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Theme : Miscellaneous

## **In vitro capillary tubes formation is enhanced by mesothelial cell VEGF secretion after RAGE activation**

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**Background.** Peritoneal dialysis fluids (PDFs) have been shown to induce peritoneal neoangiogenesis. Glucose, glucose degradation products (GDPs) and advanced glycation end products (AGEs) are considered to be possible triggers, so we investigated whether they could modify the vascular endothelial growth factor (VEGF) production by human peritoneal mesothelial cells (HPMCs) and the capacity of human umbilical vein endothelial cells (HUVECs) to form capillary tubes.

**Methods.** AGE and VEGF concentrations in PD effluents of 5 non diabetic patients were determined after short and long dwell. VEGF production by HPMC exposed to different glucose concentrations, 3 deoxyglucosone (3-DG) or carboxymethyllysine-albumin (CML albumin) a high affinity receptor of AGE (RAGE) ligand was determined in vitro. HUVEC capacity to form capillary tubes was evaluated in Matrigel (three dimensions) in a coculture system after HPMC stimulation by CML-albumin. Some blockade experiments were performed using anti-RAGE or anti-VEGF antibodies. Endothelial cell VEGF receptor (VEGFR-1 and -2) expression was measured by ELISA.

**Results.** Compared to short dwell, AGE and VEGF concentrations in PD effluents were significantly increased during long dwell. In vitro, CML-albumin increased VEGF production by HPMC (p<0.001). HUVEC capacity to form capillary tubes was enhanced when coculture was performed with HPMC stimulated by CML-albumin. Preincubation of HPMC with an anti-RAGE or addition of anti-VEGF antibody in culture medium reversed this effect (<0.001) indicating RAGE involvement in the stimulation of HPMC. Endothelial cell VEGFR-1 was enhanced by CML-albumin in HUVECs.

**Conclusion.** In a coculture system, we demonstrated that VEGF production by HPMC favors capillary tube formation through a mesothelial RAGE activation. VEGF modulation could well be considered as a new target in the prevention of neoangiogenesis and ultrafiltration failure in PD patients.