S 21-4

RENAL AQUAPORINS: PHYSIOLOGY AND PATHOPHYSIOLOGY

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The discovery of aquaporin membrane water channels by Peter Agre and co-workers answered a longstanding biophysical question of how water crosses biological membranes, and provided insight, at the molecular level, into the fundamental physiology of water balance regulation and the pathophysiology of water balance disorders. In the kidney AQP1-4, AP6-8 and AQP11 are abundantly expressed and multiple studies have underscored the essential roles of AQP1-AQP4 in renal regulation of body water balance. Vasopressin regulates acutely the water permeability of the kidney collecting duct by regulation of AQP2 trafficking from intracellular vesicles to the apical plasma membrane. This involves complex signalling mechanisms. In addition long-term regulation of AQP2 and AQP3 expression act in concert to tightly control collecting duct waters reabsorption. Development of transgenic mice including collecting-duct specific AQP2 gene knock out mice have provided further insight into the complex regulation of AQP2. Aqauglyceroporins are widely expressed in many organs although little is known about their physiological or pathophysiological roles. Development of AQP7 and AQP9 gene knock-out mice have allowed detailed analyses of cellular and organ expression. Moreover phenotype analyses have revealed roles of AQP9 and AQP7 in metabolism including diabetes mellitus.

S 22-1

OSTEOPOROSIS AFTER SOLID ORGAN AND BONE MARROW TRANSPLANTATION

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Organ transplantation is now the treatment of choice for many patients with life-threatening chronic disease. Significant advances in transplantation immunology have provided new hope for patients with end-stage renal, hepatic, cardiac, and pulmonary disease. Bone marrow transplantation (BMT) is the treatment of choice for many hematological diseases, and the number of long-term survivors has increased remarkably over recent decades. In addition to other classical complications of transplantation, many recipients unfortunately suffer from osteoporosis and fragility fracture as well. As the number of patients surviving transplantation continues to grow, transplantation related bone loss will become an increasingly common cause of secondary osteoporosis. In solid organ transplantation, risk factors for osteoporosis and exposure to drugs associated with bone loss (loop diuretics, anticoagulants, and corticosteroids) are common among patients who are candidates for transplantation. Moreover, pretransplant bone and mineral homeostasis may also be influenced by the diseased organ, particularly in renal and hepatic failure. However, it is generally believed that post-transplantation immunosupression plays the pivotal role in the pathogenesis of bone loss and fracture. Previous studies have reported that a 5~15% loss in the bone mineral density at the lumbar spine and the femoral neck within 1 year BMT. After BMT, the major part of bone loss occurs during the first 6 months, which is the period when the bone turnover markers show an increase in bone resorption and suppressed bone formation, namely, biochemical uncoupling. It has been suggested that the progressive increase in bone resorption during the immediate post-BMT period is related to glucocorticoid exposure, hypogonadism, cytokine changes, and changes in growth factors as macrophage-colony stimulating factor. Also, use of glucocorticoids, changes in the proinflammatory cytokines, damage of osteoprogenitor cells by total body radiation and high-dose chemotherapy, and down-regulation of bone growth factors (IGF-I, FGF-2) cause low bone formation during the post-BMT period. In addition, our recent data suggest that IL-7 plays an important role for bone loss after BMT. An increased IL-7 level after BMT is associated with suppressed bone formation and enhanced bone resorption, and this may result from the interaction between the IL-7 and RANKL pathways. Finally, at least in the female BMT recipients, a deficiency of estrogen appears to provoke the up-regulation of IL-7, as the previous in vitro data has suggested. Because bone loss and fracture incidence are greatest immediately after transplantation, early recognition of risk factors and rapid institution of preventive measures are needed to diminish the occurrence of fractures. Effective therapies incorporate pretransplant measures to treat preexisting bone disease and post-transplantation measures, including exercise, calcium and vitamin D repletion, and antiresorptive agents initiated before or shortly after transplantation, to counter the glucocorticoid-induced rapid bone loss.