In human ageing, changes in calcium distribution take place. The calcium content in bone tissue diminishes and extraskeletal calcifications, especially vascular calcifications, occur. Recent research has documented the fact that the vascular calcification process is regulated [1,2] and that this process is accelerated in uraemia [3]. Multiple factors have been proposed to influence the process of ageing. An interrelationship between sex hormones and calcium homeostasis is well established [4]. In the last decade, a new hormone, klotho, has emerged as an important player in the ageing process [5,6], and a connection between klotho and the kidneys has been proposed [7,8]. Furthermore, a recent article in ‘Science’ by Chang et al. [9] links klotho to calcium homeostasis.

Calcium has important extracellular as well as intracellular functions. Its extracellular functions include a role in blood clotting, maintenance of plasma membrane integrity and intercellular adhesion. Extracellular calcium provides a source of Ca\(^{2+}\), essential for intracellular processes. Furthermore, extracellular calcium provides a constant supply to the exchange of calcium within the skeleton, which represents the largest compartment of total body calcium, containing more than 99%.

Intracellular calcium is an important intracellular second messenger regulating multiple cellular functions, such as metabolism, motility, secretion and proliferation. It is a cofactor for several intracellular enzymes, e.g. mitochondrial dehydrogenases, various phospholipases and proteases [10,11]. The free extracellular Ca\(^{2+}\) concentration is maintained within a narrow range [12]. The traditional model of overall calcium homeostasis has two key components. The first comprises several distinct cell types that sense changes in extracellular Ca\(^{2+}\) leading to appropriate changes in the secretion of the calciotropic hormones, parathyroid hormone (PTH), 1,25(OH)\(_2\)D and calcitonin [13,10]. The second key component is the effector systems, specialized calcium-translocating cells of the kidneys, bones and intestine, that respond to the calciotropic hormones.

In Ca\(^{2+}\)-translocating epithelial cells in the distal tubule and proximal intestine, the active Ca\(^{2+}\) absorption is a three-step process, consisting of passive entry of Ca\(^{2+}\) across the luminal or apical membrane, diffusion of Ca\(^{2+}\) through the cytosol, where the Ca\(^{2+}\) is buffered by calcium-binding proteins (calbindin-D\(_{28K}\) and calbindin-D\(_{9K}\)), and active extrusion of Ca\(^{2+}\) across the basolateral membrane by the Na\(^+\)/Ca\(^{2+}\)-exchanger in the kidneys and the plasma membrane Ca\(^{2+}\)-ATPase in the kidneys and intestine [14]. Until recently, the mechanism by which Ca\(^{2+}\) enters the translocating epithelia was unknown. A major breakthrough came with the identification of an epithelial Ca\(^{2+}\) channel family consisting of two members of the transient receptor potential (TRP) superfamily, TRPV5 and TRPV6 [15]. TRPV5 is localized predominantly at the luminal membrane of the distal convoluted tubule and connecting tubule in the kidneys. TRPV6 is localized in the brush border membrane of the duodenum. Both channels are permeable for monovalent and divalent cations with a high selectivity for Ca\(^{2+}\). At the transcriptional level, TRPV5 and TRPV6 are controlled by 1,25(OH)\(_2\)D\(_3\), and independent of vitamin D by dietary calcium and oestrogen [16–19]. The finding that oestrogen regulates the expression of calcium channels might contribute further to understanding the pathogenesis of a negative calcium balance in ageing and post-menopausal women. TRPV5 and TRPV6 are constitutively active.
Regulation and effects of klotho

![Diagram showing the regulation and effects of klotho.](image)

Fig. 1. Regulation and effects of klotho: this schematic diagram illustrates some of the factors involved in the regulation of klotho, with 1,25(OH)₂D being a major stimulus, which is feedback regulated by klotho via an inhibition of the 1α-hydroxylase activity. Klotho has a significant impact on the Ca²⁺ reabsorption via the epithelial Ca²⁺ channel, TRPV5, in the distal convoluted and connecting tubules. Klotho is produced in the kidneys and is reduced in chronic uraemia. Mutations in the klotho gene and klotho deficiency have been related to the process of ageing, osteoporosis, arteriosclerosis, ectopic calcifications and skin atrophy.

As such, a short-term acting mechanism must exist that controls the activity of these channels located on the plasma membrane. It is suggested that TRPV5 is present in the intracellular compartments from where it can be shuttled to the plasma membrane in a controlled fashion. Trafficking of TRPV5 or TRPV6 to the plasma membrane provides a short-term mechanism to increase renal or intestinal Ca²⁺ uptake [14].

A great deal of work on the identification and clarification of the regulation of TRPV5 and TRPV6 has been performed by the group of Bindels et al. [15–22]. Recently, Chang et al. [9] from the same group published an article in ‘Science’, stating that the mammalian hormone, klotho, a β-glucuronidase, hydrolyses extracellular sugar residues on TRPV5, entrapping the channel in the plasma membrane and thereby increasing Ca²⁺ translocation. Both TRPV5 and klotho are positively regulated by vitamin D, underlining the importance of an interrelationship between both factors in controlling Ca²⁺ transport capacity in the kidneys [16,17,23]. Klotho is a membrane protein which is abundantly expressed in the kidney and shown to be co-localized with TRPV5 in mice kidneys [9]. Analysis of cDNA revealed that the klotho gene also expresses a secreted form due to alternative RNA splicing [24]. The molecular function of klotho is only sparsely known. Polymorphism in the klotho gene has been linked to reduced bone mineral density in humans [25]. A variant of klotho, associated with a decrease in survival when in homozygosity, has been proposed from a population-based association study [5,26]. Mutation of the mouse klotho gene (named after the Greek ‘Fate’ purported to spin the thread of life) leads to a syndrome resembling ageing with short life span, infertility, skin atrophy, arteriosclerosis and osteoporosis [24]. Furthermore, klotho null-mice had hypercalcaemia and hypervitaminosis D [23]. The klotho gene is expressed predominantly in the kidney [24]. It has been postulated that uraemia might be associated with diminished renal production of klotho, which might provide some background for the uraemic symptoms, resembling ageing, such as accelerated arteriosclerosis, ectopic calcifications and skin atrophy [8].

The article of Chang et al. [9] expands our knowledge on the regulation of the activity of calcium channels. The implication that klotho is so closely involved in calcium homeostasis (Figure 1) provides an interesting new association between calcium, ageing and uraemia.

Conflict of interest statement. None declared.

References

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