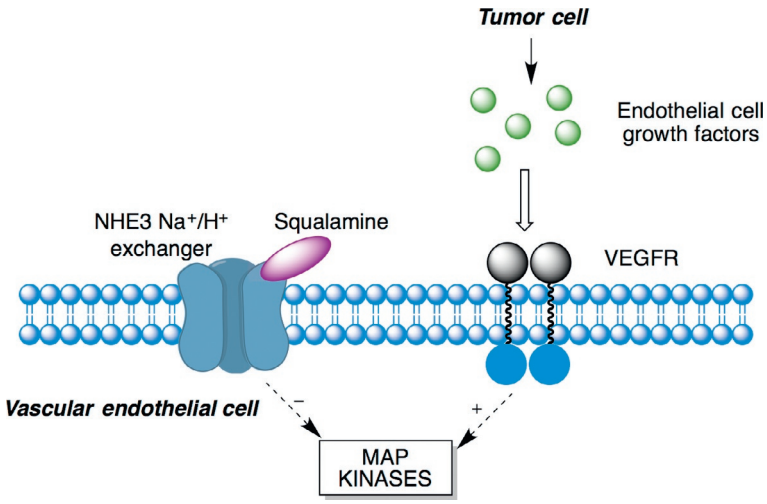

FIGURE 11.24

Inhibition of the NHE3 Na^+/H^+ exchanger by squalamine.

in other mechanisms, such as apoptosis induction.[91] On these bases, it was approved by the FDA in 2006 for the treatment of MM[92] and ENL in association with dexamethasone[93] and cytotoxic agents such as cyclophosphamide.[94] The EMA approved thalidomide in 2008 to treat MM in combination with prednisone[95] and/or melphalan. Orphan indications for this drug include primary brain malignancies, Kaposi's sarcoma, and myelodysplastic syndrome. Thalidomide is also a lead compound in the development of a class of drugs known as immunomodulatory drugs (IMIDs®).[96]

Since it was demonstrated that inhibition of angiogenesis by thalidomide requires prior metabolic activation,[97] a large number of potential metabolites have been evaluated. Lenalidomide (CC-5013, Revlimid®) is a thalidomide analog that was approved by the FDA in 2006 in combination with dexamethasone for the treatment of MM patients who have received at least one prior therapy.[98] It has also shown efficacy in the hematological disorders known as the myelodysplastic syndromes and has undergone numerous clinical trials alone or in combination with other drugs. Pomalidomide (CC-4047, Pomalyst®, Imnovid®) is another antiangiogenic and immunomodulator thalidomide analog that entered phase II assays for prostate cancer and was approved in 2013 by the the FDA and the EMA as a treatment for some cases of MM.[99,100] The *S*-isomer of pomalidomide is the more potent enantiomer, but it has been shown to undergo rapid racemization in human plasma—a finding that supports the development of these drugs in their racemate form.[101]