REVIEW

Structural Basis of So-Called Plastic Properties of the Connective Tissue

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Plastic properties of tissue are determined by regeneration and hyperplasia of cells and intracellular structures ensuring constant renewal and functioning of organs and tissues in health and disease. Connective tissue is characterized by high plasticity, which is widely used for stimulating the repair of injuries in organs and tissues. The development of methods stimulating the healing of traumatic injuries to soft tissues and bones is in progress.

A well-known manifestation of high plasticity of connective tissue: the ability of tissue to increase its volume during stretching, for instance, increase in skin volume during obesity, stretching of abdominal skin by the uterus in pregnancy, etc., has been utilized in recent decades.

Dosed stretching of soft tissues was for the first time clinically used in 1957 by an English surgeon C. Neumann [31] for auricular plasty. A rubber balloon was implanted subcutaneously behind the ear; its volume was gradually increased by injecting water in it, and thus an increment in the skin volume was attained, sufficient for plastic operation. Later this method was used for plastic repair of mammary glands after radical mastectomy and for other operations [24,26,34].

T. G. Grigor'eva *et al.* were the first to use dosed skin stretching for rehabilitation of patients after thermal injuries; they used Russian-manufactured tissue expanders. The method of skin and soft tissue stretching is used in surgical treatment of the consequences of burns, injuries, and other skin and soft tissue defects [13,15]. Dosed skin stretching by means of a constant outer force is called exodermotension. The simplest method of stretching the skin is moderate tension by partially suturing the edges of a wound formed after dissection of cicatrices [10].

For closing extensive defects of soft tissues, tissue stretching with needles implanted subdermally has been proposed [2,28]. All these methods are based on constant dosed mechanical loading of healthy skin adjacent to the wound defect. This provides an excess tissue reserve for repair. Under certain anatomical conditions, a tissue defect larger than 1000 cm^2 can be closed [9].

Connective tissues and other tissues of the organism are stretchable. In some African tribes, in order to form a long neck, which is considered as an indicator of female beauty, wooden rings are placed on the neck of a little girl, and the number of the rings is increased as the girl grows. The neck becomes longer as the skeleton grows. This implies that not only the skin, but also bones, muscles, and nerves can be gradually distracted.

G. A. Ilizarov's method of compression-distraction osteosynthesis is a great contribution to the development of dosed stretching for tissue replacement. He has formulated the concept of the stimulating effect of distraction on tissue growth. Based on this concept, distraction methods have been widely used in recent years for the treatment of patients with defects of long bones, short limbs, and with aftereffects of locomotor injuries [3,6,7,25].

The gist of the method is as follows: after application of an external fixation device on the limb,

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bone fragments adjacent to each other after osteotomy are daily distracted at a rate of 1 mm/day. As a result, regenerated bone gradually forms between the fragments, replacing the bone defect; the anatomy and function of injured bone are restored.

Bone regeneration disturbances may occur if the wounds are large or there are pronounced inflammatory changes in soft tissues adjacent to bone fragments. Active surgical strategy making use of dosed tissue distraction has been developed at A. V. Vishnevsky Institute of Surgery for treating patients with surgical infections associated with extensive defects of integumental tissues and long bones [1,9,12].

The possibility of connective tissue stretching has been widely used in clinical practice. Structural basis of this process is still unclear. The process of tissue stretching involves morphological changes ensuring the intactness of tissues and gradual increment in their bulk. Samuel [17] wrote that "progressive changes in tissue caused by direct mechanical stretching are rather frequent. At first mechanical stretching consists just in stronger tension; tissues possess a normal network of blood vessels, adapting to tissue stretching, and therefore blood supply and nutrition of stretched tissues are increased; i. e., mere mechanical stretching (at the beginning) is transformed into progressive changing of tissue" (hyperplasia). There is a wide range of opinions on what cellular elements participate in tissue stretching and how they change. Some scientists believe that cambial mesenchymal cells, which differentiate into connective tissue cells that are stretched, are the source of dividing cells in stretched tissue [11]. Cambial cells are strictly determined and specific for each tissue newly forming during stretching: hyperplasia of cambial cells — osteoblast precursors in bone distraction, fibroblast (FB) precursors in skin stretching, *etc.* Other authors claim that a universal mesenchymal cambial cell is metaplastically transformed into this or that connective cell: osteoblast, FB, lipid, smooth-muscle cell, *etc.* [14,16]. Some scientists support both specific and metaplastic cambial theories [5]. In fact, all authors admit the important role of the vascular system, specifically, capillary wall cells (pericytes) forming the outer coating of the vessels, in the regeneratory hyperplastic processes.

Morphological changes in regeneratory processes in bone tissue, specifically, in distraction osteosynthesis, are better known than in skin stretching, but both are to be further investigated, as far as it concerns more accurate characterization of cellular elements participating in these processes. We studied plastic properties of some connective tissue types by electron-microscopic radioautography [22].

Electron-radioautographic studies of the time course of maturing granulation tissue, regenerating bone in distraction osteosynthesis, and of processes occurring in stretched skin during the treatment of large wounds and other pathological states led us to the hypothesis that all these seemingly different processes follow a universal pattern of morphological changes. The key element are small vessels and the central cellular element are FB. In maturing granulation tissue, pericytes coating the small vessels most actively produce DNA and RNA, divide, gradually detach from the vascular wall, and transform into typical FB ensuring collagenogenesis and cicatrization. Simultaneously, the vascular wall disintegrates into individual cells [18]. Therefore, the granulation tissue vessels are a transporting system delivering nutrition to the wound and "construction material" for wound healing.

A similar picture is observed during the formation of bone regenerate in distraction osteosynthesis: at first typical granulation tissue with numerous vessels appears between bone fragments; the vessels are transformed as in granulation tissue during wound healing, the number of FB formed from pericytes increases, FB are transformed into osteoblasts, bone beams appear, and then compact bone is formed.

When the skin is stretched with an expander or large wounds are closed, cellular reaction is observed around small vessels. Cell number increases, the count of FB is growing, and this stimulation of vascular and FB increase in the derma provides an increase in the volume of the skin with normal structure [1,8].

Stretching stimulates tissue growth: the number of vessels, cells, and interstitium elements increases. It was reported that the number of active FB increases and blood supply to tissues improves during tissue stretching [27,30,33].

It was shown that FB is the main cell responsible for the plastic characteristics of connective tissue and stimulating the proliferation of other tissues. This property of FB was utilized by using their cultures for the treatment of patients with severe skin burns. Wound closure is the most important stage in the treatment of patients with burns, because the cleansing of the burn from necrotic and infected tissues and subsequent plasty prevent intoxication and infectious complications. Provisional wound coatings from cadaveric allografts, xenografts, amniotic membranes, etc. have been used for this purpose. Today cell cultures are applied on wound surface, and their growth promotes the formation of full-value skin integument.

There are two main options of this treatment: coating the burn surface with cultured epidermocytes (keratinocytes) or allofibroblasts (alloFB).

First, the epidermocytes were used. This approach was developed in the USA. It is widely employed at American and Western Europe burn centers [29,32]. Allofibroblasts were originally developed at A. V. Vishnevsky Institute of Surgery. This method has no analogs in world practice: the surface of burns is covered with layers of cultured alloFB [23]. These FB exert a potent stimulatory effect on the regeneration of the remaining epidermis islets and its appendages or on the autodermal graft transplanted on the epidermis.

AlloFB have been used at A. V. Vishnevsky Institute of Surgery and Department of Burns for Small Children at G. N. Speransky Municipal Pediatric Clinical Hospital No. 9 for 7 years [23]. The results of treatment of about 300 adults and children confirm the advantages of alloFB over epidermocytes. These advantages are: rapid culturing of alloFB in comparison with keratinocytes, higher percentage of alloFB taking in, a simpler culturing procedure, and lower price of the grafts. There are good grounds to expect that these advantages of alloFB make this technique the method of choice in the treatment of patients with burns.

Fibroblasts play the key role in providing high plasticity of connective tissue. Due to their potent stimulatory effect on other cells, fibroblasts contribute to the regeneration of epithelial tissues and organization and cicatrization of wound defects.

The role of fibroblasts in adaptive extension of the area and bulk of normal tissues under extreme conditions (large skin defects, strong tissue stretching, etc.) is no less important. Recent studies revealed essential advantages of cultured alloFB for treating burnt surface in comparison with other methods stimulating epithelialization.

Fibroblasts (pericytes) coating capillary walls possess the highest potential for stimulating the regeneratory processes.

In conclusion we should like to emphasize that the epithet "so-called" with the term "plasticity" in the title of this paper is not accidental: it is high time to stop using this term to denote something flexible, easily deformable, etc., as we often see it in Russian publications. In morphology the use of this vague and indefinite "so-called" became unnecessary after the introduction of electron microscopy, which clearly demonstrated that high lability, reactivity, and adaptability of tissues of an organism to changing environmental conditions is regulated by two processes, close in essence: hyperplasia and regeneration.

REFERENCES

1. Yu. A. Amiraslanov, G. G. Karmazanovskii, A. M. Svetukhin, and D. S. Sarkisov, *Byull. Eksp. Biol. Med.*, **115**, No. 2, 206-208 (1993).
2. Yu. A. Amiraslanov, D. S. Sarkisov, E. G. Kolokol'chikova, *et al.*, *Vrach*, No. 2, 25-27 (1993).
3. Yu. A. Amiraslanov, A. M. Svetukhin, V. A. Mitish, and I. V. Borisov, *Khirurgiya*, No. 4, 53-54 (1993).
4. S. I. Vozdvizhenskii, L. I. Budkevich, and L. V. Shurova, *Ros. Vestn. Perinatol. Pediatr.*, No. 4, 32-34 (1995).
5. M. I. Vorontsova and L. D. Liozner, *Physiological Regeneration* [in Russian], Moscow (1965).
6. O. N. Gudushauri and L. A. Tviliashvili, *Ortoped. Travmatol.*, No. 11, 25-30 (1983).
7. G. A. Ilizarov, *Byull. Izobret.*, No. 27 (1971).
8. E. G. Kolokol'chikova and Yu. A. Amiraslanov, *Arkh. Patol.*, No. 5, 34-39 (1994).
9. K. V. Lipatov, *Potentialities of Dosed Tissue Stretching in Purulent Surgery* [in Russian], Author's Synopsis of Cand. Med. Sci. Thesis, Moscow (1996).
10. M. M. Madazimov, *Tissue Stretching in Repair and Plastic Surgery for Consequences of Burns* [in Russian], Author's Synopsis of Cand. Med. Sci. Thesis, Moscow (1990).
11. V. O. Marks, *Healing of a Closed Fracture in Man* [in Russian], Moscow (1962).
12. V. A. Mitish, *Active Surgical Treatment of Posttraumatic Osteomyelitis of Long Tubular Bones* [in Russian], Author's Synopsis of Cand. Med. Sci. Thesis, Moscow (1991).
13. V. Yu. Moroz, V. M. Grishkevich, A. A. Madazimov, and P. F. Ganzha, *Khirurgiya*, No. 8, 140-143 (1989).
14. N. P. Novichenko, *Fundamentals of Orthopaedics and Traumatology* [in Russian], Moscow (1961).
15. D. E. Pekarskii, T. G. Grigor'eva, and G. A. Oleinik, *Klin. Khir.*, No. 3, 17-19 (1988).
16. N. N. Petrov, *Khirurgiya*, No. 11-12, 56 (1943).
17. E. Samuel', *Manual of General Pathology in Terms of Pathological Physiology* [in Russian], St. Petersburg (1879).
18. D. S. Sarkisov, A. A. Alekseev, E. V. Glushchenko, *et al.*, *Vestn. Rossiisk. Akad. Med. Nauk*, No. 6, 6-11 (1994).
19. D. S. Sarkisov, E. G. Kolokol'chikova, R. I. Kaem, and A. A. Pal'tsyn, *Byull. Eksp. Biol.*, **105**, No. 4, 501-503 (1988).
20. D. S. Sarkisov, B. M. Kostyuchenok, Yu. A. Amiraslanov, *et al.*, *Ibid.*, **98**, No. 7, 97-99 (1984).
21. D. S. Sarkisov, B. M. Kostyuchenok, Yu. A. Amiraslanov, *et al.*, *Arkh. Patol.*, No. 2, 17-23 (1985).
22. D. S. Sarkisov, A. A. Pal'tsyn, and B. V. Vtyurin, *Electron-Microscopic Autoradiography of a Cell* [in Russian], Moscow (1980).
23. D. S. Sarkisov, V. D. Fedorov, E. V. Glushchenko, *et al.*, *Byull. Eksp. Biol. Med.*, **119**, No. 6, 566-570 (1995).
24. L. C. Argenta, *Clin. Plast. Surg.*, **14**, No. 1, 143-154 (1987).
25. J. Aronson, E. Johnson, and J. H. Harp, *Clin. Orthop.*, **243**, 71-79 (1989).
26. E. D. Austad, *Clin. Plast. Surg.*, **14**, No. 3, 549-550 (1987).
27. E. D. Austad, K. A. Pasyk, K. D. McClatchey, and G. W. Cherry, *Plast. Reconstr. Surg.*, **70**, 704-710 (1982).
28. N. J. Boehm, *Aktuel. Traumatol.*, **24**, No. 8, 140-144 (1994).
29. H. Green, O. Kehinde, and J. Thomas, *Proc. Natl. Acad. Sci. USA*, **76**, 5665-5668 (1979).
30. Ch. Hong, J. B. Stark, and J. W. Futrell, *Clin. Plast. Surg.*, **14**, No. 3, 465-467 (1987).
31. C. Neumann, *Plast. Reconstr. Surg.*, **19**, 124-130 (1957).
32. N. E. O'Connor, J. B. Mulliken, S. Banks-Schlegel, *et al.*, *Lancet*, Jan. 10, 75-78 (1981).
33. K. A. Pasyk, L. C. Argenta, and E. D. Austad, *Clin. Plast. Surg.*, **14**, No. 3, 435-445 (1987).
34. C. Radovan, *Plast. Reconstr. Surg.*, **74**, No. 4, 482-490 (1984).