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Original Paper

Telocytes in Pregnancy-Induced Physiological Liver Growth

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Key Words
Telocytes • Liver growth • Pregnancy • Hepatocytes • Liver regeneration

Abstract
Background/Aims: We previously documented the presence of Telocytes (TCs) in liver and further indicated the potential roles of TCs in liver regeneration after hepatectomy. Pregnancy-induced liver growth, other than liver regeneration after hepatectomy, is a physiological hepatic adaption to meet the enhanced nutritional and metabolic demands. However, the possible roles of TCs in pregnancy-induced liver growth remain unknown. ***Methods:*** Pregnant mice were sacrificed at different time points (pregnancy day 0.5, 4.5, 8.5, 10.5, 12.5, 14.5, 16.5, and 18.5). The liver weight was used to evaluate the liver growth during pregnancy. Hepatocytes proliferation was determined by albumin and 5-ethynyl-2'- deoxyuridine (EdU) double immunostaining while TCs were counted by double immunolabeling for CD34/PDGFR-α. ***Results:*** Pregnancy-induced liver growth was preceded by increased proliferation of hepatocytes at pregnancy day 4.5, 8.5, 14.5 and 16.5. Furthermore, the number of TCs in liver detected by double immunolabeling for CD34/PDGFR-α was significantly increased at pregnancy day 4.5 and day 14.5, that was coincident with the occurrence of two peaks of hepatic cell proliferation during pregnancy. ***Conclusion:*** Our results suggest a possible relationship between TCs and hepatocyte proliferation in pregnancy-induced liver growth.

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Introduction

Liver has an extraordinary ability to regenerate after injury and surgical resection, principally mediated by the proliferation of remaining hepatocytes and the differentiation of liver stem cells [1–3]. However, liver regenerative capacity can be grievously altered upon severe and chronic liver injury [4–6], and is negatively affected by aging [7–9]. Other than liver regeneration after injury and resection, pregnancy-induced liver growth is a physiological hepatic adaption to meet the enhanced nutritional and metabolic demands for developing placenta and fetus [10–13]. It has previously been shown that pregnancy is able to increase liver regenerative capacity in aged liver, suggesting its potential therapeutic value in liver failure [14]. However, the mechanisms underlying maternal hepatic adaptions to pregnancy are poorly elucidated.

Telocytes (TCs), a novel type of interstitial cell population firstly identified by Popescu's group, are characterized by a small cell body and extremely long prolongations named telopodes (Tps) with alternating thin segments (podomers) and dilated segments (podoms) [15] (see http://www.telocytes.com). FIB-SEM tomography, the most advanced and powerful technique to visualize cells confirmed the existence of TCs [16]. Since their identification in 2010, TCs have been found in various mammalian organs and tissues and contribute to form a complex interstitial network for the maintenance of tissue homeostasis, such as heart [17-21], lung [22-24], placenta [25], pancreas [26, 27], skin [28, 29], skeletal muscle [30-32], uterus [33-38], urinary system [39-41], and others [42-55]. Furthermore, increasing evidence has demonstrated the presence of TCs within stem cell niches [23, 29, 31, 49, 56, 57] and indicated the potential involvement of TCs in tissue regeneration/repair after injury [32, 38, 58-64]. Our group has recently identified the presence of TCs in liver [54], and further demonstrated a close relationship between TCs and the cells (hepatocytes/stem cells) essentially involved in liver regeneration using a murine model of partial hepatectomy [65]. The aim of the present study was to likewise investigate the possible roles of TCs in hepatic adaptions to pregnancy.

Materials and Methods

Animals

Eight-week-old female C57BL/6 mice, purchased from Shanghai SLAC Laboratory Animal Center, were maintained in a temperature-controlled room on a 12 h light/dark cycle, with *ad libitum* access to food and water. Mice were mated and the presence of a copulatory plug in the vagina was considered as gestation day 0.5. Pregnant mice were then designed to be sacrificed at different time points (pregnancy day 0.5, 4.5, 8.5, 10.5, 12.5, 14.5, 16.5, and 18.5) (n=8 per group). The liver weight was measured to evaluate liver growth during pregnancy. Frozen liver sections were used for immunofluroscent staining. This study was approved by the local ethical committees and all animal experiments were conducted under the guidelines on the use and care of laboratory animals for biomedical research published by National Institutes of Health (No. 85-23, revised 1996).

EdU and Albumin double labelled staining

Mice were intraperitoneally injetected with 50 mg/kg of 5-ethynyl-2'-deoxyuridine (EdU) 1 h before sacrificed. The frozen sections (6 um) were fixed with 4% paraformaldehyde for 30 min after washed with PBS, and then incubated with Albumin primary antibody (1:100, BS6520, Bioworld) in diluted by PBS containing 0.25% Triton X-100 overnight at 4°C. After that, sections were incubated with anti-rabbit Rhodamine-conjugated secondary antibody (1:200, Sc-362262, Santa Cruz) for 1 h at room temperature. After wash with PBS, staining with anti-EdU working solution was performed at room temperature for 30 min according to the manual of a EdU detection kit (Click-iT Plus EdU Alexa Fluor 647 Imaging Kit, Life Technology). Finnally, sections were stained with DAPI (Prolong® Gold, Life Technology) and observed under a confocal laser scanning microscope (LSM 710, Carl Zeiss MicroImaging GmbH). The results were expressed as EdU and Albumin double positive cell number per mm^2.

Immunofluorescent staining for CD34/PDGFR-α

Double immunolabeling for CD34/PDGFR-α, considered as the specific markers for TCs, was used for detection of TCs in the present study [66]. Briefly, 6 μm-thick frozen liver sections were fixed in 4% paraformaldehyde for 15 min, washed with PBS for three times, pre-incubated in PBS supplemented with 10% goat serum for 1 h, and then incubated overnight at 4°C with rabbit polyclonal anti-PDGFR-α (Abcam, ab61219) and rat monoclonal anti-CD34 (Abcam, ab8158) primary antibodies diluted by 1:100 in PBS with 0.25% Triton X-100. After that, sections were exposed for 1 h to goat anti-rat labeled with FITC (Santa Cruz, sc-2011) and goat anti-rabbit labeled with rhodamine (Santa Cruz, sc-362262) secondary antibodies diluted by 1:200 in the same buffer. Finally, sections were stained with DAPI (ProLong® Gold, Life technology). The images were analyzed with confocal laser scanning microscope (LSM 710, Carl Zeiss MicroImaging GmbH, Germany) under an amplification of 400×.

EdU and CD34 double labelled staining

EdU and CD34 double labelled staining was used to determine the proliferative TCs. In brief, 6 μm-thick frozen liver sections were fixed in 4% paraformaldehyde for 15 min, washed with PBS for three times, pre-incubated in PBS supplemented with 10% goat serum for 1 h, and then incubated overnight at 4°C with rat monoclonal anti-CD34 (Abcam, ab8158) primary antibodies diluted by 1:100 in PBS with 0.25% Triton X-100. After that, sections were exposed for 1 h to goat anti-rat labeled with FITC (Santa Cruz, sc-2011) secondary antibodies diluted by 1:200 in the same buffer. After wash with PBS, staining with anti-EdU working solution was performed at room temperature for 30 min according to the manual of a EdU detection kit (Click-iT Plus EdU Alexa Fluor 647 Imaging Kit, Life Technology). Finally, sections were stained with DAPI (ProLong® Gold, Life technology). The images were analyzed with confocal laser scanning microscope (LSM 710, Carl Zeiss MicroImaging GmbH, Germany) under an amplification of 400×.

Statistical analysis

Data are expressed as mean ± SEM. All analyses were performed using SPSS 19.0. Statistical significance was determined with one-way ANOVA test followed by two-tailed Student's *t* test. Significance is defined as *P*-value less than 0.05.

Results

Liver weight continued to increase which appeared significant from pregnancy day 10.5 as compared to day 0.5 in pregnant mice (Fig. 1), indicating that pregnancy induces liver growth.

EdU and Albumin double immunostaining was conducted to investigate the proliferative effect of pregnancy-induced liver growth. As compared to pregnancy day 0.5, EdU positive hepatocytes number per mm^2 of liver tissues was significantly increased in early stage (day 4.5 and 8.5) and late stage (day 14.5 and 16.5) of pregnancy (Fig. 2).

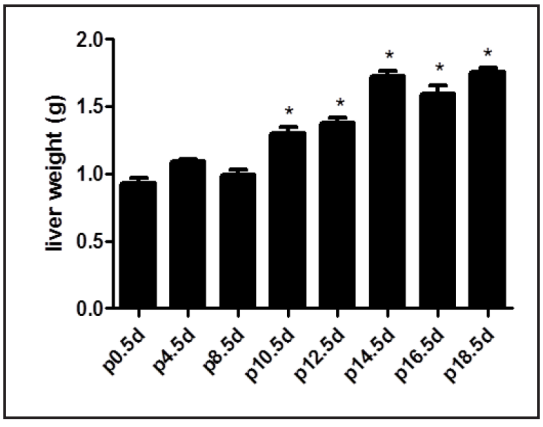

Fig. 1. Liver growth during pregnancy. Liver weight during pregnancy. *, $p<0.05$ vs. pregnancy day 0.5.

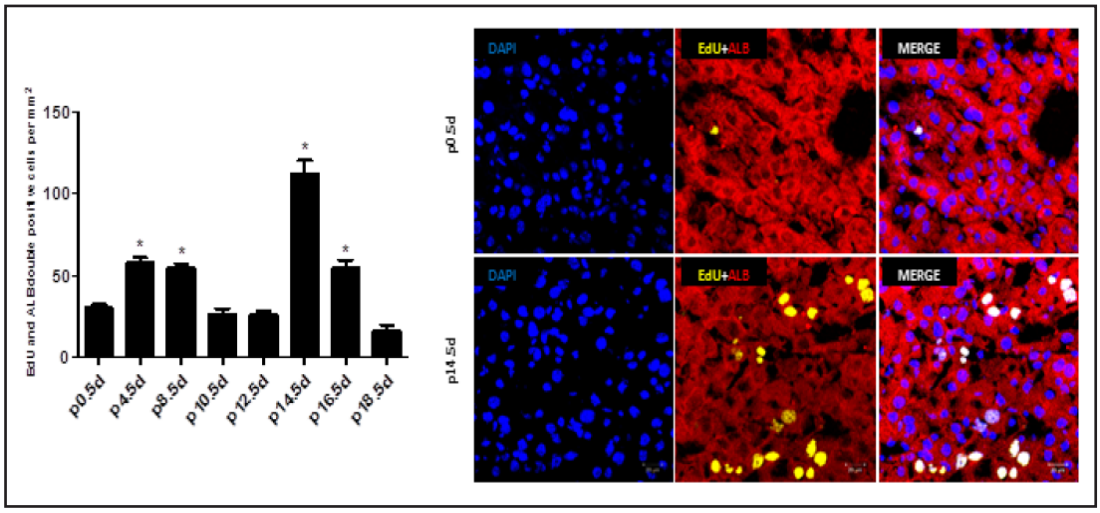

Fig. 2. Pregnancy-induced liver growth preceded via increased hepatocytes proliferation. Quantitative analysis of Albumin and 5-ethynyl-2'- deoxyuridine (EdU) double positive cells in liver tissues (left panel) showed significant increase of EdU positive hepatocytes number per mm^2 in early stage (day 4.5 and 8.5) and late stage (day 14.5 and 16.5) of pregnancy. Representative images of Albumin (red) and EdU (yellow) double positive cells, counterstained with DAPI (blue) for nuclei at pregnancy day 0.5 and 14.5 were shown in the right panel. Original magnification 400 ×; Scale bar = 20 μm. *,P<0.05 vs. pregnancy day 0.5.

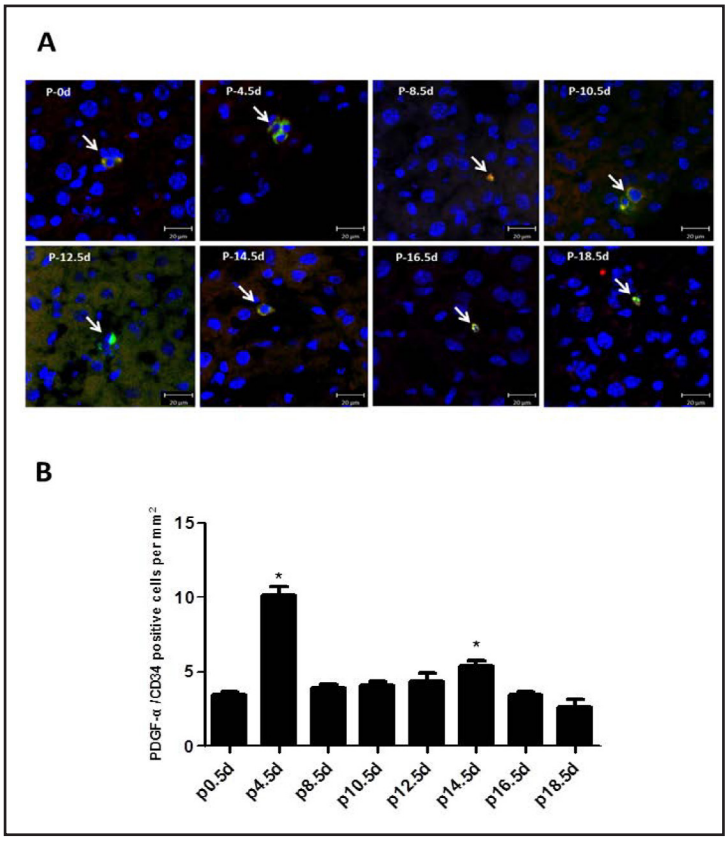

Fig. 3. Detection for TCs in liver by double immunolabeling for CD34/PDGFR-α. A Representative images of CD34/PDGFR-α double immunolabeling in pregnant liver. CD34 (green) and PDGFR-α (red) double positive cells were pointed with arrows. Nuclei were counterstained with DAPI (blue). Original magnification 400 ×; Scale bar = 20 μm. B Quantitative analysis of CD34/PDGFR-α positive cell number per mm^2 in pregnant liver. *, p<0.05 vs. pregnancy day 0.5.

As labeled by double immunofluorescent staining for CD34 and PDGFR-α, the number of CD34/PDGFR-α positive cells (TCs) per mm^2 of liver tissues was significantly increased at pregnancy day 4.5 and 14.5 (Fig. 3A and B), which was in accordance with the time points when high level of hepatocytes proliferation rate occurred during pregnancy. However, as

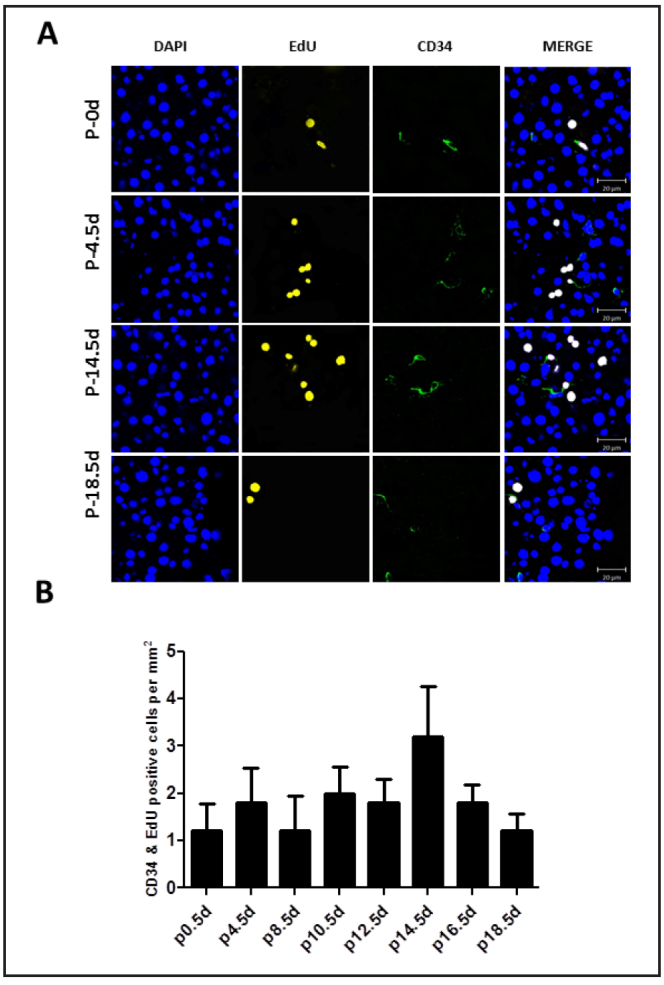

Fig. 4. Detection for proliferative TCs in liver by immunolabeling for CD34/EdU. A Representative images of CD34/EdU immunolabeling in pregnant liver. Original magnification 400 ×; Scale bar = 20 μm. B Quantitative analysis of CD34/EdU positive cell number per mm^2 in pregnant liver.

indicated by immunofluorescent staining for CD34 and EdU (Fig. 4), we did not observe significant difference among the time points we have checked, which might be due to the fact that the rate of proliferative TCs was extremely low or proliferative endothelial cells might cover up the true changes of proliferative TCs.

Discussion

The present study shows that pregnancy-induced liver growth preceded via increased proliferation of hepatocytes. Furthermore, the number of TCs in liver detected by double immunolabeling for CD34/PDGFR-α was significantly increased at pregnancy day 4.5 and day 14.5, that was coincident with the occurrence of two peaks of hepatocytes proliferation during pregnancy. These results suggest the potential involvements of TCs in hepatic proliferative adaptions to pregnancy.

To date, the mechanisms underlying hepatic adaptions to pregnancy are largely unknown [10, 11, 13, 14, 67-69]. In the present study, we demonstrated two peaks of hepatocytes proliferation occurring at early stages and late stages of pregnancy as shown by EdU and Albumin double immunostaining. The increased proliferation of hepatocytes related to pregnancy has previously been documented [13, 14, 67, 69], while the occurrence of two proliferative peaks of hepatocytes during pregnancy in the present study was firstly reported here. We hypothesized that the possible reasons may be related to different species (rat vs. mouse) [13], ages (old vs. young) [14], and animal models (pregnancy vs. ovariectomy or pseudopregnancy) [14, 67] applied in our study and in others. In addition, the metabolic

and hormonal mechanisms underlying hepatocyte proliferation during pregnancy need to be further explored.

Previously, our group documented the presence of TCs in liver and further indicated the potential roles of TCs in liver regeneration after hepatectomy, probably by influencing hepatocyte proliferation and/or liver stem cell differentiation [65]. In the present study, we further demonstrated the increased number of CD34/PDGFR-α positive TCs in pregnant liver at the same time points (pregnancy day 4.5 and day 14.5) when the two proliferative peaks of hepatocytes appeared, suggesting a possible relationship between TCs and hepatocytes proliferation in pregnancy-induced liver growth. Increasing evidence has shown that TCs are critically implicated in tissue regeneration/repair by forming a complicated network with tissue/organ-specific cells, immunoreactive cells, other interstitial cells and stem cells, and thus actively contribute to intercellular signaling coordination either by minute intercellular junctions or by paracrine effect via ectovesicles [23, 29, 30, 56, 57, 59, 70]. However, the exact mechanisms how TCs might affect the proliferative capacity of hepatocytes in pregnancy-induced liver growth remain to be further studied.

A major limitation of the present study is that the data presented here does not fully demonstrated a functional relation between TCs and hepatocyte proliferation in pregnancy-induced liver growth. We have also conducted CD34 plus EdU immunostaining, however, no significant difference was observed among the time points we had checked. We speculated that this was due to the fact that the rate of proliferative TCs was extremely low because pregnancy-induced physiological liver growth was a weak physiological stimuli. Besides that, as CD34 is also a marker for endothelial cells, thus proliferative endothelial cells might cover up the true changes of proliferative TCs. It would be interesting to check the the rate of proliferative TCs using CD34/PDGFR-α/EdU three immunostainings in other liver regeneration models such as partial hepatectomy (PH) models. Nevertheless, considering the fact that pregnancy-induced liver growth preceded via increased proliferation of hepatocytes at pregnancy day 4.5, 8.5, 14.5 and 16.5 while the number of TCs in liver was significantly increased at pregnancy day 4.5 and day 14.5, we think that TCs proliferate first (or at least at the same time) compared with hepatocytes and therefore a possible relationship between TCs and hepatocyte proliferation in pregnancy-induced liver growth might exist.

In conclusion, the present study demonstrates an increase of CD34/PDGFR-α positive TCs in pregnant liver accompanied by high level of hepatocyte proliferation. Considering that liver regeneration capacity is usually far from ideal in certain circumstances like severe liver injury or surgical resection, understanding how TCs take effect in pregnancy-induced physiological liver growth might raise bright prospect for the treatment of liver failure.

Disclosure Statement

The authors declare there are no conflicts of interest.

Acknowledgments

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