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Expression and regulation of calcium-regulatory proteins in cultured mesothelial cells

Peritoneal dialysis has been successfully used for more than three decades as a maintenance renal replacement therapy. However, local tissue toxicity is a major limitation to technique survival. Peritoneal calcification is one feature of peritoneal membrane degeneration. The incidence of peritoneal calcification increases with time on PD, is more common in children than in adults and is associated with a poor prognosis with regard to technique survival.

In the present studies, we investigated potential factors involved in the pathogenesis of dystrophic calcification, with particular emphasis to the role of locally produced calcium-regulatory proteins. We determined their expression and regulation by the components of dialysate and cytokines in cultured mesothelial cells. Our studies yielded the following results: (1) Several calcium-regulatory proteins are expressed by mesothelial cells, including matrix Gla protein, fetuin, bone morphogenic protein-2 and osteoprotegerin. (2) MGP is abundantly expressed by mesothelial cells in vivo and in vitro. (3) High glucose, acidosis and IGF-1 downregulate MGP expression in the mesothelial cell line Met5A; TGF-ß1, calcium and 1,25$(OH)_2$ D3 induced MGP expression. (4) At least in an immortalized cell line, TGF-ß1 markedly stimulates the expression of MGP gene and protein in dose- and time-dependent manner, this processes may involve multiple signaling

pathways. (5) Phosphorus increases calcium deposition in mesothelial cells. This effect is in part reduced by TGF-ß1 as well as an inhibitor of phosphorus cotransporter.

Taken together, we describe for the first time that MGP is expressed by human peritoneal mesothelial cells. MGP expression is regulated as part of a complex network by locally acting growth factros and cytokines. Conventional PD fluids substantially alter this homeostasis. Although the significance of MGP expression and regulation remains to be elucidated, our findings imply that MGP may play a role in the pathophysiology of peritoneal calcification during long-term peritoneal dialysis.