as broad multipotent stem cells [3] or potentially pluripotent stem cells [4].

Besides AFSCs, a number of groups also describe isolation of another type of stem cells from AF termed amniotic fluid mesenchymal stem cells (AF-MSCs) [5–13]. Both types have been demonstrated to possess expression of embryonic and adult stem cells markers with certain level of differentiation potential. Of these, AFSCs isolated from mid-term AF seem to exhibit greater differentiation potential, with the ability to differentiate into derivatives of the three primary germ layers [1,2]. Three groups have successfully isolated AFSCs from AF of full-term pregnancies [14–16]. However, it is still uncertain whether these cells have similar potency as of the mid-term AFSCs. In this review, we will first describe the contents of AF throughout the gestation period, particularly that of human, before discussing the isolation and characterization of stem cells isolated from both the mid-term and full-term AF from human and animals. By comparing the characteristics of AFSCs and AF-MSCs from both gestation periods, we sought to explore the prospect of having similar potency as of mid-term AFSCs from AF of full-term pregnancies.

2. Amniotic fluid (AF): functions, sources & contents

Amniotic fluid (AF) or *liquor amnii* is a clear, yellowish fluid that surrounds the fetus contained inside the amnion sac of all mammals throughout the gestation period. Brace [17] has described the main functions of AF as to protect and cushion the fetus from maternal abdominal trauma, besides defending it from infection by the fluid antibacterial properties. The fluid also cushions the umbilical cord from compression between the fetus and uterus, and serves as the source of fluid, nutrients and growth factors to support normal development of the fetus. In addition AF also povides space and lubrication for fetal movements and maintaining constant temperature by preventing heat loss [17].

The amnion is derived from ectoderm and mesoderm, and as it grows, it begins to fill up with the AF [18]. While the AF is initially an isotonic solution, containing proteins, carbohydrates, lipids, phospholipids, urea, and electrolytes, it ultimately changes its constituents and volume as gestation proceeds [19–22]. In human, the fluid forms as a result of the flow of fluid from fetal lung and bladder [23] and starts to appear as early as the 2nd week of gestation [24]. It gradually expands between the 8th and 10th day after fertilization, followed by the formation of the amniotic cavity [25].

Mammalian pregnancy, especially of human, is normally divided into three trimesters. The first trimester starts from week 1–13 gestation followed by second or mid trimester from week 14–27. While the final trimester or the third trimester begins at week 28 to full-term at weeks 38–42 [26].

2.1. AF changes throughout gestation

Early pregnancy AF is believed to be derived from the surface of embryo and placenta and maternal-amnion membrane transport. In human, the volume of AF at 10 weeks gestation is approximately 10–20 ml and will markedly increases as pregnancy goes into the mid trimester [27].

During mid-trimester or mid gestation, the daily volume flows are small as the fetus begins to excrete urine into the amniotic sac and also starts to swallow the AF [28,29]. The fetal lungs also begin to secrete liquid into the AF at this time. The volume of mid-term AF in human during this term ranges from 200 to 300 ml up to 800 ml which is multiple times larger than the volume of the fetus [17,27].

During the late gestation or the third trimester, fetal urine and fetal lung liquid contribute as the major sources of AF production and fewer from fetal oral-nasal cavities discharges., The developing fetus then becomes of adequate size nearing time of delivery causes a reduction in the ratio of AF volume to fetal size [30].

2.2. Heterogeneity of AF cells

AF is now known to harbor various types of differentiated and undifferentiated cells [31,32]. Cell count of AF cells is influenced by the gestation age and by the presence of fetal diseases during pregnancy (reviewed in [2,33]). Temporal fetal changes also cause changes of the cell population found within the AF. The total number of cells and viable cells also may vary widely between samples of different pregnancies [31]. It was observed that the number of AF cells during mid-term gestation generally varies between 10 and 1000 cells/μl [34].

Even in normal pregnancies, the AF cells are heterogeneous in terms of shape, size, nuclear/cytoplasmic ratios, cytoplasmic characteristics, cell surface and biochemical properties [32]. The heterogeneity of AF cells might be due to the direct contact of the fluid with the fetus [35] via different type of fluid flow between the fetus and the amnion, as shown in Table 1. The cells were identified to originate from the developing fetus, shed by the fetal skin and amnion membrane, in addition to the alimentary, respiratory, and urogenital tracts [34]. For this reason, AF cells have been routinely

Table 1
Full term daily amniotic volume flow estimation.

Type of fluid flow	Volume
Fetal urine production	800 to 1200 mL/day
Fetal swallowing	500 to 1000 mL/day
Intramembranous flow	200 to 400 mL/day
Fetal lung liquid secretion	170 mL/day
Oral nasal secretions	25 mL/day
Transmembranous flow	10nmL/day

(Adapted from [90]).