DEVELOPMENT OF THE PSEUDOINTIMA IN A SYNTHETIC PROSTHESIS IN A MODEL OF EXPERIMENTAL HYPERCHOLESTEROLEMIA

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The development of methods of surgical treatment of atherosclerosis and its complications is associated with the use of synthetic and biological prostheses. A wide range of prostheses differing in the structure of the tissue and the quality of the covering now exists [1, 2, 5]. It has been shown that the porosity of prostheses is an essential condition for the development of a neointima, and the formation of the latter is regarded as a factor determining the good condition of the prosthesis [9]. At the same time it has been noted that, for example, when a Dacron prosthesis with a small diameter is used on infants (replacement of the pulmonary artery) a thick layer of pseudointima develops rapidly [8]. In the extensive literature on experimental replacement of arteries by prostheses, the progressive course of the disease against the background of which the prosthesis is implanted, i.e., atherosclerosis, is virtually ignored. The reason is that most studies have been carried out on dogs and rats, which do not develop experimental atherosclerosis. Yet it has been shown that arterial prostheses in patients with atherosclerosis are frequently patent for only 1-3 years after the operation [2].

The aim of the present investigation was an ultrastructural analysis of the development and function of a pseudointima in a prosthesis implanted into the rabbit aorta during the development of experimental hypercholesterolemia.

EXPERIMENTAL METHOD

We have carried out for the first time an experimental study of the pattern of development of the pseudointima in a synthetic prosthesis implanted into the rabbit aorta, constituting a model of experimental atherosclerotic lesions. Experiments were carried out on 32 rabbits, 22 of which were kept on an atherogenic diet (500 mg cholesterol dissolved in 5 ml sunflower oil per animal per day) starting with the 5th week after the operation; 10 animals constituted the control group. A synthetic Lavsan vascular prosthesis (MPL-79; diameter 3 mm, length 15-20 mm), such as is widely used in surgical practice, was chosen. The animals were exsanguinated at intervals between 1 and 28 weeks after the operation. Besides standard histological methods, histoautoradiography also was carried out with ^{3}H-thymidine, the labeled precursor of DNA synthesis, using the technique described previously [3]; ^{3}H-thymidine was injected 4 times during the 24-h period (specific activity 19.8 Ci/mole, 0.5 μCi/g body weight). Scanning (SEM) and transmission (TEM) electron microscopy also was used (more than 370 blocks were studied). Material was prepared for electron-microscopic study by the method described previously [4]. Samples for SEM were dried by passage through the critical point of CO in a Hitachi HCP-1 (Japan) apparatus, and sprayed with gold in the EIKO-IB-3 apparatus (thickness of the sprayed layer 30 nm). The material was then studied in a Hitachi H-300 electron microscope (Japan), using both SEM and TEM.

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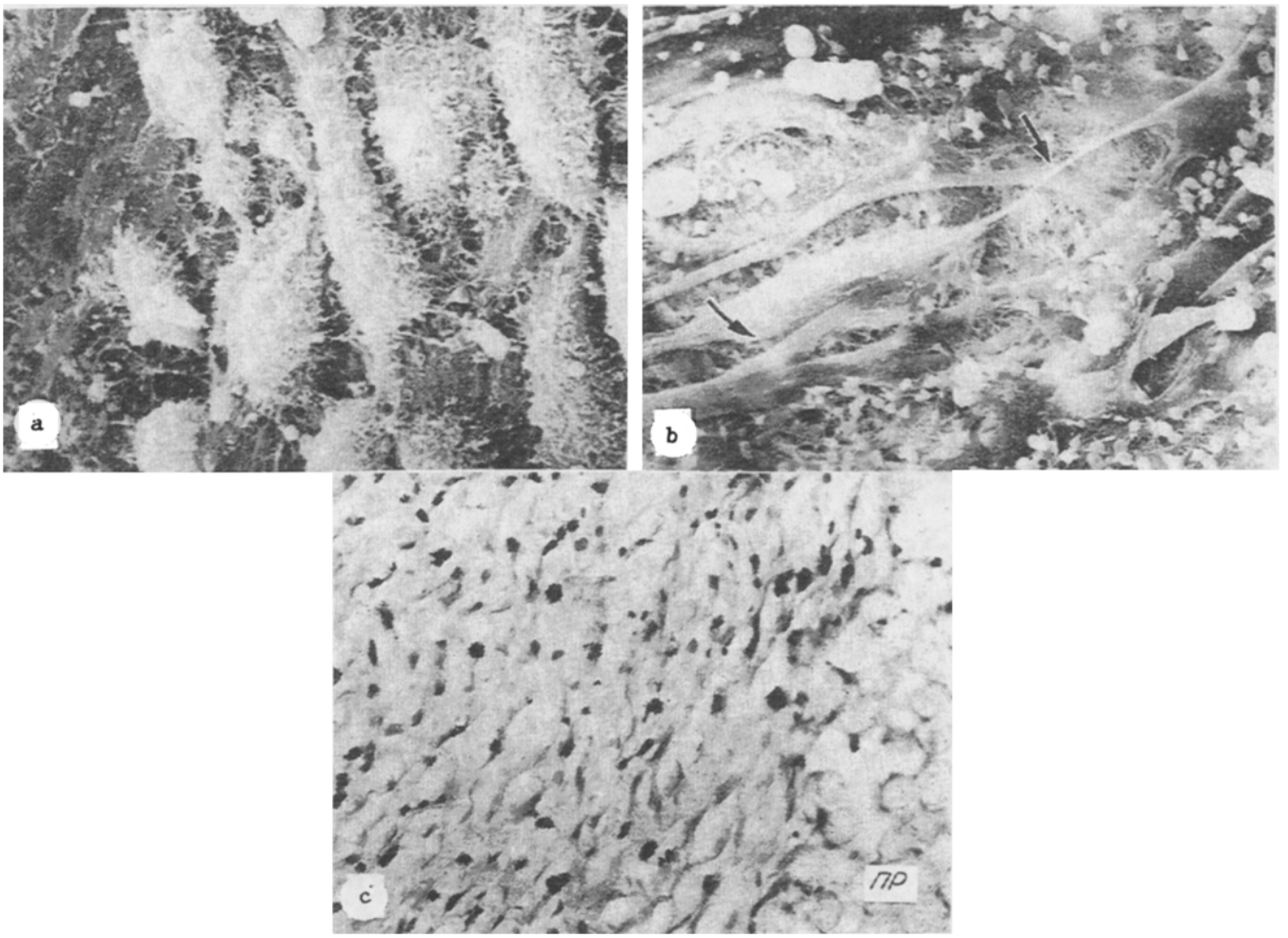

Fig. 1. Formation of pseudointima on inner surface of synthetic Lavsan prosthesis implanted into rabbit aorta. a) Activated SMC with multiple microvilli, forming a pseudointima (SEM, 3200×); b) transformation of SMC into endotheliallike cells (arrows; SEM; 2800×); c) fibroplasia of newly formed pseudointima, most SMC nuclei incorporate ^{3}H-thymidine. PR) Prosthesis. (Histoautoradiograph, 420×).

EXPERIMENTAL RESULTS

Ultrastructural analysis of pseudointima formation showed that pericytes (undifferentiated mesenchymal tissue cells according to Maximow) migrate through pores in the prosthesis on its internal surface as early as 1 week after the operation, and actively proliferate. By the 4th week a pseudointima consisting of 8-10 layers of pericytes, transformed into smooth-muscle cells (SMC) is formed. Under these experimental conditions virtually all nuclei of mesenchymal cells forming the pseudointima take up ^{3}H-thymidine. Adhesion of platelets and monocytes is absent on the inner surface of the pseudointima, which consists of activated SMC (Fig. 1a). This state of affairs indicates the incorrectness of the views of those workers who regard denudation of the endothelium as a factor promoting platelet adhesion and the formation of microthrombi [10].

By the 8th week of the experiment (4 weeks of experimental hypercholesterolemia) the process of pseudoepithelium formation on the prosthesis was complete. By SEM the stages of transformation of SMC from pericytes into endothelial cells could be studied. At certain stages of pseudointima formation, moreover, intercellular bridges could be seen clearly between the endotheliallike cells and SMC (Fig. 1b). The view that endothelium formation above a pseudointima takes place through creeping of cells from the intima of the vessel through the zone of anastomosis [7] was confirmed only partially. Actually, creeping of the endothelium onto the inner surface of the prosthesis does take place, but no further than for 3-4 mm. Under these circumstances the creeping endothelium undergoes rapid destructive changes, one condition for thrombus formation in this zone of the head of the prosthesis.

Proliferation of SMC does not cease with the formation of a pseudointima covered by endotheliallike cells, and by the 12th week of the experiment it leads to a marked narrowing of the lumen of the prosthesis (Fig. 1c) on account of hypertrophy of the synthetic phenotype of SMC. Despite the high hypercholesteolemia (the plasma cholesterol level was raised 20-30-fold), deposition of lipids did not take place in the zone of the pseudointima, whereas 40% of the intima of the aorta of these same animals (10% of the total area of the vessel) was occupied by atherosclerotic lesions.

Fibroplasia of the pseudointima 20 weeks after implantation of the prosthesis into the aorta (16 weeks of hypercholesterolemia) led to the almost complete obliteration of the lumen of the prosthesis, whereas in the group of control animals this process took place much more slowly and was not accompanied by such marked narrowing of the lumen of the prosthesis. This state of affairs indicates the important role of hypercholesterolemia in the development of fibroplasia of the pseudointima. Intensive proliferation of mesenchymal cells in the pseudointima against the background of developing hypercholesterolemia is responsible for the mitogenic effect of apoB-containing lipoproteins [6].

These data demonstrate the importance of taking account of the state of the recipient into whom a prosthesis is implanted, with particular reference to the severity of the course of atherosclerosis and the depth of the disturbance of lipid metabolism.

Besides thrombus formation in the zone of anastomosis and fibroplasia of the pseudointima, the list of postoperative complications may also include the formation of many vessels of capillary type throughout the thickness of the pseudointima and the formation of arterioles, whose rupture leads to multiple hemorrhages, which cause necrosis of the surrounding tissues.

Implantation of a synthetic porous prosthesis into the aorta of rabbits with developing hypercholesterolemia is thus accompanied by migration and proliferation of pericytes, which are transformed into SMC and endotheliallike cells, with rapid obliteration of the lumen of the prosthesis against the background of experimental atherosclerosis. The high degree of thrombogenicity of the anastomotic zones is another reason why these two processes can be regarded as basic postoperative complications.

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