Mesothelial cell transplantation

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Abstract: Mesothelial cells are an integral part of the peritoneum and play an important role in maintaining its structural and functional properties. In the recent years a number of studies on mesothelial cells have been performed to evaluate the localization, secretional properties and the ability of regeneration and transdifferentiation of these cells. They are also involved in the repair of the peritoneum damage following surgery or peritonitis. Mesothelial cells produce several cytokines, growth factors and extracellular matrix components, possessing anti-inflammatory and immunomodulatory properties. Because of their plasticity, these cells are able to form a new cell type like fibroblast, endothelial and smooth muscle cell, chondrocyte, osteoblast, adipocyte or neuron. The first step involves mesothelial cell transdifferentiation into progenitor cells with the capacity of further differentiation. In this paper the current knowledge concerning the mesothelial cell differentiation and transplantation has been reviewed. Own mesothelial cells of a patient are used in transplantation. They are sampled, cultured *in vitro* and then they can be used in the prevention and treatment of post-operative abdominal adhesions, incisional hernias, repair of peritoneal membrane of patients on long-term peritoneal dialysis, the prevention of ischemic myocardial damage, nerve regeneration and genetically modified recombinant protein secretion. Inevitably, more potential applications of transplanted mesothelial cell will be available over the next few years.

Key words: gene therapy, mesothelial cell, mesothelial transplantation, myocardial infarction, peritoneal dialysis

Mesothelial cell structure and localization within the peritoneum

The peritoneum is formed of mesothelial cells placed on the basement membrane, and of connective tissue of diverse thickness containing blood and lymph vessels and neuronal endings [1]. Due to their placement, excretory properties, regeneration and transdifferentiation abilities mesothelial cells have been the subject of in-depth studies for several years. The mesothelium is a single layer of mesodermal origin cells of various structure depending on the localization. Within the parietal peritoneum, mesothelial cells are flat (2.5–3 μm) with an elongated nucleus, small cytoplasm content and with sparse microvilli. The visceral peritoneum mesothelial cells are larger (12–15 μm), cubic, with a large nucleus, numerous cell organelles and microvilli. The transitional cells which are part of the extra-gastric peritoneum have digitate cytoplasmatic processes on their surface [2]. Mesothelial cells are covered with microvilli, which increases the peritoneal surface by some 40 times. These villi are about 2 μm long, formed of actin fibers and covered with glycocalyx. The density of the microvili on the cell surface depends on the localization and is higher on visceral peritoneum mesothelial cells than parietal peritoneum [3]. Mesothelial cells are rich in cell organelles. They have numerous mitochondria, endoplasmatic reticulum, 2–3 Golgi apparatus and multiple lysosomes. In their cytoplasm there are actin fibres formed of desmin, vimentin and cytokeratin. It has been demonstrated that cytokeratin 8 and 18, as well as vimentin are mesothelial cell specific compounds [4]. Pinosomes join together and form a channel between the peritoneal cavity and the connective tissue. The mesothelial cell nucleus is placed centrally. In flat cells it is oval or kidney shaped, and bulges into the peritoneal cavity lumen. In cubic cells the nucleus is circular. Under the layer of mesothelial cells there is a basement membrane made of type IV collagen, of laminin, fibronectin and proteoglycans. The basement membrane is negatively charged and functions as the protection against macromolecules penetration, and thus plays an important role in the mesothelium repair process [5]. Underneath the mesothelium there is the interstitial tissue made of type I and III collagen, fibrin fibres and colloidal gel [1]. Numerous cells including; fibroblasts, mast cells, macrophages, leucocytes and adipocytes, blood and lymph vessels and nerve fibres are located in this matrix. The main component of the peritoneal interstitial tissue is the hialuric acid which together with proteoglycans binds water molecules forming a gel layer which plays the role of a filter. The interstitial tissue has abundant vascularization. There are 3 types of vessels such as the proper capillaries, venous capillaries formed of a confluence

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of 2–3 proper capillaries, and venules. The majority of vessels (71.2%) are located in the peritoneum covering the viscera and the mesentery [6]. Blood vessels are laid with endothelial cells through which the transport of molecules between the blood and the peritoneal interstitial tissue takes place. The mesothelial cells of the pericardium and the pleura do not differ in their biology from the peritoneal mesothelial cells [7].

The role of mesothelial cells

Being part of the peritoneum, mesothelial cells participate in its structural and functional activity. One of the basic functions of mesothelial cells is the formation of a smooth surface of the peritoneum. To achieve this they produce phospholipids - phosphatidylcholine, lysophosphatidylcholine, sphingomyelin, phosphatidylethanolamine, phosphatidylinositol, phosphatidylserine, lysophosphatidic-ethanolamine, which together with the glycocalyx form a layer protecting this membrane from abrading during abdomen organ movements [8]. The interaction between the negatively charged microvilli and positively charged phospholipids allows for an ideally smooth surface formation [6]. Mesothelial cells produce many cytokines and growth factors, vascular endothelial growth factor (VEGF) [9], basic fibroblast growth factor (bFGF) [10], transforming growth factor β (TGF-β) [11], platelet growth factor (PGF) [12], insulin-like growth factor [13], hepatocyte growth factor (HGF), epithelial growth factor (EGF) [14], endothelin-1 and keratinocyte growth factor [12,15]. Mesothelial cells also synthesize extracellular matrix components; cytokeratin, vimentin, cadherins, fibronectin, laminin, actin, vinculin, type I and III collagen [16,17]. Mesothelial cells have anti-inflammatory and immunomodulatory properties through the secretion of stromal derived factor-1α (SDF-1α), prostaglandins, prostacycline, surfactant proteins A and D, plasminogen activator inhibitor and tissue inhibitors of metalloproteinases [17-19]. Mesothelial cells maintain a balance between fibrin formation and degradation through the secretion of fibrinolysis activators and enzymes taking part in the fibrin deposit formation. Mesothelial cell damage results in the activation of the blood coagulation and fibrinolysis [20].

Mesothelial cell regeneration and differentiation

Mesothelial cells have large regenerative capacities. Peritoneum damage may result from a surgical procedure, peritonititis or peritoneal dialysis. Regenerative processes begin within 24 hours of damage occurrence. Cells filling the damaged area may stem from:

1) proliferation of cells lying on the margin of the tissue defect
2) the layer of mesothelial cells on the opposite surface of the peritoneum
3) immature mesothelial cells circulating in the serous liquid
4) macrophages transformation
5) mesenchymal precursor cells located in the peritoneum interstitial layer.

The healing of the damaged surface of the mesothelium takes 7–10 days and differs in relation to endothelial cell healing which involves uniquely marginal cell propagation [21]. Mesothelial cells derive from the mesoderm; they demonstrate, however, phenotype features of both epithelial (of endodermal origin) and mesenchymal cells. They are characterized by great plasticity; placed in the appropriate environment they may differentiate to various cell lines [17]. With the influence of the following factors: TGF-β, HGF, EGF and interleukin-1β, mature mesothelial cells transform into fibroblast cells [22]. During this transformation the cells change their phenotype. They adopt an elongated shape, the intercellular connections disappear, the cytokeratin content decreases; the vimentin expression and the cell migration abilities increase. Such a transformation (transdifferentiation) of mesothelial cells to myofibroblasts has been reported when adding TGF-β to a culture of human mesothelial cells [23]. A similar transdifferentiation has also been noticed *in vivo*, in patients on peritoneal dialysis [24]. The long-term TGF-β effect on the peritoneum results in its fibrination and ultrafiltration decrease. The advanced glycation end products (AGEs), which occur with the use of dialysis liquid of a high glucose level, stimulate the formation of TGF-β and peritoneal fibrination. The use of the AGEs and bone morphogenetic protein-7 receptors antagonists prevents from the mesothelial cell transdifferentiation [25,26].

Mesothelial cells of fetal epicardium may differentiate into endothelial cells and vascular smooth muscle cells [27]. It has been demonstrated in animal models that mesothelial cells may also differentiate to skeletal muscle cells, chondral cells, bone cells, adipocytes and nerve cells [22]. During the healing phase of chemical peritonitis in a rat, skeletal muscle fibres were found in the peritoneum covering the diaphragm [28]. In the course of sclerosing peritonitis in humans, bone and/or chondral foci have been reported in the peritoneum. Similarly, in the histopathological examination of mesothelioma, an expression of markers typical for chondral and bone tissue has been shown [29].

The first stage of mesothelial cell transformation to a fibroblast, endothelial cell, smooth muscle cell, chondrocyte, osteoblast, nerve cell or adipocyte involves the formation of a progenitor mesothelial cell, which translocates to the submesothelial layer [30]. This cell displays the features of a multipotential cell which may differentiate to various phenotype cells deriving from one or more primordial cell layers (Fig.) [30].

The mesothelial cell use in grafting

Because of their structural and functional features and the ability of differentiation to other cell types, mesothelial cells are thoroughly studied to use them in organ transplants (Tab.) [22]. The patient's own cells previously propagated in cell culture are used for transplantation (autologous graft) [2].

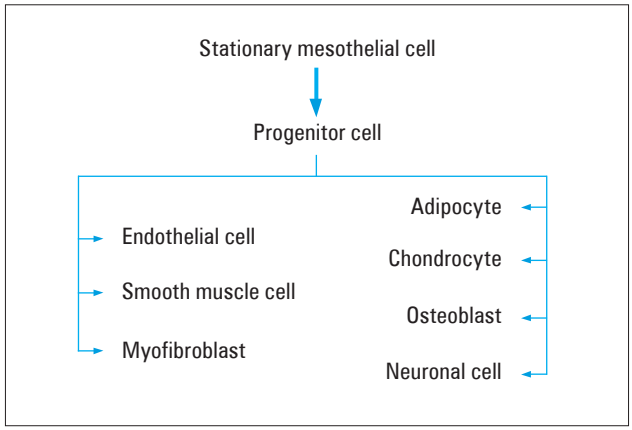

Fig. Mesothelial cell transdifferentiation

Table. Potential use of mesothelial cells

- Prevention and treatment of peritoneal adhesions resulting from surgical procedures
- Treatment of abdominal hernias
- Peritoneal restoration in patients receiving long term peritoneal dialysis
- Prevention of ischemic damage of myocardium after myocardial infarction
- Damaged nerves regeneration
- With appropriate modification, producing proteins by genetic recombination

There are several ways of obtaining mesothelial cells. In animals a tissue sample from the omentum is obtained during laparoscopy, or a trypsin solution peritoneal cavity lavage with the use of a peritoneal catheter is performed [31]. In humans a small sample of the lesser omentum is collected during a surgical peritoneal catheter implantation [32]. In culture mesothelial cells are distinguished with the use of flow cytometry, from the phospholipids content in the cell supernatant, prostacyclin production, cytoskeleton proteins, or lipids content [32,33]. Mesothelial cells are able to replicate 9 times in the culture [32]. After replication, the cell suspension in fetal plasma with 10% dimethyl sulfoxide is stored in liquid nitrogen [34]. Another method of obtaining mesothelial cells is their isolation from the tunica vaginalis. During fetal growth, the peritoneum fragment goes down to the scrotum forming the tunica vaginalis which contains mesothelial cells. Those cells have been previously isolated from the tunica vaginalis in animals (dogs) and from a patient during a surgical procedure of hydrocele testis removal [35]. Taking a sample of this tunica is less dangerous for the patient as it does not require intraabdominal intervention.

Peritoneal dialysis

Mesothelial cell transplantation could be used in chronic renal failure patients receiving peritoneal dialysis. Biologically non-compatible dialysis liquids with high glucose level, high molality and low pH, containing glucose degradation products released during thermal sterilization, and AGEs induce structural and functional peritoneal damage. Long-term exposure to these liquids and episodes of acute peritonitis, result in the damage (decrease of the number of microvilli), or mesothelial cell atrophy, neoangiogenesis, fibrination and peritoneal sclerosis. These alterations induce ultrafiltration and decreased peritoneal dialysis efficacy [36]. The first mesothelial cell transplantation was performed at the end of the 80ies of the 20th century. The cells propagated in culture were used to rabbits with staphylococcal peritonitis. Already within 3 days, a layer of transplanted mesothelial cells was reported on the damaged peritoneal surface. These cells were identified through the presence of large vacuoles and microvilli on the surface of the whole cell [33]. A similar procedure was performed in patients with acute peritonitis receiving peritoneal dialysis who were given mesothelial cells propagated in culture. In the peritoneal biopsy performed within 3 and 6 days after the transplantation, a damaged peritoneum surface inlay of transplanted cells was reported [33]. Positively charged mesothelial cells are attracted by the negatively charged peritoneal surface at the mesothelial defect. This is how the continuity of the peritoneum is restored. Similar attempts have also been reported by other authors [37,38]. Mesothelial cells have been marked with fluorescents which enabled an accurate observation of time, migration path and the area of their incorporation to the peritoneum [16,37]. Mesothelial cell transplantation may make it possible to restore peritoneal continuity. However, restoration of physiological functions of these cells and of the whole peritoneum has not been achieved so far [38]. Following mesothelial cell transplantation in animals, experimental peritonitis would result in a larger contribution of these cells to the activation and a longer duration of the inflammatory state [38].

For several reasons mesothelial cell transplantation has not yet been accepted as a method of damaged peritoneum restoration in patients on peritoneal dialysis. First, the transplanted cells enhance the inflammation via increased release of proinflammatory factors. Second, there are difficulties in obtaining mesothelial cells for transplantation in elderly patients treated with long-term dialysis. Third, the optimal moment for performing such transplantation cannot yet be precisely determined [39].

Peritoneal adhesions and abdominal hernias

One of complications after abdominal surgical procedures is peritoneal adhesions formation. They may result in ileus, female infertility or chronic pain. Fibrotic peritoneal adhesions are the result of fibrin deposits formation and an inadequate fibrinolytic activity of damaged mesothelial cells. An intraperitoneal administration of mesothelial cells propagated in

culture during the surgical procedure prevents adhesion formation [40]. A more beneficial effect has been demonstrated with the transplantation of the so-called "artificial peritoneum". It is formed of collagen gel containing fibroblasts, and of a single layer of mesothelial cells [41]. The transplantation of such a graft in the area of the damaged peritoneum in experimental animals significantly diminished the adhesions formation [41]. The transplantation of autologous mesothelial cells placed in a layer of fibrin gel to dogs after surgical procedures prevented peritoneal adhesion formation [42].

For treatment of incisional hernias after surgical procedures artificial materials are used (polypropene, polytetrafluoroethene, polyester, polyglycol acid) or natural, e.g. small intestinal submucosa, acellular dermal matrix or bovine epicardium covered with glutaraldehyde. Another approach involves the utilization of materials which are easily covered with mesothelial cells (mesothelialization) *in vivo* [22]. In the first stage there is mesothelial cell adhesion and proliferation. Subsequently this material undergoes degradation leaving a layer of mesothelial cells which may show their biological function. Mesothelial cells adhere most rapidly to material consisting of polypropylene and polyuretan (PL-PU99), less rapidly to polytetrafluoroethene; it depends mainly on the size of pores [23,43].

Myocardial infarction

Experimental studies have been performed recently. The studies were focused on transplantation of mesothelial cells in the treatment of myocardial infarction. The rationale for such studies were reports by Campbell et al. who transplanted a silicone tube to the peritoneal cavity of a rat [44]. In 2 weeks, vessel prosthesis was obtained, formed of an internal layer of mesothelial cells, a middle layer of myofibroblasts and external collagen matrix. Such a prosthesis has been successfully used to form a vessel graft [44]. The ability of mesothelial cell transformation to endothelial cells has also been studied in the myocardial infarction model in a rat. Mesothelial cells were grafted to the necrosis area [45]. After one month, the proliferation of these cells in the myocardial infarction scars and their incorporation to newly formed blood vessels where they phenotypically and functionally transformed into endothelial cells was observed. It has been demonstrated that with the mesothelial cell transplantation, the ejection fraction improves and the left ventricle end-diastolic volume decrease in comparison with the control group [45]. Anticoagulant and fibrinolytic properties of mesothelial cells lining the new vessel lumen are also advantageous. Mesothelial cells administered in the area of the myocardial infarction scar produce several cytokins and growth factors, including VEGF, bFGF, TGF-β, PGF, SDF-1α [46]. These factors influence the neovascularization and acceleration of damaged myocardium tissue restoration. The SDF-1α exerts a particularly strong chemotactic effect on stem cells. It induces the mobilization of these cells from the bone marrow and their attraction to the post infarction area where they undergo further differentiation [46]. There are ongoing studies on mesothelial cell modification with the use of genes coding growth factors, which will allow for an even larger contribution of the genetically modified mesothelial cell to the restoration process [46]. This is how the mesothelial cell transplantation may become a novel myocardial infarction treatment strategy by affecting those cells and their impact on neovascularization (differentiation into endothelial cells, vascular smooth muscle cells and adventitial fibroblasts), the anti-inflammatory, immunomodulatory effect and the production of proteins which accelerate tissue repair [46].

Nerve reconstruction

A novel method of damaged nerve reconstruction is the employment of a tube covered with mesothelial cells. Lundborg et al. used this method to fil a 10 mm defect which occurred as a result of a transected ischiatic nerve in a rat [47]. Within several days a nerve cord was formed between the proximal and distal stump. No difference in density and localization of fibers and conduction velocity between the model which used the mesothelial cell and standard nerve transplantation was demonstrated [47]. In another experiment a 25–30 mm defect of the ischiatic nerve in a rat was filled with an omentum fragment which allowed for obtaining full nerve regeneration [48]. Due to mesothelial cell surfactant production there is no friction of the filled nerve defect with the surrounding tissues. Artificial materials covered with mesothelial cells seem to be an alternative to previous nerve reconstruction methods [22].

Genetic engineering

There are numerous experimental studies with the use of mesothelial cells in genetic engineering currently going on. With the genetic modification of those cells, gene expression for the following proteins has been obtained; thrombomoduline, growth hormone and alfa1 antitrypsin [22]. The intraperitoneal administration of mesothelial cells with an erythropoietin gene inserted in uremic mice results in anemia resolution [49]. After mesothelial cell transplantation with a gene for cytotoxic factor into mice with ovarian cancer, a migration of those cells to the tumor area and prolonged animal survival was reported [50]. The introduction of a gene for the synthesis of factors decreasing neoangiogenesis into mesothelial cells located in the pleura, inhibits the growth of the pulmonary tumor in rabbits [51].

SUMMARY

The first autologous mesothelial cell transplantation was performed in 1991. Since then, the knowledge on the structure and function of these cells has broadened significantly.

Mesothelial cell transplantation has not yet been introduced into clinical practice due to certain limitations. First, there are difficulties in obtaining cells for culture. They may be isolated in humans from a fragment of the lesser omentum or from the dialysis liquid in individuals treated with peritoneal dialysis [32,34]. The mesothelial cell transplantation in order to prevent postoperative adhesions occurrence would therefore be associated with the need for an additional laparotomy or laparoscopy before the actual surgical procedure. This procedure is, however, hardly acceptable for the patient, it has not therefore been implemented to practice. In patients on peritoneal dialysis, the majority of mesothelial cells obtained from the dialysis liquid have the phenotype of a fibroblast cell (they undergo transdifferentiation) [39]. In this way it is therefore difficult to obtain an appropriate number of cells suitable for propagation in culture.

Another factor limiting the use of mesothelial cell transplantation in clinical practice represents an unclear method of eliminating the excess of transplanted cells administered to the peritoneal cavity. They may undergo apoptosis, be removedd by macrophages, or taken up by the lymphatic system [34]. In the current studies there is no sufficient data on methods aiming at removal the excessive transplanted cells, or on the consequences of such a process.

In patients on peritoneal dialysis, mesothelial cell transplantation may induce peritonitis. This is the reason for the ongoing studies on the possibility of genetic modification introduction in culture derived mesothelial cells by introducing antiinflammatory factor genes into them (i.e. the interleukin-1 antagonist receptor gene) [39]. Depriving mesothelial cells of the ability to alter their proinflammatory properties affecting the peritoneum will lead to transplantation of those cells to restore the peritoneum in patients treated with long-term dialysis.

At last, one of the most important issues regarding the introduction of mesothelial cell transplantation to clinical practice is the potential risk of their malignant transformation [39]. After its differentiation the mesothelial cell demonstrates properties of a multipotential cell and as such may also differentiate to a cancer cell. This confers a significant risk of inducing cancer with the mesothelial cell transplantation. There have been, however, few clinical studies performed so far for an unequivocal determination of the degree of such a risk [39].

Solving these issues associated with mesothelial cell transplantation will result in the use of this method in tissue restoration and regeneration, and in genetic engineering in the future.

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