Characterization of IL-17-induced VEGF production by human peritoneal mesothelial cells in the context of peritoneal dialysis

Dialysis is a means of removing waste and excess fluid from the body when the kidneys have failed. In contrast to "artificial kidney", peritoneal dialysis (PD) uses the patient's own peritoneum as a dialysis device. A sterile PD fluid is introduced into the peritoneal cavity through a catheter placed in the abdominal wall. As the fluid bathes the extensive network of capillaries covering the peritoneum, any waste moves down the concentration gradient from blood into the PD fluid until equilibrium is reached. At this point, the spent PD fluid ("effluent") is drained and replaced with fresh solution. The main clinical benefit of PD is that it enables removal of waste in a continuous manner similar to that provided by the kidneys. Moreover, PD can easily be performed at home and thus offers flexibility and lifestyle choices. However, although PD is used by an estimated 200,000 patients worldwide and is the most commonly practiced form of home dialysis, the method is still considered underutilized. One of the barriers to proliferation of PD is a commonly held view that the peritoneum can function effectively as a dialysis membrane only for few years. Indeed, for reasons that are incompletely understood, the peritoneum of some patients becomes unable to sustain treatment. The peritoneal membrane dysfunction is largely related to angiogenesis, i.e. the formation of new (and often abnormal) capillaries. Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis. The main source of VEGF in the peritoneum is the fine layer of mesothelial cells (HPMCs) that covers the peritoneal membrane. It is, however, unclear what makes HPMCs release increased quantities of VEGF in some patients. It has recently transpired that certain infections plus chronic exposure to PD fluids may result in the accumulation in the peritoneum of cells known as T_H17 and γδ T lymphocytes. These cells secrete a molecule designated as interleukin-17 (IL-17) that can profoundly affect the function of HPMCs. Having performed pilot experiments, we have a good reason to hypothesise that IL-17 drives effectively peritoneal VEGF production.

Here, we propose to further characterise in detail the molecular processes responsible for this effect using HPMCs cultured in the laboratory. In particular, the analysis will aim at identifying the transcriptional mechanisms whereby IL-17 activates the VEGF gene. Furthermore, we will want to determine whether VEGF released by HPMCs in response to IL-17 displays biological activity towards vascular cells so that they can proliferate and form new capillaries. We will also compare the magnitude of VEGF production by HPMCs treated with clinical samples of PD effluent that differ in the level of IL-17. And finally, we will determine whether by silencing the molecular pathways identified it is possible to inhibit VEGF expression and adverse angiogenesis triggered by PD effluent containing increased levels of IL-17.

The need for the studies proposed is dictated by the fact that VEGF is an exemplary gene whose expression is regulated strictly in a context-dependent manner. It means that the same stimulus may produce different effects in different tissues or in health and disease. Conversely, the same effect can be achieved through different mechanisms or may require a different combination of stimuli. Therefore, it is essential to study VEGF regulation in cells isolated exactly from the organ of interest rather than to draw conclusions based on the observations made in other tissues or in laboratory animals. We believe the present project may shed new light on the pathogenesis of adverse changes that develop in human peritoneum during PD and suggest potential target molecules for interventions that may increase the longevity of the peritoneal membrane.