Advanced Glycation End-Products and Peritoneal Sclerosis

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Long-term continuous ambulatory peritoneal dialysis (CAPD) often causes peritoneal fibrosis and sclerosis with a loss of function, and some CAPD patients develop sclerosing encapsulating peritonitis. Glucose-based peritoneal dialysis fluids readily produce glucose degradation products by heat sterilization, and glucose degradation products accelerate the formation of advanced glycation end-products (AGE) in the peritoneal cavity. The accumulation of AGE is observed in peritoneal mesothelial and submesothelial layers in CAPD patients, accompanied by enhanced expression of various growth factors and peritoneal thickening. The expression of transforming growth factor-β1 (TGF-β1), macrophage-colony stimulating factor, and vascular endothelial growth factor (VEGF) is distributed in the peritoneum similarly to that of AGE. In CAPD patients with low ultrafiltration (UF) capacity, peritoneal membrane is thickened owing to an increase in the number of cells such as fibroblasts and macrophages and collagen in the submesothelial layer. AGE is detected in the fibroblasts and macrophages as well as degenerated collagen. These cells in the submucosal layer are almost positive for the receptor for AGE (RAGE) and uptake AGE. The intensity of AGE accumulation and the expression of growth factors are associated with the severity of UF impairment. In fact, the accumulation of AGE and the expression of growth factors are recognized most markedly in the peritoneum of CAPD patients with low UF and sclerosing encapsulating peritonitis. In conclusion, long-time CAPD with heat-sterilized peritoneal dialysis fluid promotes AGE accumulation in the peritoneal membrane and alteration in peritoneal cell function and dialysis quality, followed by peritoneal sclerosis, and, finally, sclerosing encapsulating peritonitis.

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It is a serious problem that continuous ambulatory peritoneal dialysis (CAPD) patients gradually lose peritoneal membrane function and finally develop sclerosing encapsulating peritonitis. In past decades, glucose-based peritoneal dialysis fluids have been used for CAPD treatment. However, a large amount of glucose degradation products formed through a heat-sterilization procedure1,2 accelerated the formation of advanced glycation end-products (AGE).3,4 AGE is involved in the pathogenesis of diabetic complications, atherosclerosis, and aging.6,8

AGE in the Peritoneum of CAPD Patients

In the peritoneum of CAPD patients, long-term contact with peritoneal dialysis fluids containing high concentrations of glucose degradation products promotes AGE accumulation,4,9 and contributes to a loss of ultrafiltration (UF) capacity.4,5 The distribution pattern of AGE in the peritoneum is different between various chemical structures of AGE. Imidazolone is detected mostly in degenerative collagen including vascular walls, whereas Nε-(carboxymethyl) lysine exists both in peritoneal cells and collagen.10 In addition, a ligand for AGE receptor on macrophages, an AGE mainly originated from glycolaldehyde (ODI-GLC 19-positive AGE), is localized exclusively in peritoneal cells.10 In low-UF patients, imidazolone is distributed widely in the submesothelial layer, colocalizing with increased collagen.10 Imidazolone seems to directly affect the structural integrity of peritoneal tissues by...
cross-linking matrix molecules such as collagen, leading to alteration in membrane quality.

**AGE Receptors**

The uptake of AGE by peritoneal cells including fibroblasts is performed via AGE receptors. Both receptor-dependent and -independent processes are responsible for the deterioration of UF capacity. There are several subclasses of AGE-specific receptors according to their soluble components, which may play different functional roles. The receptor for AGE (RAGE) is a well-characterized AGE receptor that is involved in intracellular signal transduction rather than AGE turnover. Nε-(carboxymethyl) lysine is a representative ligand for RAGE and up-regulates its expression. Cell-surface AGE receptors such as RAGE, galectin 3, and macrophage scavenger receptor are identified on circulating monocytes, endothelial cells, and renal cells. The mouse macrophage cell line expresses macrophage scavenger receptor and galectin 3 on its surface. Recently, glycolaldehyde was shown to be an active ligand for macrophage scavenger receptor. We showed by immunohistochemistry that increased RAGE expression in peritoneal fibroblasts colocalized with intracellular AGE. This finding suggests that AGE is taken up by peritoneal cells at least via RAGE, and this event is followed by cellular reactions and subsequently up-regulation of various growth factors.

**Growth Factors**

Peritoneal mesothelial cells produce many cytokines and growth factors. All types of AGE are colocalized in the peritoneum with growth factors, such as transforming growth factor-β1 (TGF-β1), macrophage-colony stimulating factor (M-CSF), and vascular endothelial growth factor (VEGF). The expression intensity of the growth factors are paralleled with severity of AGE accumulation. Hepatocyte growth factor (HGF) is expressed moderately in peritoneum without severe morphologic alteration. TGF-β1 plays a central role in the process of fibrogenesis and promotes the proliferation of fibroblasts to increase the expression of collagen type 1 and 3, and tissue inhibitor of metalloproteinase 1. In a cell culture study, a high concentration of glucose induces expression of TGF-β1 in mesothelial cells.

M-CSF is a main growth factor driving the recruitment and the local proliferation of macrophages in injured organs. TGF-β1 and M-CSF co-exist mostly in infiltrating macrophages and fibroblasts. VEGF is a mitogen for endothelial cells inducing angiogen-
esis, and a vascular permeability factor inducing endothelial cells to increase cellular fenestration. Increased expression of VEGF was colocalized with TGF-β1 and M-CSF. Glucose degradation products in CAPD fluids enhances the production of VEGF by mesothelial cells. Furthermore, mesothelial cells are responsible for VEGF production after TGF-β1 exposure.

HGF protects organs from various injuries. HGF expression is increased substantially in the peritoneal tissues of CAPD patients before TGF-β1 is expressed markedly. HGF released from peritoneal mesothelial cells is suggested to be involved in the healing process of peritonitis. HGF may play a role in preventing the peritoneum from further damage in injured lesions, although its expression is reciprocally suppressed owing to an increase in TGF-β1.

**Role of AGE and Growth Factors in Peritoneal Sclerosis and UF Failure**

Figure 1 indicates the process of UF failure after an increase in AGE formation. A large amount of AGE formed during CAPD treatment binds to AGE receptors in various cells in the peritoneum. Interaction between AGE and the receptors leads to the activation of secondary messenger systems, and increases the production of VEGF and TGF-β1. The increased expression of VEGF enhances angiogenesis and vascular permeability, followed by increased leakage of macromolecules, and, finally, contributes to UF failure. TGF-β1 promotes the proliferation of fibroblasts, which increases the production of M-CSF, leading to both the recruitment and local proliferation of macrophages. These macrophages further increase the production of TGF-β1, creating a vicious cycle. TGF-β1 suppresses HGF expression and simultaneously promotes the peritoneal fibrosis via the progression of fibroblast proliferation, the production of collagen types 1 and 3, and tissue inhibitor of metalloproteinase 1. Thus, the increased expression of TGF-β1 induces mesothelial thickening and peritoneal fibrosis, and contributes to UF failure.

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