History of Medicine, 2023, 9(2): 66–72
DOI: 10.17720/2409-5834.v9.2.2023.009

An Appraisal of the Role of Telocyte During Liver Formation Using CD34

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Received: 12 May 2023 **Accepted:** June 2023

Citation: Mahdi NMH, Alhabib MF (2023) An appraisal of the role of telocyte during liver formation using CD34. History of Medicine 9(2): 66–72. https://doi.org/10.17720/2409-5834.v9.2.2023.009

Abstract

Telocyte has a small size cell body with numerous thin and long telopodes that make them easily recognizable, the typical size of the cellular body may be seen on the TEM images, and the three-dimensional network formed by these Tps may serve as a frame to specify the proper arrangement of tissues and organs. CD34 is a transmembrane phosphor glycoprotein, first identified in 1984 on hematopoietic stem and progenitor cells. This study aims to investigate the possible role of TCs in liver formation, differentiation, and maturation using CD34. This study design enrolled four groups; 2nd week and 3rd-week groups of gestation embryos (prenatal stage), newborn group, and adult groups (control) the liver tissue was collected and processed for paraffin block and then sectioned and stained, nuclear differentiated special stain (NDS) was specifically used and helpful due to the fine thickness of the section Immunohistochemical antiCD34 antibody to demonstrate telocyte cells reactivity. Histomorphometric quantification of anti-CD34 antibody reactivity was estimated using Aperio software. A high significant difference was recorded in 2nd and 3rd, there was less activity of Immunohistochemical reactivity labeled with CD34 Antibody in the newborn & adult control group, than in the 2nd & 3rd -week gestation group.

During the perinatal transition, the liver plays a crucial role in several physiological functions, including metabolic, and synthetic. These processes are necessary for the viability of the fetus, which in turn benefits the progeny (Cowett 2011), it has an exclusive ability to regenerate after trauma or various injuries like toxic or infectious (Popescu and Lucchinetti, 2012). The liver performs a wide range of essential functions, including producing bile and secreting it into the intestines, as well as numerous metabolic processes involving fats, proteins, and carbohydrates, filtering

the blood of bacteria and foreign objects, producing anticoagulant substances like heparin, and detoxication (Snell, 2011; Popescu et al., 2012). The liver develops at a similar rat to that of humans relative to the production of biliary epithelial cells (BECs), and hepatocytes, which come from the endodermal germ layer, while the stroma, stellate cells, Kupffer cells, and blood arteries all come from the mesodermal germ layer (Zorn, 2008). The cellular body of the telocyte (TCs) is small and oval in shape. It has a nucleus and a small quantity of cytoplasm around it. The telocyte (TCs) has a small, oval-shaped cellular body containing a nucleus surrounded by a small amount of cytoplasm. The nucleus occupies about 25% of the cell volume and contains clusters of heterochromatin attached to the nuclear envelope. The peri nuclear cytoplasm is rich in mitochondria, particularly in podom, (which occupy about 5% of the cell body), is abundant in the element of rough and smooth endoplasmic reticulum, contains a small Golgi complex, and cytoskeletal components(thin and intermediate filaments), (Mirancea, 2016; Popescu & Pellegrini., 2010). Telocytes have the amount of very long cellular extensions called telopodes (Tps) which are the longest cellular prolongations in the human body, Tps are made by an alternation of dilated portions, named podoms, containing endoplasmic reticulum, mitochondria, and podomers, the podomers in nonpregnant myometrium are thicker than in pregnant one, and

the podoms in pregnant myometrium were thicker (Cretoiu & Popescu., 2014; Cretoiu D.& Cretoiu S., 2016). The number of telopodes determines the shape of TCs (Tps): for one prolongation piriform, for two Tps spindle, for three triangular, stellate, etc. Due to the recent discovery of telocytes, researchers are now focusing more on TCs' intercellular communication and their functions in cell niches. A gradual increase in publications reflects the significance of these cells as well as their relationship to smooth muscle cells, arteries, nerve endings, and stem cells, they are essential to numerous pathogenic processes. (liver fibrosis, myocardial infarction, heart failure, renal ischemia- reperfusion injury, and others) and adaptive reactions or responses (Ardeleanu & Bussolati., 2011; Niculite et al., 2015). The current study investigated the role of TCs during the late stages of development in embryonic rat liver. Using TEM, and IHC, naturally recognized TCs had strong immunoaffinity for CD34, CD34 is a member protein of the transmembrane sialomucin protein family and is used for the documentation of hematopoietic stem cells and non-hematopoietic progenitors, including vascular endothelial progenitors and embryonic fibroblasts, interstitial dendritic cells, multipotent mesenchymal stromal cells, and epithelial progenitors. Functional implications of CD34 are linked to cell, proliferation, adhesion, and inhibition of differentiation of progenitor or stem cells. (Nielsen & McNagny, 2008; Sidney et al., 2014).

Experimental Animals and Housing

30 adult female rats (Rattus rattus norvegicus) were kept for fertilization with 5 male rats, the animal aged (2-3) months, and weight (250- 300) g. They were kept under controlled illumination (14) hours light and (10) hours dark and room temperature (22 ± 2 C), with free access to water and food (ad libitum). Pregnancy onset was investigated by the presence of a vaginal plug after fertilization, the pregnant rat was separated from the male, representing day one of pregnancy. The gestation period length is about 19-21 days. The embryos from pregnant females were collected at 2 gestational age animals age 7 days (postnatal) and adults.

Embryos were collected according to their gestational age and washed after their extraction from the uterus with normal saline, Then after washing the embryos they were immediately fixed in 10% formalin for 48 hours, and the abdominal cavity of newborn animals in their 1st week of postnatal period and the adult animals was opened, they were immediately dissected for liver tissue, and fixed in 10% formalin for 48 hours. The sample became ready for histological preparation of fixation, dehydration, clearing, paraffin embedding and sectioning dewaxing, and hydration. According to (Bancroft et al., 2013). Newborn and late pregnancy group livers were dissected and collected separately. Plastic Section was processed using araldit and then the 0.5 .micron section was stained with Nuclear differentiation special stain (NSD) it`s composed of two solutions: Solution A) Basic fuchsine& methanol. Solution B) Prepared by mixing equal volumes of: Azure II, Methylene blue, Na2Co3&Absolute methanol alcohol.This staining technique was based on modification and a combination of methods suggested by (Alhabib,2000) Immunohistochemistry (IHC) technique is used for the detection of a specific antibody bound to an antigen in tissue sections. Primary antibody: In this study Rabbit monoclonal Anti-CD34 antibody [EP373Y] will use.Detection kits: ab236466_mouse and rabbit-specific HRP/DAB IHC detection kit/ micro/polymer (Abcam).

Result

Plastic Semi-thin section of 0.5 microns stained with NDS was examined for the identification of the different types of cells in the liver depending on their morphological appearance**.**

Cells of liver parenchyma in mid-gestational age (day 12-14) showed small cells arranged in the form of irregular cords in between blood sinuses. A closer look at higher magnification showed a view of small hepatoblasts with few hepatocytes in between irregular cords, a further closer look showed details of different types of cells including hepatoblast gaining maturity hepatocytes and few blood cells, yet some cells showed signs of cell division, figure (1) & figure (2) Towards the beginning late stages of embryogenesis, the number of hepatocytes overcomes the blood cells with increased maturity of hepatocytes . Between hepatocytes, & adjacent to blood sinusoids elongated cells were seen frequently, Between the parenchymatous cells, a unique cell drove attention by the specific appearance it was found in between the cells of parenchyma not in the connective tissue nearby, blood sinusoid with an elongated nucleus and extended cytoplasmic process (telopodes) property identical to prescribed Telocyte, these cells showed a persistent appearance surrounding blood sinusoid, although it was seeing some time away from blood sinusoids. figure (3) &

figure (4) Hepatocytes by the end of the age of late gestational stage showed well-recognized cords of hepatocytes in we'll arrange (1-2) thickness cord with the beginning appraisal of bi-nucleated hepatocytes, figure (5). A well-organized sinusoidal network between these hepatocytes cord was seen in the late 3rd week of embryogenesis.

Thin section allowed us to notice certain structural criteria which could not be seen in general H&E sections, the most striking of this was the clear appearance of bile canaliculi in between hepatocytes which appeared as a thickening of one side of the adjacent hepatocytes and long telopodes of telocyte. In the newborn examination, the field showed a classical configuration of both hepatocyte and blood sinuses the frequency of appearance of cells thought to have Telocyte properties was diminished figure, and multiple bile canaliculi well easily identified, figure (6). In adults, typical hepatic lobulation was seen with its cords arrangement, and blood sinusoids were seen in between hepatocytes cords, some cells indicated thinking of the cell's membrane in a certain location forming the bile canaliculi and others the space of dis. Regarding Telocyte they were seen in between hepatocytes less frequently as elongated compressed cells with a long cytoplasmic process.

The expression of cd34 reactivity in different age groups where assists both objectively and statistically. Comparison between groups enrolled in this study showed an expression reactivity ranged from a very faint brown color to a dark black brown coloration objectively The control group intensity of objective examination was mainly seen around blood vessels with a dark brown coloration additionally blood sinusoids showed extreme reactivity around blood sinusoids figure (7 A). Assessment of these findings in the control group using Aperio software showed strong positive intensity around blood vessels and weakly positive reactivity around blood sinusoids, and sum time there is no reactivity in blood sinusoids at all. Comparison between the 2nd-week group & control group showed that the reactivity is mainly confined around hepatocytes in a network-like appearance surrounding hepatocyte, which properly represented the telopodes of TCs A quantitative assessment for the intensity of reactivity for CD34 antibodies was performed using the Aperio algorithms software program & the reflection of this reactivity showed different degrees of strong positive reaction surrounding hepatocytes variety from light to brownish color figure (7 B). The highly intense reactivity of the CD34 antibody was easily identified objectively in 3rd week group, the reaction seems to be distributed all over the region in the liver with a dark brown coloration, the quantitative assessment of the reactivity by Aperio showed different positivity expression, the average of positivity reflection was between yellow to dark orange with few focuses of red brawn coloration figure (8A). The newborn age group was examined both objectively and statistically. The picture differs in this group where it was a notification marked absence of reaction except for the area around the blood vessels which showed well brownish demarcation. The picture of the newborn was similar to having been seen in the control group, still sinusoid showed a very weak yellow reactivity figure (8B)

Sharpie –wilk test of Normality applied to the 4 groups enrolled in this study showed a highly significant difference with a P value of <0.001. (Table 1& Figure 9) The number of each group is 33, P value by the Kruskal-Wallis Test depending on the Shapiro-Wilk test of normality.

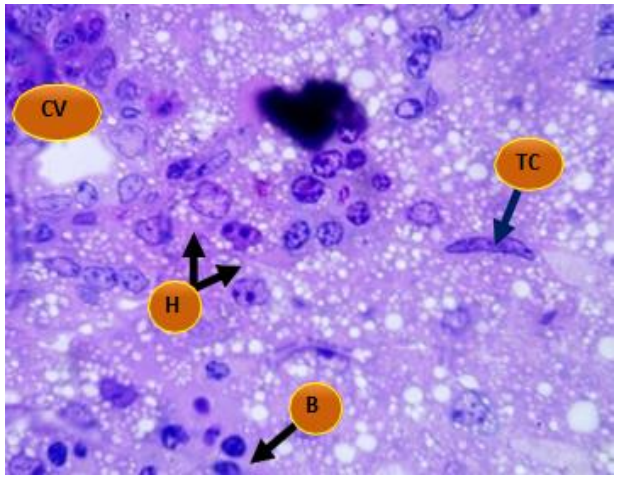

Figure 1: a higher magnification of the2nd week field howing the irregular distribution of non-parenchymal ells around the central vein (CV) with hepatoblast (B), hepatocyte (H), and telocyte(TC). NDS X40

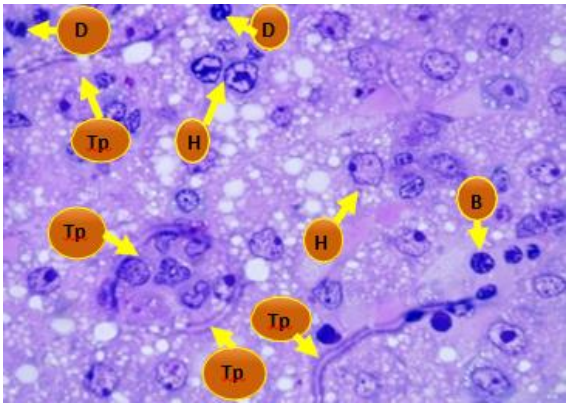

Figure 2: 2nd-week group showing hepatocyte (H), hepatoblast (B), telopodes (TP), and cells undergoing division (D). NDS X40

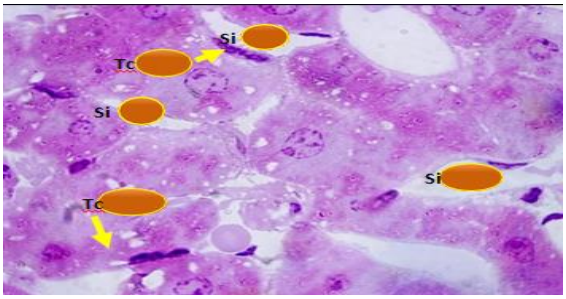

Figure 3: Section in the liver 3rd week showing multiple Hepatocytes between which blood sinusoids (Si) are located, elongated cells attached to hepatocytes seen frequently properly represented telocyte (Tc). NDS X100

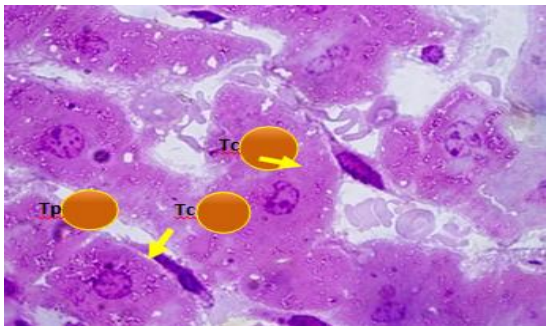

Figure 4: Section of the liver 3rd week showing clearly the appearance of telocyte (Tc) between hepatocytes with their long telopodes (Tp) adjacent to the walls of hepatocytes. NDS X100

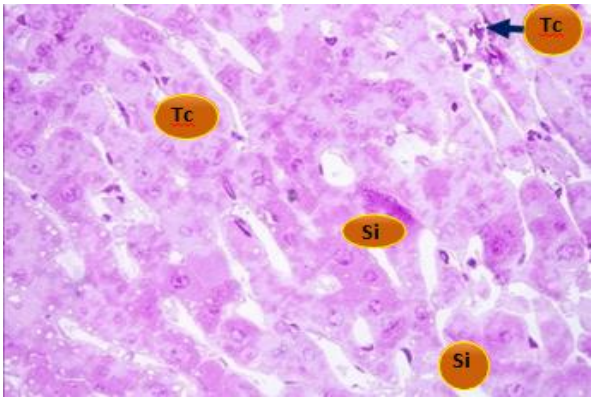

Figure 5:in 3rd week Hepatocyte cords arranged in one or two cell cords with blood sinusoids (Si) & telocytes (Tc). NDS, X10

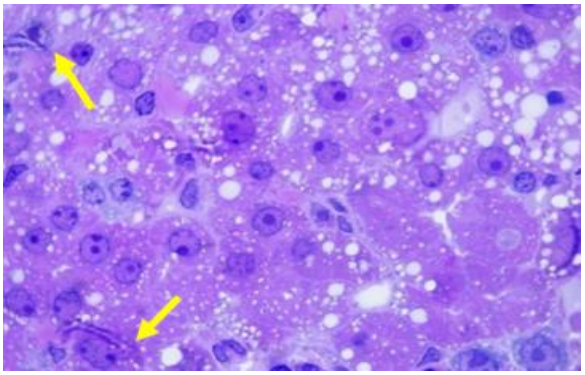

Figure 6: Section in the newborn liver showing fewer appearance of TCs (→) between their cells, NDS X 40

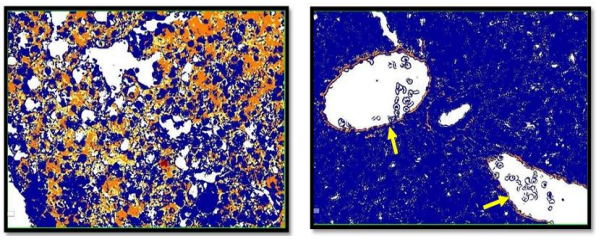

Figure 7: A) section in the liver of the 3rd-week group shows: The high intensity of reactivity can be seen objectively as dark brown coloration all over the field. The high intensity reflected by Aperio is a deep dark orange color
B) section of the newborn liver showing: Blood vessels and cords, with the intense brownish expression of CD34 were mainly located around blood vessels assisted by Aperio with orang coloration around blood vessels (→)

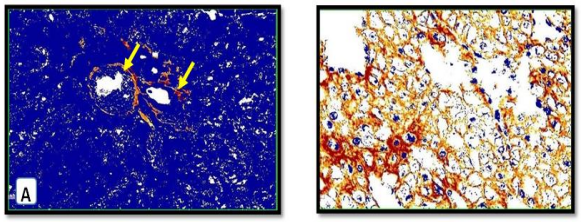

Figure 8: A) Section in the liver of the control group at the portal area shows The intensity of the reaction is mainly confined around the blood vessels with a no-nonsense reaction between hepatocyte cords (→). The section assists by using Aperio proofed that the reaction is mainly around blood vessels' appearance as dark orange coloration (→)
B): Section in the 2nd-week group showing:A network-like appearance of CD34 antibody reactivity around hepatocyte & blood vessels.Reflects CD34 reactivity by Aperio in the 2nd-week group represented by positivity color ranging between yellow to dark orange

Table 1: Comparison of positivity between each pair of the four groups:

Group	Median (Range)	Mean±SE	P value
2nd week	358725 (81455-970264)	465759.52±59327.587	<0.001
3rd week	492218 (223038-976378)	515307.55±38417.314	
Newborn	72909 (11033-464207)	114153.67±20193.471	
Control	113553 (10953-638891)	178127.12±29004.847	

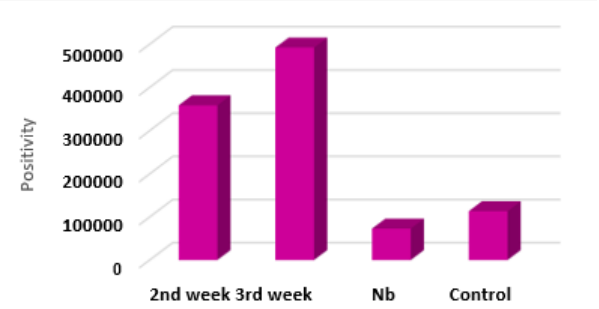

Figure 9: Comparison of positivity between each pair of the four groups.

Discussion

Telocytes (TCs) are a distinct type of interstitial cell that was first identified by Popescu's group in 2005 and was officially named in 2010. TCs exist in various organs and tissues and are characterized by small cell bodies and one to five extremely long (ten to one hundred µm) and thin (less than 0.2 µm) processes called telopodes (Bei et al., 2015). In various organs, including the intestine, skeletal muscle, heart, lung, and skin, TCs appear to constitute a component of stem cell (SC) niches. In fact, significant data suggests that TCs may regulate the activity of tissue-resident SCs and influence the SC niche habitat, so supporting tissue renewal and repair (Rosa et al., 2021). In a study done in 2017 by Soliaman, the author found that telocytes formed homocellular and heterocellular contacts. Heterocellular contact was established with the myogenic cells during various differential stages. They were connected with skeletal precursors, myotubes, nascent myotubes, and fusing myoblasts. This result speculated that telocytes might act as the main player in myogenesis. Recent research investigated telocytes in tissue regeneration and repair. A closed association of telocytes and stem or progenitor cells is identified in skeletal muscles, meninges, and choroid plexus, heart. Lung .skin liver, and blood vessels. The authors attempt to interpret the mechanism of telocytes and stem cell interaction. The structural evidence support that telocytes control the stem cell microenvironment through direct contact and the paracrine pathway (Soliman, 2017)

So regarding telocyte, in this study they were seen in the late stages of embryogenesis between hepatocytes as elongated compressed cells with a long cytoplasmic process Between the parenchymatous cells, a unique cell drove attention by the specific appearance it was found in between the cells of parenchyma not in the connective tissue nearby, blood sinusoid with an elongated nucleus and extended cytoplasmic process (telopodes) property identical to prescribed telocyte, that in agreement with Abd-Elhafeez who indicate the typical morphological features of TCs in the intestinal bulb of grass carp distinguished by that had a cell body contained the nucleus and telopodes, in light microscopic examination used semi-thin sections stained by toluidine blue, & PAS stains (Abd-Elhafeez et al., 2020). TCs demonstrate specific direct (homocellular and heterocellular junctions) and/or indirect (chemical, paracrine/juxtacrine signaling, microvesicles and exosomes, sex hormone, and microRNAs) contacts with various surrounding cells. Homocellular junctions allow TCs to keep an architecture of tissue, generating 3D (three-dimensional) networks. Moreover, they contain elements of the cytoskeleton such as microfilaments, microtubules, and Vimentin (Cretoiu et al., 2013). Also, Soliman, identified TCs in the developing skeletal muscles Using the H&E Grimelius silver nitrate procedure and Marsland silver stain, they served as a significant cellular componentIn the interstitial elements, TCs in embryos showed the characteristic morphological features of adult TCs, which contained a cell body as well as differentiated podomeres and podoms (Soliman, 2017a)

In this study in the adult group, (TCs) cells showed a persistent appearance surrounding blood sinusoids although it was seeing some time away from blood sinusoids. the same found by Soliman, TCs were located in the surroundings of blood capillaries, major vessels, vascular plexus, and small vessels. They have an effect on angiogenesis by establishing direct contact with blood vessels and releasing secretory vesicles for paracrine singling. And Faussone found TCs establish functional connections with a wide range of adjacent cells by using vesicles/exosomes and cell- to-cell contacts. In the various layers of the digestive wall (Soliman, 2021; Faussone & Gherghiceanu, 2016).

Until telocytes, previously identified as interstitial Cajal-like cells, are typically observed in the pancreas, liver, gallbladder, and hepatobiliary tree, which are glands associated with the digestive tract, they are suggested as a potential origin of extra gastrointestinal stromal tumors (eGISTs) that are observed in these organs. (Padhi&Nayak,2016). Our research previously identified the existence of TCs in the liver and suggested further possible functions for TCs in liver regeneration and proliferation following hepatectomy, possibly by activation of the hepatic progenitor cells in the liver by using double labeling immunofluorescence methods (CD34/PDGFR-a, CD34/PDGFR-ß, and CD34/Vimentin) for TCs identified and show a close association between TCs and hepatocytes and stem cells essentially in hepatocyte proliferation and liver stem cell differentiation (Zhao et al.,2014)

Immunohistochemical staining of CD117 revealed that TCs were mainly located in the dermis of the human scalp, surrounding the HFs and sweat glands. Under TEM, TCs were seen and confirmed by their special morphological features. These cells were spindle-shaped, had small cell bodies and long thin processes, and surrounded stem cell clusters in the bulge region of HFs. These results demonstrate that TCs in the human scalp were positive for CD34

and CD117, and their strategic positioning

surrounding stem cells suggests their possible involvement in local regeneration, remodeling, and homeostasis of the skin (Wang et al., 2020).

In this study significant variations of Anti CD34-antibody that reflect the specific periods of liver reaction telocyte on the prenatal developments exposed significantly, there was an increase in anti-CD34 antibody activity in the 2nd week of gestation that suggested to increase of telocyte in this stage of liver formation due to the TCs roles during embryogenesis of the liver and another organ. Soliman showed that during the embryonic development of the spinal ganglia, TCs formed homo-and heterocellular contacts with the neuroblasts, and satellite capsular cells, and concluded that TCs may act as a major player in regulating cell differentiation and cell death during embryogenesis (Soliman, 2017b)

In this study, the raised in Immunohistochemically expression of the Anti CD34 Antibody in the liver embryonic tissue section during 3rd week of the prenatal period reflect the activity of TCs and proves its role in cell maturation and differentiation of hepatoblasts gives rise mature hepatocytes and investigated other roles such as in the angiogenic formation in this period of gestation it has been shown by Zheng, who investigate the role of telocyte in regulate angiogenesis and the proliferation of endothelial cells by secret VEGF and endothelial growth factor (Zheng et al., 2014) A high significant difference was recorded in this study when a comparison was done between the prenatal period and postnatal period, there was less activity of Immunohistochemical reactivity labeled with CD34 Antibody in the newborn & adult control group, than in the 2nd & 3rd -week gestation group.

Wang suggested telocyte induces hepatocyte proliferation and liver growth during the pregnancy stage when indicating Increased hepatocyte proliferation was observed at 2nd & the 3rd week in adult pregnancy rat liver related with a significant rise in the number of TCs in this period was seen that reach two peaks at days 4.5 and 14.5 when used CD43 and PDGFR as a double immunolabeled (Wang et al., 2015)

Conclusions

It was concluded from this study that the telocytes were mainly identified depending on the long telopodes which extended between cells for a long distance & this could be probably explained by the indicated fact that telocytes establish functional connections with a wide range of adjacent cells due to their direct effect on angiogenesis & endothelial cell and may act as a major player in regulating cell differentiation and cell death during embryogenesis.

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