Regional Variations In The Immunohistochemical Expression Of P75 NGF Receptors Between Term And Post-Term Human Placenta

Hassan Abd AL-Kareem Abood AL-Jawaheri and Huda Rashid Kareem Kamoona[1]

[1234] *Department of Human Anatomy, College of Medicine, Al-Nahrain University, Iraq*

KEYWORDS

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ABSTRACT

Background: The placenta has lately attracted increased attention due to its potential as a significant source of many types of stem cells, such as trophoblastic, hematopoietic, epithelial, and mesenchymal stem cells (MSCs). Placental cells are readily and ethically obtainable. In addition, the human placenta has the potential to provide a significant quantity of stem cells that can be readily isolated, expanded, and differentiated into several kinds of cells. Both the maternal and the fetal components of MSCs are present in the human placenta. Previous investigations have found that the origin of mesenchymal stem cells has a significant impact on their capacity to treat diseases. As a result, placental MSCs have a lot of potential for therapeutic use. Compared to the immunomodulatory activity of MSCs derived from mothers, fetal MSCs have a higher capacity to promote immunological health. The p75 protein has been demonstrated to be the most effective marker for the isolation and identification of human bone marrow-derived mesenchymal stem cells. CD271 was considered a versatile marker that would allow the isolation and culture of multipotent stem cells derived from mesenchymal tissue. No prior work reported P75 NGFR utilized in placental tissues as a marker for mesenchymal stem cells in connection to various gestational ages (term, and post-term) and diverse placental locations including (chorionic plate and placental villi sides).

1. Introduction

The placenta is crucial during pregnancy; it serves as the only physical connection between the mother and the baby during that time and is vital to the fetus's growth and safety [1]. In addition to playing a critical function in preserving maternal-fetal tolerance throughout pregnancy, the placenta is an intriguing, multilayered organ made up of both maternal and fetal components that provide nutrition and eliminate waste [2]. The timing of parturition is likely influenced by placental aging (term, post-term); however, premature or accelerated initiation of these processes earlier in gestation may contribute to a number of pregnancy pathologies, such as stillbirth, preterm birth, preeclampsia, and fetal growth restriction (FGR) [3].

The placenta is a significant source of many types of stem cells, such as trophoblastic, hematopoietic, epithelial, and mesenchymal stem cells [4]. Mesenchymal stem cells from both the mother and the fetus may be found in the human placenta. Stem cells are necessary for cell treatment regimens for regenerative medicine to be used clinically [5].

The chorionic mesenchymal stromal cells and chorionic trophoblastic cells are the pure stem cell populations obtained from human placenta tissues; they both exhibit different degrees of plasticity [6][7]. The findings of earlier research indicate that the origins of mesenchymal stem cells may have a major influence on their therapeutic potential and should be taken into account in clinical applications [8].

Because it is easily accessible, noninvasive, ethically acceptable, and superior to other tissues, the placenta is regarded as a particularly appealing source of mesenchymal stem cells (MSCs) [9]. Because placental-derived MSCs are not always acceptable because of the intrusive collection technique, some studies have indicated that placental-derived MSCs have superior proliferative capability, life duration, and differentiation potential compared to other place-derived MSCs [10].

The p75 neurotrophin is describe as a low-affinity receptor that is also referred to as CD271, or nerve growth factor receptor (NGFR). As a transmembrane glycoprotein and a member of the tumor necrosis family (TNF) of receptors, CD271 is thought to be of special interest because it is linked to multipotency, a trait of mesenchymal stem cells [11].

P75 NGFR appears to be the most reliable marker for identifying and sorting mesenchymal stem cells, CD271 is a versatile marker that can be used to identify and maintain multipotent mesenchymal stem cells with properties that support immunosuppression and lymphohematopoietic engraftment. Cells with higher CD271 expression have a higher differentiation and proliferation potential compared to CD271-negative cells. In addition, we found that it is crucial to consider the source of MSCs when selecting cells with significant proliferation and differentiation potential [12].

2. Methodology

The study involved 30 human placenta samples gathered from the departments of obstetrics and gynecology at Al-Imamein Al-kadhimein medical city and Al-Kadhimiya Private Hospital. The samples were gathered from mothers between the ages of 20 and 45 through elective caesarian sections. The samples were segregated into two clusters (peripheral region and central region) with 15 samples each, and the two groups were designated as term and post-term based on their gestational age. When fresh placental tissue is observed, many gross features need to be assessed, including the number of cotyledons, the shape of the placenta (oval, round, or irregular), and the location of the umbilical cord's insertion (central, paracentral, or marginal). Additionally, a conventional histological exam of each sample in the study was performed using H&E staining. Also, the image analysis method called Aperio-scope was employed to assess the effectiveness of immunohistochemical studies with the P75-NGFR antibody. To calculate the mean and standard deviation, the data were evaluated using Microsoft Excel 2010. These findings were then subjected to analysis of variance, and values of $p < 0.05$ were considered significant.

3. Result and Discussion

There are differences in the gross appearance of the number of cotyledons that were observed between the term group (19.33±0.79) and the post-term group (18±0.63). Placental measurements were taken between different developmental ages (term, and post-term) and different regions of the placental (such as the chorionic plate and the side of the villi). The circular shape of the placenta was the most common observed shape in samples from different age groups. The widest diameter of the samples did not differ significantly between the different age groups, and it increased to (19.73±0.52) in the term group and decrease to (18.6±0.54) in post-term. However, the central thickness of the samples increased significantly with the term group Table (1). There were significant discrepancies in the position of the umbilical cord in regard to insertions in each age bracket: the paracentral position was most commonly observed, and it was most frequent in the post-term group (8.0 ± 0.57). The fetal surface of human placenta in the post-term group showed congested bluish discoloration, compared to a bright color in the term group. P75-NGFR staining was observed to be spread out and brownish in color on both the fetal and maternal surfaces in the post-term group compared to the term group placenta, the amount of staining expressed on the fetal surface was greater than the lowest level on the part of the maternal surface nearest to the placental villi. The central portion of the chorionic plate's side demonstrated a high degree of marker expression, which differed by 0.517 ± 0.049 in the two different groups of gestation and on the fetal and maternal surfaces of each group. The marker's expression was primarily evident in the perivascular region, Table (2).

Table (1): Measurements of central thickness and widest diameter in the term and post-term human placenta groups.

parameters	**Term group**	**Post-term group**	**P-value**
Central thickness(cm)	**1.91 ± 0.10**	**1.8 ± 0.11**	**0.0057**
Widest diameter(cm)	**19.73 ± 0.52**	**18.6 ± 0.54**	**0.128**

Table (2) Immunohistochemical expression value of P7**5** NGFR in different regions of different placental gestational ages (term and post-term groups) with P-value by ANOVA test (Mean ± SE.

Gestational age			
Parameters Placental region	Term	Post-term	P-value
Central Chorionic side	0.387 ± 0.040	0.517 ± 0.049	0.038
Peripheral Chorionic side	0.289 ± 0.038	0.427 ± 0.056	0.048
Central Maternal side	0.194 ± 0.035	0.320 ± 0.057	0.023
Peripheral Maternal side	0.182 ± 0.024	0.255 ± 0.033	0.042

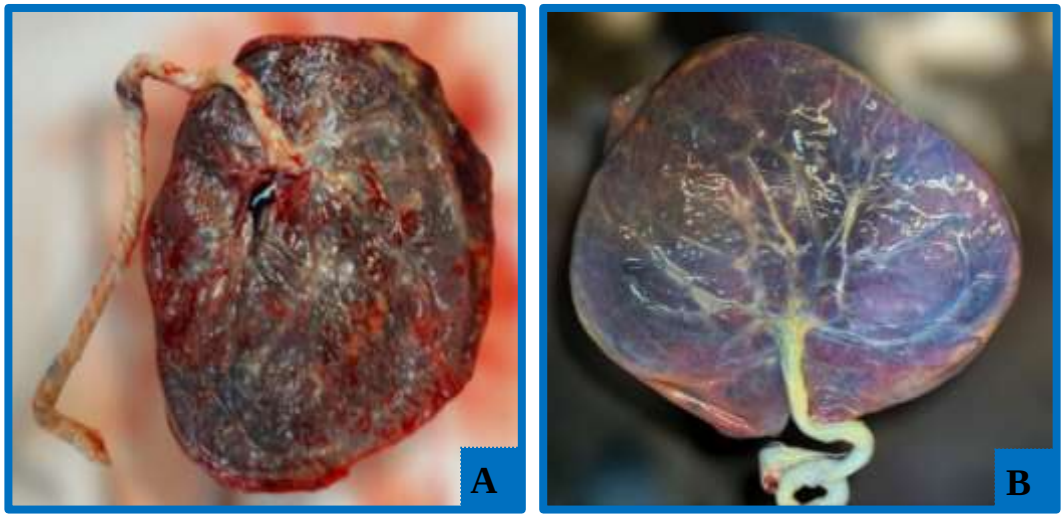

Figure (1): Macroscopic image showed the fetal surface of fresh placenta at a different gestational age: A: Term placental group, B: Post-term placental group

Discussion:

Placental stem cells have a tremendous capacity for utilization in regenerative medicine, because they are easily accessible, non-invasively harvested, and are ethically approved. These properties, as well as the number of MSCs in their mesenchyme, differentiate them from other stem cell sources. Recent research has demonstrated that mesenchymal stem cells (MSCs) derived from different parts of the placenta have a greater variety of functions and a longer lifespan than other sources, after birth, PMSCs can be stored for use in autologous and allogeneic procedures.

Macroscopic features of human placenta:

In this study, the macroscopic features of samples of the two different gestational age groups (term and post-term) human placentae showed variations, and that reflect the variation in placental growth and morphology which is linked with placental functional capacity as mentioned by [13], also placental morphological changes reflect retrospective pregnancy related intrauterine problems, uteroplacental blood flow and fetal growth as mentioned by [14].

Studying the gross features of placenta is important in evaluating pregnancy associated abnormalities [15]. In this concept, these features were examined in term and post-term. A significant difference was noticed in the number of cotyledons on the maternal surface among the two gestational age groups, as cotyledons numbers were increased in term, reduced in post-term groups, it was stated that aging of the placenta may be related to the reduction in cotyledons number, and that due to an increase in their size during maturation, as well as this reduction may be associated with fibrin deposition lead to obliteration of a wide area of cotyledons when the gestational age of the placenta goes toward post-term and the decrease in count may due to septum deviation and more bulging in term and post-term groups [16]. Another reason for this highest count in the term group could be related to the small size of the cotyledon and the minimum amount of fibrin deposition and its reduction in term group may be due to vascular lesions that interfere with the vascular supply of placental tissue that lead to atrophic

changes that gradually increased in the post-term groups. This agreed with [17] who reported a percentage of minimal villous tissue loss ranged from 10% to 30% in the case of significant placental infarcts and 20% to 30% in perivillous fibrin deposition in placentae beyond term, at the same time [18] mentioned that placental growth certainly slows, but clearly does not cease, during the last few weeks of gestation. As gestational age increases, placental length, width, thickness and weight increase in different ways [19], while another study confirmed by [20] showed that the oxygenation and functional efficiency of placenta effects on its cotyledon count.

A non-significant change in placental shape among gestational age groups; the common shape recorded in this study was circular in term and oval in post-term groups. Placenta term group samples showed a circular shape, as well as post-term group samples showed a more regular oval shape because of their maturation, this agreed with [21][22]. They were mentioned that placental shape could be affected by the maturation and vascular functions of placenta from both the fetal and maternal sides.

The central thickness showed variation among different gestational age groups, being increased in the term group more than the post-term groups due to its full functional maturation of the placenta. Also [23] mentioned a significant decrease in the central thickness by 37% of the placental area in preterm compared to term placenta. The central thickness increase signifies an increase in the number of blood vessels sprouting in order to lead to increased placenta efficiency and increased penetration into the maternal decidua, this agreed with [24] who mention that placental growth is not purely genetically determined but occurs in response to fetal demand and maternal supply with local control of blood flow in its villi.

While the widest diameter of the placenta showed variation among different gestational age groups, it was highest in the term group. This is due to a circular shape of the placenta and a decrease in subsequence post-term groups that are correlated with fibrin deposition and placental fibrosis. [25] who demonstrate the relationship between broad and flat placenta with slower fetal growth, this supports our finding that the term group has the widest diameters.

Cord insertion showed variation among different gestational age groups; the paracentral group was the most common finding, followed by marginal and central as the sites of cord insertion in all gestational age groups. This was related to the unequal growth rate of the placental disc during pregnancy and the site of implantation of the placenta. Conflicted reports about cord insertion into the placental disk and placental functions, [26] reported eccentric or marginal insertion was related to low birth weight while [27] reported central insertion positively influences placental sufficiency. On the other hand, the cord insertion in relation to the edge of the placental disk is not correlated with birth weight, as the eccentric cord insertion that is commonly seen does not compromise efficiency of the normal human placenta as mentioned by [28].

One of the most important placental morphological changes that was noticed between the two gestational age groups is the appearance and color of placenta due to the changes that happen to the placenta in maturation of vessels and difference in thickness and deviation between the two gestational ages.

The placental surfaces showed variation in appearance between the two gestational age groups samples, with the fetal surface of the placenta in the post-term group rather than the term groups samples that showed a congested blue color compared to a bright red color in the term groups, this may be related to the vascular supply of the cotyledons and branching of the villous tree since in the term group most of the placental villi are immature, which reflected on the paler of the placental color, while in the term group placental villi reach full maturity, leading to a bright red color of the placental disc.

On the other hand, the post-term group fibrin deposition impedes placental blood flow, leading to congestion of the placental disc. These are also reflected on the maternal surface of the placenta, which is bright color in term groups and congested bluish with fibrin deposition in the post-term group. These color changes of the placenta are related to involutive dystrophic changes in the placenta with aging,

calcification, thrombosis in the intervillous space, and fibrin deposition that prevent the normal flow of nutrition and oxygen to the fetus [29][30].

4.2. General histological study of human placenta

In this study, placental samples of the two gestational age groups (term and post-term) from different regions (central and peripheral) on the fetal and maternal surfaces of each part were evaluated. Several studies have shown structural alterations in the placenta throughout a normal pregnancy in order to understand the role of the placenta in fetal growth, and to find out placental changes in relation to gestation and the variations that have been found in the placenta at different gestational ages [31].

Examining the histology of the fetal placental vasculature in the chorionic plate and the maternal villi in both the central and peripheral regions of term and post-term placentae revealed differences in their vascular morphology that are mainly related to the size of the vessels, the thickness of the smooth muscle layer, and their distribution. To the best of our knowledge, no previous studies have examined the placental samples of the two gestational ages (term and post-term) with different regions (central and peripheral) and compared the fetal and maternal surfaces of each part. However, many studies have investigated other vascular morphometric characteristics like vascular diameter, length, tortuosity, and luminal perimeter in relation to placental pathological conditions [32][33].

The fetal surface is made of the chorionic plate, which is the primary core of the connective tissue stroma traversed by chorionic vessels, and covered by the amniotic membrane. The central region of the chorionic plate showed an increase in the connective tissue core, numbers, size, and branches of chorionic vessels with aging. The chorionic vessels showed a thick muscular wall with a relative wider lumen in this region. While in peripheral regions, reductions in both numbers, size, and branches of chorionic vessels and their muscular elements compensated for an increase in the connective tissue core. This agreed with [34] who mentioned a significant reduction was evident in placental weight, central thickness, and the widest diameter in placenta, with a borderline increase in smooth muscle layer thickness in the blood vessels of the central chorionic plate and a significant reduction in peripheral chorionic plate in term placentas.

Fibrin deposition starts to appear in a term group in the central region; this is related to the vascular changes of anchoring villi prior to labor that lead to placental vascular insufficient, as confirmed by [35] who mentioned that during normal gestation the fibrinoid deposition is influenced by the quality of vascular perfusion and emphasize that the extent of the surface of the villous is a more generally important factor. In the peripheral region, fibrin deposition occurs in term group leading to hypoxic oxidative stress due to the distance from cord blood vessels; this leads to villous recreation and fibrin deposition [36][37][38][39], and increased in the post-term group placenta, and this agreed with histological and histochemical studies of [40] who provide some evidence that intervillous fibrinoid is a result to placental degeneration that is induced by aging and immunological processes, and in this study, it was noticed that fibrinoid volume increased toward the pots-term group, this agreed with [41] who mentioned that fibrin increased in volume in relation to intervillous volume.

The amniotic membrane appeared as a single layer of columnar epithelium over the upper surface of the chorionic plate in the central and peripheral regions and showed the greatest thickness in the central region and least in the periphery region and this agreed with [42].

The maternal surface showed various types of placental villi, including stem, intermediate and terminal villi, which branched from the chorionic plate vessels. The main type of villi that appeared on the maternal side in the central region of term placentae was the stem villi, while the main type that appeared in post-term placentae was the terminal villi. Stem villi are characterized by large vessels with muscular walls embedded within rich connective tissue stroma, while the peripheral region of the maternal side showed a predominant presence of intermediate and terminal villi containing small vessels with a reduction of smooth muscle in the vascular wall. This is related to the quantity of maternal blood flow to the placenta. This is related to structural changes during pregnancy. This agreed

with [43], a study on vascular generation in term and post-term placentas conducted by [44] showed no significant differences in the diameter of terminal villi blood vessels, but there was a significant reduction in the length and number of terminal villi in term placenta compared to the other, another study presented by [45] who studied the morphological features of stem villi blood vessels in term placenta showed no significant differences in the thickness of blood vessels in stem villi of term placenta.

Intervillous space showed widening in post-term group placenta compared with a reduction in the population of placental villi, this is related to the functional efficiency of villi and fibrin deposition that affect the rate of exchange with the maternal circulation, impairing villous capillaries and intervillous spaces, as mentioned by [46], as variation in the relative size of intervillous space could be related to the villous population and the smooth muscle elements in the vascular wall in the stem and intermediate villi in the term groups and absent in the post-term group by these contractions and relaxations changing intervillous space dimensions this agreed with [47] who mentioned smooth muscle components in villous stem and blood vessel tunics are of great importance for fetoplacental blood flow, as contraction and relaxation of myofibroblasts regulate inter-villous space volume and control placental hemodynamics.

4.3. P75 NGFR immunohistochemical expression changes in different gestational age groups of different placental regions:

Placental mesenchymal stem cells (pMSCs) are characterized by their growth kinetics, various cell marker expression, and multilineage differentiation into osteocytes, chondrocytes, adipocytes, and neuron - like cells from the placenta [48].

P75 NGFR has been proposed as a versatile marker to selectively isolate and expand multipotent mesenchymal stem cells. P75 NGFR, also known as the p75 neurotrophin receptor. This protein plays a crucial role in regulating cell survival, growth, and differentiation in the placenta. P75 NGFR was shown to be expressed in various types of stem cells and has been used to prospectively isolate stem cells with different degrees of potency. It mediates functions related to survival, apoptosis, migration, and differentiation, and can modulate cell-fate decisions through its highly ramified signaling pathways [49].

In this study, P75 NGFR showed variable expressions at different gestational ages of the placenta. As it showed low expression in the term, as well as an increase in gestational age and placental development, the expression of P75 NGFR increased gradually until it reached its highest level in the post-term.

4.3.1 Chorionic plate side:

Immunohistochemical expression of P75 NGFR in the central region of the chorionic plate side was evidenced in the connective tissue stroma of the central region of the chorionic plate, especially in the upper part of the overlying amniotic membrane. While in the peripheral region of the chorionic plate side showed preference for connective tissue stroma in the core of the chorionic plate away from its borders and the over lining amniotic membrane and perivascular area.

The highest expression of P75 NGFR was recorded in the post-term group compared with other gestational age groups, with a predominant distribution in the perivascular area in addition to the connective tissue stroma and amniotic membrane. This agreed with [50] who mention the amniotic membrane as the source of pluripotent cells for differentiation, as amniotic epithelial cells have the capacity to differentiate into the three germ layers, as the amniotic membrane formed before gastrulation, this means prior to cellular specification and differentiation also amniotic fluid act as the source of mesenchymal stem cells that show capacity for differentiation [51].

In this study, the localization of P75 NGFR in the perivascular area in the chorionic plate in the region surrounding arterioles and venules away from endothelial cells. This agreed with [52] who identified

CD271 in the adventitial of perivascular area in ovine endometrium, and the immunohistochemical expression of P75 NGFR in perivascular area, these CD271 positive cells at same time were not stain with alpha smooth muscle actin indicate that these are not related to pericyte indicating that there a population of mesenchymal stem cells [53][54].

Also [55] mentioned the percent of mesenchymal stem cell progenitors in the outermost layer of arterial adventitia. In this study, the positive immunohistochemical expression of P75 NGFR in connective tissue stroma may be related to fibroblast cells within stroma. This agreed with [56] who found low affinity of fibroblast to CD271 in the human skin fibroblast, as P75 NGFR is play an important role in wound healing and its expressed in various cell types, such as fibroblasts and macrophages [57][58].

In conclusion, the immunohistochemical expression of P75 NGFR in placenta varies across different gestational age groups. From the early stages of pregnancy to the post-term period, the highest expression recorded in the post-term group may be related to the central thickness of the chorionic plate, where it is the highest value recorded in the post-term group, and the fibrin deposition. In the term of pregnancy, the expression of P75 NGFR in the placenta is relatively low. This is due to the placenta is still in the process of development, and the focus is more on structural changes rather than protein expression. However, as the pregnancy progresses, the expression of P75 NGFR starts to increase gradually. This finding disagreed with [59] who mentioned that human stem cells are formed only within a limited time window during embryogenesis, after which the human stem cells pool is maintained by self-renewing cell divisions. Unlike post-natal hematopoiesis that is confined to the bone marrow, fetal hematopoiesis occurs in multiple different anatomical sites in a temporally defined manner.As we enter the term of pregnancy, the expression of P75 NGFR in the placenta begins to peak, the central region of the chorionic plate shows a significant increase in P75 NGFR expression, especially in the connective tissue stroma. Moreover, the upper part of the chorionic plate with the overlying amniotic membrane also exhibits a high level of P75 NGFR expression this finding disagreed with [60] who mentioned that the isolation cells that MSC characteristics from human fetal membranes, expressing CD271 were enriched by immunomagnetic isolation. $CD271^+$ cells were demonstrated to possess higher clonogenic and osteogenic differentiation potentials than CD271-depleted fractions.

In the post-term group, the expression of P75 NGFR in the placenta reaches its peak compared to other gestational age groups, the central region of the chorionic plate side shows the highest expression of P75 NGFR, with a predominant distribution in the perivascular area, connective tissue stroma, and amniotic membrane this finding disagreed with [61] who mentioned that late post-term decidual-MSCs, when compared to term decidual-MSCs, showed significantly lower cell proliferation and a significant higher level of cell apoptosis. late post-term decidual-MSCs showed significantly lower resistance to oxidative stress and a significant decrease in antioxidant capacity compared with term decidual-MSCs.

4.3.2 Maternal side:

The Immunohistochemical expression of P75 NGFR in the central region of the maternal side showed wide distribution in the connective tissue core of the stem and intermediate villi and absent in the terminal villi and perivascular area around the vessels, while in the peripheral region of the maternal side showed restricted distribution in the stem villi and absent in the perivascular area, intermediate and terminal villi of the two gestational age groups (term and post-term).

Placental villi on the maternal surface showed a positive staining for CD271, specifically in the core of stem and intermediate villi, while it's absent in the terminal villi, previous studies mentioned placental mesenchymal stem cell are routinely isolated from villous core [62] and its population increased in post-tem group since the placental mass increased with gestational age increasing of the proportion of placental villi and connective tissue stroma, and this agreed with [63] who mentioned placental development over gestation lead to increase in placental mesenchymal stem cell in perivascular niche where they influent, and the lowest of CD271 expression in the maternal surface of the placental villi that contain little connective tissue stroma and less vascular compared to term. This

agrees with [64] who mentioned poor vascularization in early placental villi with infrequent capillaries reducing efficiency of the placental barrier, also [65] who mentioned the expression of CD271 in perivascular cells at the villous core in the term placenta.

It has been suggested that pMSCs prepared from human term placental chorionic villous explants are an attractive source of MSCs for cell therapy [66] who mentioned that the chorionic villi of human term placentae are a rich source of mesenchymal stem cells (PMSCs). The stem cell "niche" within the chorionic villi regulates how PMSCs participate in placental tissue generation, maintenance and repair [67].

P75 NGFR immunohistochemical expression in this study showed an obvious significant variation between the different regions of different placental gestational age groups (term and post-term groups), when the post-term in the central region of the chorionic side group showed a widely mesenchymal stem cells distribution along the villi trophoblastic tissue, as well as surrounding the structure that found within villous core. In addition, some batches of strong positivity were expressed within the villous connective tissue core.

It has been suggested that both the presence of CD271 surface antigen and the MSC isolation source might strongly influence the proliferative and differentiation capability of this cell subset. Such evidence would suggest the choice of MSC as the most promising cell model for regenerative medicine applications. Further studies are necessary to better understand the cellular mechanisms underlying the functions of CD271 in placenta-derived MSCs [68].

4. Conclusion and future scope

- The study's results, which show macroscopic and microscopic changes in various placental regions relative to two gestational ages (term, and post-term), including the chorionic plate and the maternal sides (central and peripheral) of the placental villi, support the theory that increasing gestational age may have an impact on placental function. Additionally, it showed that the intermediate placental villi's stem and connective tissue core have preferred expressions.
- In the placental villi and chorionic plate, P75 NGFR-stained mesenchymal stem cells were distributed in a range of regions that were broadly associated with their closeness to a virtually vascular structure. This implies that a fantastic source of PMSC is the post-term placenta.
- The distribution of P75 NGFR varied across different places and gestational ages; in future research concerning the different placenta gestational ages, this may be the main reference for selecting PMSC isolation sites..

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