



Histogenesis of the rabbit liver (pars hepatica) with particular reference to the portal area

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Abstract

Rabbits are small mammals used as standard lab animals in biomedical research. The liver is the largest internal organ, providing essential metabolic, exocrine, and endocrine functions. The present study was performed on rabbit embryos and fetuses at different gestational periods and neonatal kittens to find out the histological structure of the liver. Histogenesis of the liver was performed by using different histological stains, Harris's H and E and Masson's trichrome. The liver bud was developed around the 10th day of gestation from the caudo-ventral part of the foregut. In comparison, the hepatoblasts developed at the 12th day of gestation. Then, the liver increased in size, and cellular differentiation occurred throughout the entire length of the gestation period. The hepatic parenchymal cells, central vein, and hematopoietic cells were studied for their developmental sequences. The portal area differentiation was the focus of our study. This study clarified that this area was essential for detecting mesenchymal stem cell markers through immunohistochemistry.

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Introduction

Rabbits (*Oryctolagus-Cuniculus*) are small mammals in the family Leporidae order Lagomorpha found in several parts of the world. They are very docile, non-aggressive, and easy to be handled and observed. Rabbits have short vital cycles (gestation, lactation, and puberty) (1). Rabbits are phylogenetically closer to primates than rodents and are standard laboratory animals in biomedical research. The rabbits are animal models for various human diseases (2). The liver is the largest internal organ, providing essential metabolic, exocrine, and endocrine functions (3,4). Hepatocytes are the primary cell type in the liver, accounting for 70% of the mass of the adult organ. Hepatocytes, along with biliary epithelial cells, were of endodermal origin. At the same time, the stromal cells, stellate cells, Küpffer cells, and blood vessels were of mesodermal origin. The hepatoblasts proliferated on the 12th day of embryonic life in domestic rabbits, and mitotic division occurred. At this stage,

the primordial hepatoblasts were arranged as short hepatic cords (4). The liver developed as a hollow ventral diverticulum from the caudal region of the foregut. This diverticulum is divided into the hepatic cranial part (Pars hepatica), which forms hepatic parenchyma, and the caudal cystic part (Pars cystic), which forms the gall bladder. The endodermal epithelial cells of the hepatic portion proliferated and formed Figures of hepatocytes. Liver cords differentiated into the parenchyma (liver cells) and formed the lining of the biliary ducts (5-8). The relatively large endodermal cells are differentiated into hepatocytes and arranged in rods or plates with intervening sinusoids. Later, the hepatocyte Figures became oriented radially around the central vein. Even later, the connective tissue became organized around the lobules. The liver proliferated and expanded to occupy most of the abdominal cavity, creating the liver prominence on the outside of the embryo. Hence, with the caudal growth of the liver, the organ gradually became almost detached from the Septum transversum.

During its growth, the liver was of great significance as a blood-forming structure (7). After the specification of the liver, hematopoietic cells moved into this organ and emitted signals, which induced the maturation of hepatocytes (9).

A superior understanding of liver development would provide effective treatment for liver diseases. So, this work aimed to explain the liver histogenesis in rabbits to understand fetal and neonatal liver histology better.

Materials and methods

The present study applied on ten white New Zealand pregnant women (1.5-3 years old, and 2-4.5 kg, weight). They were collected from the Faculty of Veterinary Medicine and Faculty of Agriculture, Zagazig University farms. Thirty embryos and fetuses at different periods and 10 neonatal kittens were used for histogenesis and embryogenesis of the liver. The pregnant does were anesthetized with an intramuscular injection of 35 mg/kg ketamine Hcl (KETALARKETALAR, 100 mg/ml, Pfizer, NY) and five mg/kg xylazine (Xylaject, 20 mg/ml, ADWIAADWIA, Egypt) according to Enoka (10) and Mahmood (11). For the histological study, the following steps were applied on the 10th, 12th, 14th, 16th, 18th, 20th, 22nd, 26th, and 30th day's old embryos and fetuses and neonatal kittens. After the laparotomy of pregnant does, the fetuses were pulled out from the fetal sacs. Also, the liver samples were extracted from the neonatal kittens' bodies. Then, they were fixed with 10% neutral buffered formalin for 24-72 hours and Bouin's solution for 6-8 hours, followed by 70% ethyl alcohol (12). All embryos, fetuses, and neonatal liver samples were subjected to dehydration, clearing, embedding, blocking, cutting, and staining with different stains, including Harris' H and E and Masson's trichrome stain, according to (13). The stained sections were examined with a standard light microscope (Objectives Xs 4, 10, 40) and a stereomicroscope (Objectives Xs 10, 20) and photographed with a Moticam X3 plus camera (a compact Wi-Fi camera with a resolution of four megapixels) according to Drury and Wallington (14). The CVR length of fetuses used in our study was clarified in figure 1 (15-17). The nomenclature used in this work was adopted (18-20).

Ethical approve

The research protocol was reviewed by the Institutional Animal Care and Use Committee, Zagazig University (No, ZU-IACUC/2/F/13/2021). All surgical approaches were performed under general anesthesia, and all efforts were made to minimize animal pain.

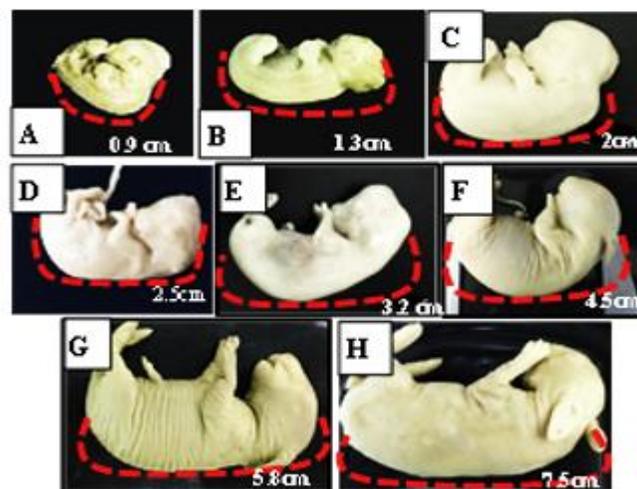


Figure 1: The CVR length of the embryos and fetuses in cm at 12th (A), 14th (B), 16th (C), 18th (D), 20th (E), 22nd (F), 26th (G), and 30th (H) days of gestation.

Results

The results revealed that the hepatic bud was developed from the ventral part of the foregut on the 10th day of embryonic life ± 0.54 cm (Figure 2). The hepatic bud invaded Septum transversum and formed from two types of cells: endodermal cells and Septum transversum mesenchymal cells. The endodermal cells of the foregut formed from cuboidal cells. They had large rounded vesicular nuclei, which showed mitotic division and pale cytoplasm. The mesenchymal tissue was undifferentiated c.t with fibroblasts and had large and intensely stained nuclei (Figure 2). The hepatic diverticulum developed on the 12th day ± 0.9 cm, and the hepatoblasts invaded Septum transversum mesenchyme (Figure 2). The hepatoblasts are arranged as irregular aggregations of hepatic masses separated by blood spaces (Figure 2). The hepatoblasts at this stage showed high mitotic division, and the liver revealed high hematopoietic activities (Figure 2). The hepatoblasts appeared as large, rounded, pyramidal cells with heterochromatic, highly vesicular nuclei. The nucleus contained multiple basophilic nucleoli with pale eosinophilic cytoplasm (Figure 2). The blood sinusoids were formed at this stage with a wide diameter (Figure 2). They contained both nucleated erythroblasts and K upffer cells. This indicated the beginning of hematopoietic activities in the liver (Figure 2). For the first time, we observed scattered K upffer cells on the margin of sinusoids in the 12th week. Megakaryoblasts were first detected at this stage and increased in number until the end of gestation (Figure 2). On the 14th day of gestation ± 1.3 cm, the size of the liver expanded considerably and inhabited a significant part of the cranial half of the abdominal cavity (Figure 2). The central vein appeared within the liver parenchyma at this stage (Figure 2). The liver, at this stage,

became the essential blood-forming organ at gestation. Hence, the hematopoietic activities increased, and most hematopoietic cells were nucleated erythroblasts. A group of hepatoblasts organized themselves in the periportal area. So, both hepatocytes and cholangioblasts originated from the hepatoblasts.

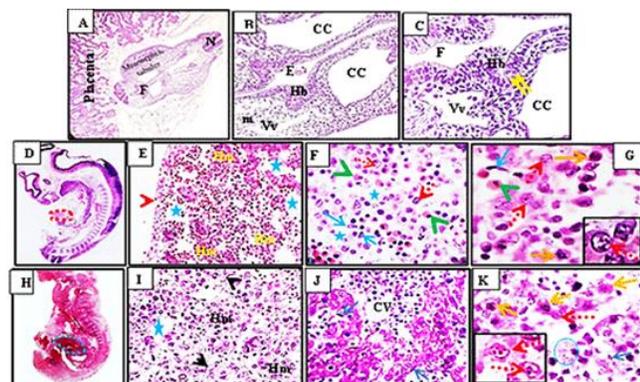


Figure 2: Histogenesis of the liver on the 10th day (A, B, and C), 12th day (D, E, F, and G), and 14th day (H, I, J, and K) of old rabbit embryos, showing vitelline veins (Vv), coelomic cavity (cc), blood spaces (blue stars), central vein (CV), hepatoblasts (dotted red arrow), mitotic division of hepatoblasts nuclei (blue circle), foregut (F), endodermal epithelium lining of foregut (double yellow arrow), nucleated erythroblasts (green arrowhead), hepatic bud (Hb), hepatic masses (Hm), mesenchyme (m), megakaryoblasts (orange arrow), endothelial lining (black arrowhead), septum transversum (red arrowhead), k upffer cells (blue arrow), H and E stain, Xs 4 (A, D, H), 10 (B, C, E, I, J), and 40 (F, G, K).

On the 16th day of gestation ± 2 cm, the hepatic parenchyma consisted of highly mitotic divided hepatoblasts and blood sinusoids filled with nucleated erythroblasts. Some erythroblasts began to extrude their nuclei on reaching maturity (Figure 3). On the 18th day of gestation ± 2.5 cm, the sinusoid endothelium became more organized as a thin layer of endothelial cells (Figure 3). At this age, a mixed population of both hepatoblasts and hepatocytes coexisted (Figure 3). The fetal hepatocytes were oval or rounded and smaller than the hepatoblasts. They had a large rounded heterochromatic nucleus with one or two nucleoli. On the 20th day of gestation ± 3.2 cm, the blood sinusoids began to converge around the central veins (Figure 3). Fatty vacuoles were detected within the hepatocyte's cytoplasm at this stage (Figure 3).

On the 22nd and 26th days ± 4.5 cm and ± 5.8 cm, respectively, the hepatic parenchyma showed crowded hepatic cell masses with intervening blood sinusoids. Central veins were randomly distributed inside the parenchyma. The hepatocytes were the primary cells accounting for the hepatic parenchyma (Figure 4).

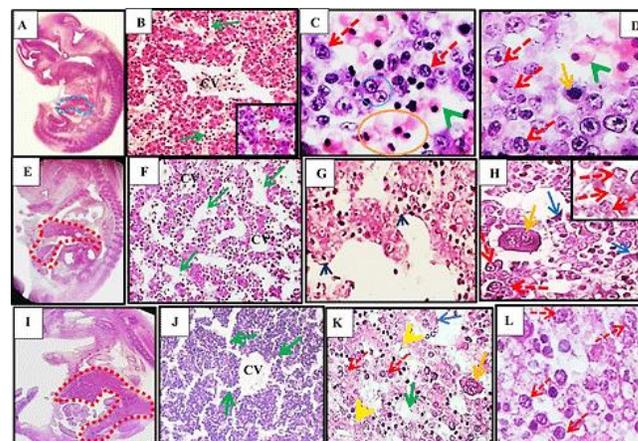


Figure 3: Histogenesis of the liver on the 16th day (A, B, C, and D), 18th day (E, F, G, and H), and 20th day's old rabbit fetuses (I, J, K, and L), showing central vein (CV), hepatoblasts (dotted red arrow), nucleated erythrocytes (green arrowhead), developing sinusoids (green arrow), megakaryoblasts (orange arrow), endothelial lining (black arrowhead), k upffer cells (blue arrow), shedding of erythrocyte nuclei (orange circle), lipid vacuoles (yellow arrowhead), H and E stain, light microscope, Xs 10 (B, F, J, K) and 40 (C, D, G, H, L) and stereo microscope, X 20 (A, E, I).

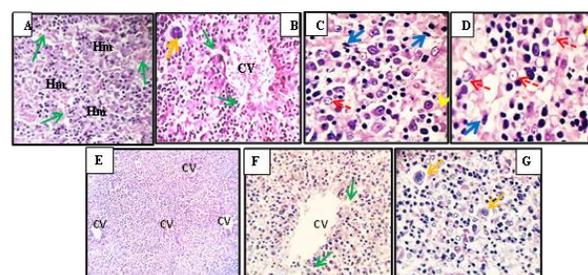


Figure 4: Histogenesis of the liver on the 22nd day (A, B, C, and D) and 26th day's old rabbit fetuses (E, F, and G), showing central vein (CV), hepatic masses (Hm), hepatocytes (dotted red arrow), developing sinusoids (green arrow), megakaryoblasts (orange arrow), Kupffer cells (blue arrow), lipid vacuoles (yellow arrowhead), H and E stain, Xs 4 (A, E), 10 (B, F) and 40 (C, D, G).

Granulopoiesis was detected in the livers of the 30th-day fetus ± 7.5 cm and neonatal kittens (Figure 5). The neonatal liver showed the same liver architecture as the adult liver tissue (Figure 5). No lobular pattern was detected at the parenchyma of the liver in rabbits, even in neonatal liver. The central veins and portal area were randomly distributed within the parenchyma (Figure 5).

On the 20th day of gestation, the intrahepatic bile duct differentiation occurred within the portal mesenchyme. We

found that the portal area on the 22nd day consisted of only a tributary of the portal vein and one or two bile ducts with a scanty amount of collagen fibers (prominent by Masson's trichrome) (Figure 6). No hepatic arteriole was detected in the portal area at this age due to delayed arterial vascular organization than the venous one. While at 26th day, the portal area began to be more organized. It consisted of a portal vein tributary, a hepatic artery branch, and one or two bile ducts. At this stage, it contained a moderate amount of collagen fibers (Figure 6). On the 30th day, we noticed increased collagen fibers in the portal area (Figure 7).

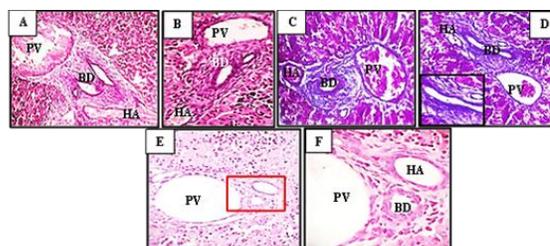


Figure 7: Histogenesis of the portal area in rabbit liver at 30th day of gestation in rabbit (A, B, C, D), and neonatal kitten (E, F), showing bile ducts (BD), hepatic artery (HA), portal vein (PV). H and E stain and Masson's trichrome stain (C, D), Xs 10 (A, B, C, D, E), and 40 (F).

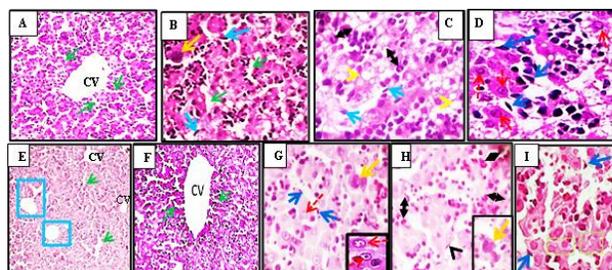


Figure 5: Histogenesis of the liver at 30th day's old rabbit fetus (A, B, C, and D) and neonatal kitten (E, F, G, H, and I), showing central vein (CV), portal area (blue square), hepatocytes (dotted red arrow), developing sinusoids (green arrow), megakaryocytes (orange arrow), Kupffer cells (blue arrow), granulocytes (black double-headed arrow), bile canaliculi (green rectangle), lipid vacuoles (yellow arrowhead), H and E stain, Xs 4 (E), 10 (A, B, C, F), and 40 (D, G, H, I).

Discussion

The present study aimed to clarify liver histogenesis at different gestational periods. The hepatic bud was developed from the foregut on the 10th day of embryonic life. On the 12th day, the hepatoblasts invaded Septum transversum mesenchyme. This result was in line with those found in the rabbit (4). In mice cleared that the liver diverticulum formed at 9th-9.5th days of gestation (21-24). However, mice observed this diverticulum on the 8.5th day (25). In humans showed it at the fourth week of fetal life, at the 18th day of gestation, and at the third week of gestation (23,26,27).

The hepatoblasts are arranged as irregular aggregations of hepatic masses. This result was similar to that in rats (28). They saw a cluster of disorganized hepatoblasts surrounded by many nucleated blood precursor cells at 12.5th-14.5th days. Also, the result of this study came to an agreement with humans (29), that the parenchymal cells are arranged as irregular clumps and cords. At the same time, in rabbits mentioned the hepatoblasts arranged as short hepatic cords (4,30). Also, in rats revealed that hepatoblasts arranged as cords invaded Septum transversum at 9.5th day, and in mice showed this result at 10th-10.5th days. The hepatoblasts at this stage showed high mitotic division, and the liver revealed high hematopoietic activities (22,31).

The hepatoblasts appeared as large rounded or oval cells with heterochromatic, highly vesicular nuclei with multiple basophilic nucleoli. This result agrees in rats and in mice in that blood sinusoids were formed at this stage with a wide diameter (22,28). This was achieved in mice on the 11.5th day (22). They contained both nucleated erythroblasts and Kupffer cells. This result was per in rabbits and in rats (28,30). Nevertheless, in humans appeared at 6th-8th weeks of gestation. Megakaryoblasts were first detected at this stage and increased in number until the end of gestation (32). However, rabbits said they appeared on the 15th day of gestation (30).

On the 14th day of gestation, the liver inhabited a significant part of the cranial half of the abdominal cavity. However, in mice mentioned this result at 10.5th-11.5th days.

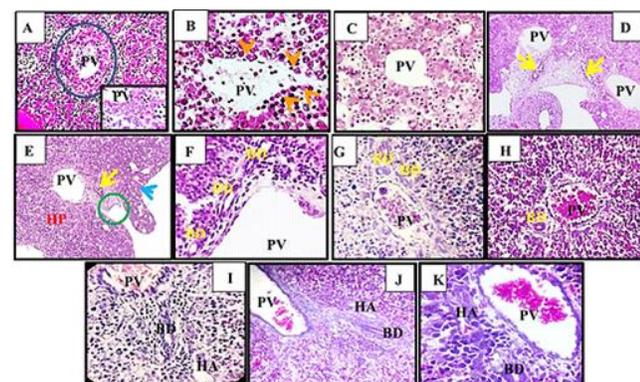


Figure 6: Histogenesis of the portal area in rabbit liver at 14th (A), 16th (B), 18th (C), 20th (D, E, F), 22th (G, H), and 26th (I, J, K) days of gestation in rabbit, showing bile ducts (BD), hepatic artery (HA), hepatic parenchyma (HP), portal vein (PV), beginning of portal area formation (green circle), developing ductal plate (blue circle, orange arrowhead), common bile ducts (yellow arrows), H and E and Masson's trichrome stains (H, J, K), Xs 4 (D, E), 10 (A, B, C, G, H, J), and 40 (F, I, K).

Intrahepatic portal vein ramification was developed (22). Mice detected this result at 11th-11.5th days (33). Central vein appeared within the liver parenchyma at this stage, while rabbits showed them first at the 18th day of gestation and humans showed it at the 17th-20th weeks of gestation (29,30).

On the 14th day, the liver became the most critical blood-forming organ at gestation. This finding concurred with results in rabbits (4), and in mice revealed this result at 10th-15th days (24). The ductal plates were formed at this stage. This result corresponded with results in rabbits, in rats, in mice, and in humans (4,25,27,31). While in mice revealed this result on the 15.5th day (33). On the 18th day of gestation, the sinusoid endothelium became more organized. However, humans revealed that the sinusoid endothelium was detected in the 6.5 cm CRL fetuses (34). On the 18th day of gestation, both hepatoblasts and hepatocytes coexisted. While rats showed this finding on the 14.5th day (28). In humans, mentioned that the fetal hepatocytes were appreciated from CRL of 6.5 cm (34). The fetal hepatocytes had a large rounded heterochromatic nucleus with one or two nucleoli. This result was found in humans, except that they said that the hepatocytes contained diffuse chromatin (34).

On the 20th day of gestation, the blood sinusoids began to converge around the central veins, while rats revealed this result on 15.5th days (28). However, humans said that the sinusoids were dilated and seen to be open into a central vein and filled with hematopoietic cells during the late gestation period (34). While, in humans said that the central vein was well formed with radiating cords of cells toward the periphery and portal triad at the 10th week of gestation (32). Fatty vacuoles were detected within the hepatocyte's cytoplasm at this stage. While in rabbits showed them at the 22nd day of embryonic life (30). These vacuoles increased until they reached their maximum at the 30th day of gestation. This result follows those mentioned in rabbits (30). On the 20th day, the intrahepatic bile duct differentiation occurred within the portal mesenchyme. Mice saw this result on the 14th day, and humans at the 10th week of gestation (26,33). At the same time, rabbits showed portal veins surrounded by one or two bile ducts on the 18th day of gestation (30). Delayed hepatic artery development than venous development (35).

Granulopoiesis was detected in the liver of the 30th-day fetus and the neonatal liver. While in rabbits said that it began to be observed on the 26th day and increased on the 30th day of gestation (30). No lobular pattern was detected at the parenchyma of the liver in rabbits, even in the neonatal liver, and hepatic cells were arranged as irregular hepatic masses. This result found in rabbits and in mice (30,36). However, in rats, in humans, and in rabbits showed that the hepatocytes were arranged as regular cords around the central vein (37-39). While in humans said that the liver architecture showed an ill-defined lobular pattern of fetal hepatocytes of 10.4 cm CRLCRL embryo with a well-defined pattern noticed only in late gestation of 28 cm

CRLCRL embryo (34). This study showed the sequential developmental stages of the developing portal area (the leading site of in-vivo localization of mesenchymal cells stem cells in liver tissue) as reported by the previous study (40). In rats showed that in 20th day's old fetus, the portal areas appeared containing branches of the portal vein, hepatic artery, lymphatic vessel, and bile duct (41).

Conclusions

This work supplied good data for hepatic parenchymal cell differentiation in different embryonic and fetal periods. This study concluded that liver histogenesis developed at the 10th day of gestation. In contrast, hepatoblasts and hematopoietic cells proliferated on the 12th day of fetal life. This study focused on the sequential developmental stages of the developing portal area. Its formation began on the 20th day of gestation and wholly developed on the 26th day.

Conflict of interest

The authors declare no conflict of interest.

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التكوين النسيجي لكبد الأرنب مع إشارة خاصة إلى منطقة الباحة البابية

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الخلاصة

تعتبر الأرانب من الثدييات الصغيرة التي يتم استخدامها كحيوانات تجارب معمليه في البحوث الطبية الحيوية. يعد الكبد أكبر عضو داخلي في الجسم، حيث يقوم بوظائف التمثيل الغذائي الأساسية بالإضافة إلى وظائف كغدة صماء. تم إجراء الدراسة الحالية على أجنة الأرانب في فترات الحمل المختلفة وكذلك عينات الكبد الخاصة بالأرانب حديثي الولادة لمعرفة التركيب النسيجي للكبد. تم دراسة تكوين النسيج الكبدي وتمييزها باستخدام صبغات نسجية مختلفة مثل ملون الهيماتوكسيلين هارس والايوسين وملون ماسون ثلاثي اللون. يتكون برعم الكبد في اليوم العاشر من الحمل، من الجزء الذنب البطني من المعى الأممي. بينما تتمايز الخلايا الكبدية في اليوم الثاني عشر من الحمل. بعد ذلك يزداد حجم الكبد والتمايز الخلوي طوال فترة الحمل. تم تركيز هذه الدراسة على الخلايا الكبدية والوريد المركزي ومنطقة البوابة الكبدية والخلايا المكونة للدم من أجل دراسة تسلسلها النمائي في مراحل مختلفة من الحمل. يعد تمايز منطقة البوابة الكبدية هو محور هذه الدراسة حيث أن هذه المنطقة هي موقعًا مهمًا لوجود الخلايا الجذعية المتعلقة بالحممة المتوسطة التي يتم الكشف عنها بواسطة الكيمياء النسيجية المناعية.