DOI 10.26724/2079-8334-2021-3-77-249-254
UDC 616.7-001-091.8]-092.9

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REPARATIVE CHONDROGENESIS AT RATS SHINBONE PROXIMAL EPIPHYPHIS TRAUMATIC INJURY WITH THE USE OF WARTON DRUGS STAR CELLS MEZENCHENICHEMIS IN THE EXPERIMENT

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The purpose of the study was to perform a comparative morphological study of damaged cartilage tissues in the conditions of applying mesenchymal stem cells of Wharton's jelly and without them. Experimental studies have confirmed the positive effect of mesenchymal stem cells of Wharton's jelly to restore the structure and function of articular cartilage after experimental traumatic injury. The results of morphological studies indicate the acceleration of reparative osteochondrogenesis with the use of mesenchymal stem cells for 1.5-2 weeks than in the control group. The influence of mesenchymal stem cells on the formation of structured timely osteogenesis without the formation of excessive early production of the ossifying matrix and dystrophic changes of chondrocytes and chondroblasts is proved. The authors argue that the results of the study pave the way for an effective and safe method of cellular regenerative medicine of the musculoskeletal system.

Key words: experimental joint trauma, morphological disorders, mesenchymal stem cells, regenerative medicine, Wharton's jelly.

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РЕПАРАТИВНИЙ ХОНДРОГЕНЕЗ ПРИ ТРАВМАТИЧНОМУ ПОШКОДЖЕНІ ПРОКСИМАЛЬНОГО ЕПІФІЗУ ВЕЛИКОГОМІЛКОВОЇ КІСТКИ ЩУРІВ З ЗАСТОСУВАННЯМ МЕЗЕНХІМАЛЬНИХ СТОВБУРОВИХ КЛІТИН ВАРТОНОВИХ ДРАГЛІВ В ЕКСПЕРИМЕНТІ

Мета дослідження – проведення порівняльного морфологічного дослідження тканин пошкодженого хряща в умовах застосування мезенхімальних стволових клітин вартонових драглів та без них. Проведені експериментальні дослідження підтвердили позитивний вплив мезенхімальних стволових клітин вартонових драглів для відновлення структури та функції суглобових хрящів після експериментального травматичного пошкодження. Результати морфологічних досліджень свідчать про прискорення репаративного остеохондрогенезу із застосуванням мезенхімальних стволових клітин на 1,5-2 тижні, ніж у контрольній групі. Доведено вплив мезенхімальних стволових клітин на формування структурованого своєчасного остеогенезу, без формування надмірної ранньої продукції осифікуючого матриксу та дистрофічних змін хондроцитів і хондробластів. Автори стверджують, що результати дослідження відкривають шлях до ефективного та безпечного методу клітинної регенераційної медицини опорно-рухового апарату.

Ключові слова: експериментальна травма суглобу, морфологічні порушення, мезенхімальні стволові клітини, регенераційна медицина, вартонов драгель.

The work is a fragment of the research project "Early diagnosis of dysplastic and neoplastic changes in pathology of the gastrointestinal tract, respiratory, urogenital and neuroendocrine systems", state regidtration No. 0117U000001.

Regenerative medicine requires a new search of stem cells (SC) influence on various damaged organs and tissues regenerative process.

Cellular material is constantly restoring in the body of an adult during life. The dead cells are replaced by newly formed cells in their apoptosis process, such self-renewal ensures the full organism vital activity throughout the animal life, depending on the compensation and adaptation processes strength and nature. The main updating material for tissues structure are stem cells. These are the multicellular organism's primary cells, capable of self-renewal by division with subsequent differentiation into specialized cell types. It is due to this that the body provides a stable level of self-healing processes.

The peculiarity of stem cell division is that it gives rise not to two daughter cells, but only to one daughter and one stem. Due to this asymmetric division, each stem cell returns to a state of rest, and the daughter proliferates, continuing to divide symmetrically a certain number of times, thus ensuring cellular homeostasis of special cells in tissues and organs. Thus, stem cells provide a constant restoration of the cellular composition of tissues throughout the body life.

In the latest 20 years, the possibilities of SC using for the structure of damaged or pathologically altered tissues restoring have been intensively studied [1, 14]. Its main task is to stimulate the restoration of lost structure and function of tissues by body stem cells activity mobilizing or the cellular material cultured outside the body in vitro additional introduction [4, 12].

The use of cell technologies is now one of the most important areas in bioengineering. A large number of injuries to the human body can be successfully treated only with the use of modern transplantology [7, 15]. However, transplants of organs, parts of them or a certain number of relevant cells are associated with a number of serious problems. These include the recipient's immune response, which must be suppressed; this, in turn, is significantly detrimental to the overall health of the patient. Transplantation of autologous material for many reasons is not always possible. The amount of material available in this case is usually limited, and the relevant procedures are complex [9, 10]. The use of mesenchymal stem cells (MSCs) in regenerative medicine can obviously be a significant breakthrough in transplantation.

For the successful use of MSCs in medicine, it is necessary to create certain conditions for the cultivation of such cells, which in the future will either be able to direct differentiation, or will be able to maintain their stem potential (depending on specific needs). For this, it is necessary to identify in detail the phenotypes subpopulations in cell culture and select the optimal cultivation conditions (quantitative and qualitative composition of the nutrient medium, substrate type, cells atmosphere surrounding gas composition etc.).

The purpose of the study was to perform damaged cartilage tissues morphological study under the conditions of mesenchymal stem cells of application.

Materials and methods. The shinbone proximal epiphyses tissues of 27 rats (Wistar line aged 1 year) after experimental trauma and intra-articular injection of MSC were examined for 7, 14 and 28 days (main group), the shinbone proximal epiphyses tissues of 15 rats injured without intra-articular MSC were studied on days 7, 14 and 28 (control group). Fibral epiphyseal fragments were fixed in 10 % neutral buffered formalin for 48 hours. Decalcification was performed in a commercial solution SoftDec (Biovitrum, Russia) according to the manufacturer's protocol. Further processing was carried out according to the standard generally accepted unified method. After impregnation of the object with liquid paraffin at the temperature of 55–56 ° C, the tissue samples were allowed to harden at room temperature with paraffin in paraffin blocks. In order to undertake a histological examination, histogram sections of 5 μm size were made of paraffin blocks, cut out on a rotary microtome Leica RM (Germany). Staining was performed according to standard methods with hematoxylin and eosin (ready-made solutions of Mayer's hematoxylin and eosin produced by BioOptika, Italy). The sections were covered with BioMount (BioOptica, Italy), cover glass. The histological sections were examined under a light-optical microscope LeicaDM750, photomicrographs were performed using the microscope Leica DM 750/4 (Germany) with digital camera Leica DFC 420 (Germany) and software Leica Application Suit Version 3.8 was also used. The study was performed in accordance with the requirements of the Law of Ukraine “On Protection of Animals from Cruelty” (2006) and the provisions of “European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes” (1986).

Results of the study and their discussion. In the experiment, the pathological process was modeled on mature laboratory animals (rats) and allogeneic mesenchymal stem cells of warthon’s were used. Examination microscopy of proximal epiphyses sections’ decalcified tissue of the rats shinbone (7 days after the experimental trauma and intra-articular injection of MSCs of Wharton's jelly) revealed quite mosaic changes. All experimental animals had the dominated signs of hematoma organization with the fibrocartilage tissue formation at the injury site, in which numerous blood vessels, mostly formed capillaries were identified. Attention was drawn to the synthesized extracellular matrix (PMC) large foci, which had an unstructured homogeneous appearance in some places, and fibrous collagen and elastin structures characteristic for fibrous cartilage were found in some places. In contrast to the control animals, in the experimental animals at this time of observation in the active angiogenesis and PMC synthesis areas, the early chondrogenesis processes were detected, which consisted in the presence of mature chondroblasts and chondrocytes differentiation. They were disseminated localized in PMK, characterized by high activity before separation and small clusters formation, which are separated from each other by large layers of PMK.

Mature chondroblasts and chondrocytes were also found singly in fibrocartilage tissue, which replaced the hematoma. In this case, this orientation of mature cartilage cells may be the result of bone marrow SCs differentiation that are present in the blood, actively migrate to different organs and can be substitutes for cells of all mesenchymal tissues, including dead chondrocytes. When using MSC Wharton's jelly, they are activated before the division and differentiation earlier than those in the control. Differentiation of migrating bone marrow SC into chondroblasts and chondrocytes in the early period of regenerative repair generally reduces the recovery time of damaged tissue, because there is a revival of mitotic activity and the formation of mature chondrocytes. Cartilage cells are known to be labile in the reparative process and due to various sources of SC self-healing in full not only in normal but also in case of damage.

In experimental animals, 7 days after the start of the experiment with the use of MSCs, other sources of chondrogenesis were connected. Thus, there was an active proliferation and differentiation of the periosteum and perichondrium. They have an elongated fibroblast-like shape and are transformed not only into chondroblasts and chondrocytes, but also into endotheliocytes, which form blood vessels such as sinusoids, which is characteristic of the first stage of angiogenesis.

The source of chondrogenesis were small foci of intact old cartilage, the cells of which were dystrophically altered, as evidenced by edema of the cytoplasm, karyopyknosis, karyorrhexis. On the periphery of such cells there was an active division of chondrocytes and chondroblasts with partial replacement of the newly formed fibrocartilage tissue. These sources of chondrogenesis, sometimes quite common, contribute to the pannus formation, in which the neoplasm of chondrocytes in the phase of mitosis, were of the same type, the stratification of the layers was absent.

After 7 days from the experiment beginning, the synthesis of fibrous cartilage was quite common. Focally, it was formed in the shape of the low thickness pannus. The formation of fibrous cartilage was also observed in the holes of the bone marrow, which were located near the injury. Fibrous cartilage in the experiment was sometimes replaced by hyaline, which was not found in the control. The formation of hyaline cartilage, which replaced the fibrous, was characterized by the formation of the pannus of uneven thickness, but the cells were arranged in a chaotic manner, with signs of architectural disturbances, which emphasizes its immaturity (fig. 1).

With regard to the control, namely animals without the use of MSCs, after 7 days from the experiment start in most cases there were still foci of unorganized hematoma with signs of severe inflammatory infiltration, mainly mononuclear cells (macrophages, lymphocytes, fibroblasts) and moderate neutrophils. In parallel, fibrous structures of chaotically placed collagen were detected, and in some places delicate unstructured clusters of synthesized PMK were found (fig. 2).

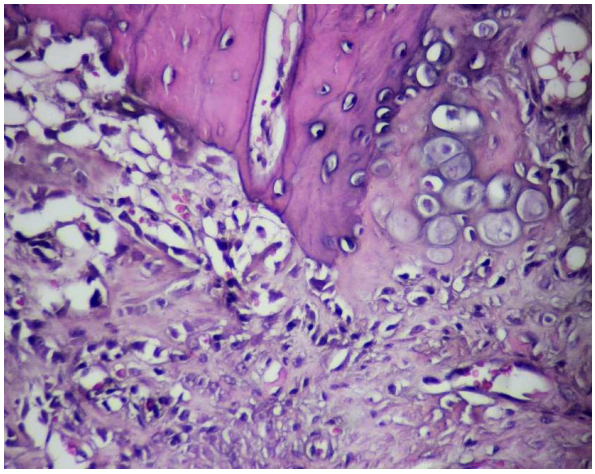

Fig. 1. Active replacement of the formed fibrous cartilage with hyaline. Hematoxylin-eosin staining. X400

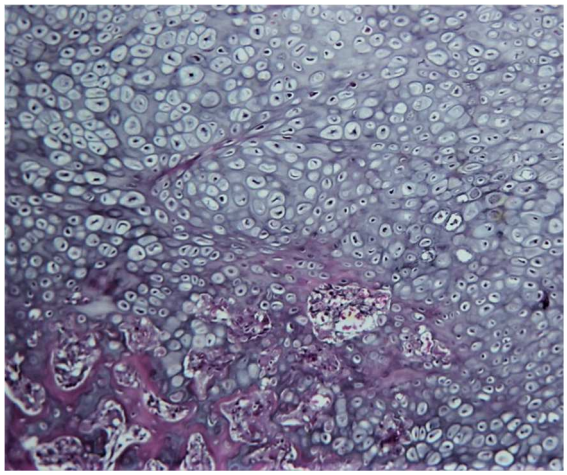

Fig. 2. Organization of hematoma. Chaotic focal neochondrogenesis. Hematoxylin-eosin staining. X200

After 14 days from the beginning of the experiment using MSC of Wharton's jelly, a regenerative process fairly noticeable positive dynamics at the rats shinbone damaged proximal epiphysis site of all experimental rats was determined. First, draws attention to the active replacement of fibrous cartilage with hyaline with the pannus formation. During this period, there was a particularly pronounced division of chondroblasts and chondrocytes, which was confirmed by multiple mitoses in different phases, including many and asymmetric. Asymmetric mitoses indicate the restoration of not only specialized cells – chondrocytes, but also the SC reserve, located in “niches”.

There were nests of early angiogenesis. In dense infiltrates of SC – endotheliocytes were oriented in rows between which the lumen was determined, the basement membrane has not been formed yet. Instead, multiple branches were observed – “buds” of potential blood vessels. Such early angiogenesis was practically not observed in experimental rats injected with MSCs. It may have occurred earlier before the seven-day observation. In contrast to the subjects, in the control cases, large segments of the pannus were detected not with hyaline, but mainly with fibrous cartilage, which has not been replaced by hyaline yet. In the control, as well as in the experiment, all sources of SC were connected to the process of regenerative repair, but at this time of observation their activity and number were significantly lower than in the subjects.

In contrast to the previous observation period, the sources of SC in chondrogenesis were not so clearly defined. The main source of chondrogenesis was the division of mature highly differentiated chondrocytes and chondroblasts, resulting in the formation of mature cartilage tissue large areas, which

were built of one type of compact cells, had no signs of layer stratification and clear restriction, which emphasized incomplete maturity of neoplasms.

There is also active angiogenesis, as evidenced by the formed numerous blood vessels (capillaries, veins, arteries), especially at the border between the cartilage and bone tissue, as well as in fibrocartilage tissue; the cells of which still occurred. It is noteworthy that the sometimes formed pannus and hyaline and fibrous have an uneven thickness, penetrate into the bone marrow, which is sometimes replaced by delicate fibrous structures. Rarely, there were small foci of secondary damage to the surface of the pannus with a defect, around which inflammatory infiltration was observed, which indicates the imperfection of its surface congruence. There were large areas of cartilage that did not border on bone fragments, but penetrated between them.

At this time of observation, small clusters of chondroclasts have already occurred in young cartilage tissue, which early remodeling the cartilaginous pannus shortened the period of full recovery of the defect, i.e. reduced the period of complete regenerative repair. At the same time, foci of incomplete stratification of layers were detected in the restored pannus and the number of mitoses decreased, which indicates the completion of the regeneration process.

After 14 days of experiment start, control rats' active regenerative processes were also observed. They were similar in nature and distribution to those detected after 7 days in the experiment. (3 rats after 14 days had active sources of chondrogenesis: the bone marrow SC, periosteum and perichondrial were still clearly defined). There were fragments of incompletely organized hematoma with varying degrees of inflammatory infiltration and the fibrocartilage formation. Fibrous cartilage was sometimes replaced by hyaline, but for this period was not as constant as in the experiment. Pannus was mainly represented by fibrous cartilage, which was unevenly replaced by non-compact hyaline. Rarely there was a tendency to stratification of layers, but the congruence of the surface in places was not clearly defined. Instead, the mitotic activity of chondroblasts and chondrocytes was similar to the experiment. Angiogenesis was variegated – in some foci of regeneration it was characteristic of the early stage, and in others were completely formed capillaries, arteries and veins. As in the experiment, the mosaic of regenerative repair of cartilage tissue of the damaged pineal gland was enhanced by active bone regeneration.

At the final stage of microscopic examination of the chondrogenesis of damaged tibial cartilage of the shinbone in an experiment using MSC of Wharton's jelly, i.e. after 28 days, almost complete restoration of hyaline cartilage architecture in the epiphyseal surface was revealed. No secondary damage was detected. The cartilaginous surface is mostly congruent. The pannus was represented by hyaline cartilage with a clearly defined stratification of the layers. At the border with the bone tissue it was a sufficient, normal, the number of formed blood vessels. Fragments of fibrous cartilage deep into the bone tissue, as well as small foci of resorption of cartilage and bone tissue by osteoclasts, which were localized deep under the pannus, were rarely detected. The significant inhibition of mitotic activity of chondrocytes draws attention, which was confirmed by a significant decrease in the number of chondrocytes in the state of division. Characteristic signs of positive dynamics of chondrogenesis at this time of observation were signs of remodeling of cartilage tissue with restoration of layer stratification and congruence of the pannus surface.

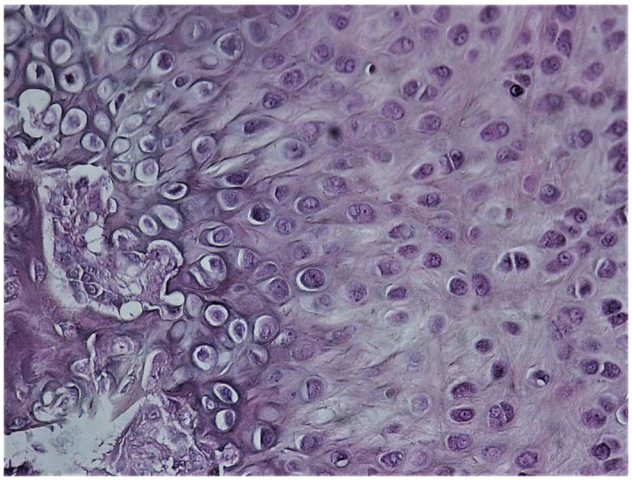

Fig. 3. Remodeling by chondroblasts and chondroclasts of young cartilage tissue from the endost and perichondria. Hematoxylin-eosin staining. X400

The pannus is represented in places by fibrous cartilage, and hyaline cells were placed not compactly, not completely stratified into layers, surface congruence was unevenly determined (fig. 3).

In the control, 28 days after the experiment start, only one animal had dynamic changes of regenerating cartilage tissue similar to those in experiment. In most cases, the dynamics of the positive regenerative process was the development of changes characteristic of the observation period after 14 days. Large fields of cartilage resorption and bone tissue were determined.

Thus, in the conditions of intra-articular introduction of MSC of Varton gems regenerative repair of the damaged epiphysis of a proximal rats shinbone occurs noticeably more actively than in control at all stages of development. In the early period, after 7 days, there is mobilization of SC of all known sources of chondrogenesis: bone marrow, periosteum, perichondria to division and differentiation, resulting in an

increase in the number of differentiated chondroblasts and chondrocytes. Mitotic activity and differentiation of specialized chondrocytes and those that remain intact and newly formed is revived. After 14 days, mitotic activity of specialized chondrocytes dominated as a source of chondrogenesis. There was an active replacement of fibrous cartilage with hyaline. In the final period of observation, i.e. after 28 days, almost complete replacement of fibrous cartilage with hyaline was characteristic, in which stratification of layers was restored, surface congruence was ensured. The mitotic activity of chondrocytes was suppressed, which indicated the connection of contradictory regulation mechanisms of the regeneration process. Large and small foci of resorption of both cartilage and bone tissue appeared. That is, signs of the cartilage tissue remodeling of the damaged tibial epiphysis in fully dominated. In general, regenerative repair in rats treated with MSCs was faster than in the controls for 7-10 days or more.

Literature data confirm the prospects for the use of autologous tissues (surgical treatment of osteochondral lesions of the talus by open-field autologous chondrocyte implantation), the clinical outcome after a one-step autologous subchondral cancellous bone graft and autologous matrix-induced chondrogenesis (AMIC) in medial OCLs of the talus and the assessment of the repair tissue. However, there is no data on the use of Wharton's jelly cells for therapeutic purposes [5, 6].

Single studies are devoted to the clinical and radiological assessment of the use of mesenchymal stem cells and are not subject to morphological examination [13]. Apprich S., Trattnig S., Welsch G.H. compared patients after matrix-associated autologous chondrocyte transplantation and microfracture therapy of the talus using diffusion-weighted imaging, with morphological and clinical scoring, but no significant clinical differences were found between the study groups, and the differences were only in the magnetic resonance imaging of the joints [2].

The study by Legendre F. at al. offers the opportunity to develop a combinatory cellular therapy strategy for cartilage tissue engineering, they aimed to determine the best culture conditions to induce chondrogenesis of mesenchymal stem cells isolated from bone marrow of aged osteoarthritis patients [8]. However, the proposed method, although tested on rats, concerned only this disease.

There are reports of a new method of hyaline cartilage treatment – particulated autologous chondral-platelet-rich plasma matrix implantation for treatment of full-thickness cartilage osteochondral defects [3]. However, the authors themselves emphasize only the proposals and search for new methods of cartilage lesions treatment and the need for further research.

Calculating the cost-efficiency of modern methods of treating cartilage damage indicates that some techniques are cheaper, but the use of matrix-induced chondrogenesis to microfracture is the most cost-efficient method [11]. Note that the use of stem cells of Varton gems was not evaluated in this study.

Conclusions

1. A study of the use of mesenchymal stem cells of Wharton's jelly in animal experiments proved the efficiency of their use to restore the structure and function of articular cartilage after traumatic injury.

2. Reparative osteochondrogenesis with the use of mesenchymal stem cells of Wharton's jelly permitted to accelerate repair processes by 1.5-2 weeks than in the control group, with the formation of structured timely osteogenesis, without the formation of excessive early production of ossifying matrix and dystrophic changes of chondrocytes and chondroblasts.

3. The results of the study confirm the high safety profile of cellular therapy with mesenchymal stem cells and open the way to an effective and safe method of cellular regenerative medicine of the musculoskeletal system.

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Стаття надійшла: 25.07.2020 р.

DOI 10.26724/2079-8334-2021-3-77-254-258
UDC 612.273.2+616.155.32+616.423.428]-091

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THE ULTRASTRUCTURAL FEATURES OF THE ADRENAL GLANDS UNDER THE COMBINED EFFECT OF HYPOBARIC HYPOXIA AND STAPHYLOCOCCAL PERITONITIS

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The research work is devoted to the study of the pathogenesis and morphogenesis of ultrastructural changes of the adrenal glands under the combined influence of hypobaric hypoxia and staphylococcal infection. Hypoxia and infection develop ultrastructural changes in glandular tissue separately, as well as in combination, which are of a phase nature. In particular, the combined effect of both factors violates the structure of intracellular organelles, reduces their size, leads to deformation and atrophy of adrenocytes, focal growth of connective tissue, and in the course of the experiment, glandular cells adapt to a new environment.

Keywords: hypoxia, staphylococcal infection, adrenal glands, ultrastructure

С.М. Ягубова

УЛЬТРАСТРУКТУРНІ ОСОБЛИВОСТІ НАДНИРНИКІВ ЗА ПОЄДНАНОГО ВПЛИВУ ГИПОБАРИЧНОЇ ГІПОКСІЇ І СТАФІЛОКОКОВОГО ПЕРИТОНІТУ

Робота присвячена вивченню патогенезу і морфогенезу ультраструктурних змін надниркових залоз за одночасного впливу гипобаричної гіпоксії і стафілококової інфекції. Гіпоксія і інфекція розвивають ультраструктурні зміни залозистої тканини окремо, а також в поєднанні, які носять фазовий характер. Зокрема, спільна дія обох факторів порушує структуру внутрішньоклітинних органел, зменшує їх розмір, призводить до деформації і атрофії адреноцити, вогнищеве розростання сполучної тканини, а в ході експерименту залізисті клітини адаптуються до нового середовища.

Ключові слова: гіпоксія, стафілококова інфекція, наднирники, ультраструктура.

The work is initiative.

Various scientific studies in recent years have shown that microenvironmental factors alter cell morphology, cell surface marker expression, metabolic activity, viability, phagocytosis, and cytokine secretion by macrophages, as well as bacterial pathogenicity [4]. Any stress factor results in the activation of the hypothalamo-hypophyseal-adrenal axis (HHA) in the body, which increases the secretion of corticosteroids to optimize the stress response. According to research, the strongest irritants of the HHA axis are hypoxia, hypotension, infections of various origins, and sepsis [7].