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A review of the latest insights into the mechanism of action of strontium in bone

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ABSTRACT

Interest in strontium (Sr) has persisted over the last three decades due to its unique mechanism of action: it simultaneously promotes osteoblast function and inhibits osteoclast function. While this mechanism of action is strongly supported by in vitro studies and small animal trials, recent large-scale clinical trials have demonstrated that orally administered strontium ranelate (SrRan) may have no anabolic effect on bone formation in humans. Yet, there is a strong correlation between Sr accumulation in bone and reduced fracture risk in post-menopausal women, suggesting Sr acts via a purely physiochemical mechanism to enhance bone strength. Conversely, the local administration of Sr with the use of modified biomaterials has been shown to enhance bone growth, osseointegration and bone healing at the bone-implant interface, to a greater degree than Sr-free materials. This review summarizes current knowledge of the main cellular and physiochemical mechanisms that underly Sr's effect in bone, which center around Sr's similarity to calcium (Ca). We will also summarize the main controversies in Sr research which cast doubt on the 'dual-acting mechanism'. Lastly, we will explore the effects of Sr-modified bone-implant materials both in vitro and in vivo, examining whether Sr may act via an alternate mechanism when administered locally.

Strontium (Sr) is an alkali earth metal that was first discovered as a result of lead mining in Scotland in the 18th century (Hope, 1798). It is an abundant trace element in ocean water, ground water and the earth's crust and is naturally occurring in the human diet, with the highest concentrations found in leafy greens (64 mg/kg), grains (18 mg/kg) and seafood (24 mg/kg) (Watts and Howe, 2010; Rosenthal et al., 1970). The physiological role of Sr was first observed in 1870, when it was discovered that it could naturally incorporate into the bones of animals fed small doses of the element. (Papillon, 1870) The observation that Sr was a bone-seeking element like calcium (Ca) led to further research into its effects in other organs. In later years it was found that Sr, like Ca, could affect the contractility of the heart, was able to control parathyroid secretions and stimulate uterine contractions (Dow and Stanbury, 1960).

Cell replication The targeted knockdown of CaSR attenuates Sr-mediated cell replication in vitro, suggesting it plays a critical role in Sr's anabolic effects on osteoblast cells, Differentiation and survival Osteoblasts differentiate from bone-marrow mesenchymal stem cells (MSC's) after they express specific osteogenic genes such as alkaline phosphatase (ALP), bone sialoprotein and osteocalcin (OC) (Peng et al., 2009). . Effects of Sr on osteoclast cells Osteoclast precursors and mature osteoclasts express the CaSR on their cell membrane, and therefore, we will first briefly discuss the effect that Ca exerts on osteoclasts and relate this to Sr's effect.

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Apoptosis Sr has been shown to dose-dependently stimulate apoptosis in mature osteoclasts, similarly to Ca stimulation. For Ca, this is mediated by the activation of PLC and the production of inositol phosphate (IP), which leads to the nuclear translocation of NF-kB. The mechanism of action of Sr in bone remains elusive, even after decades of in vivo, in vitro and clinical studies. Even though Sr has been shown to activate the CaSR in osteoblast and osteoclast cells, experiments where a receptor is transfected to a cell line that does not endogenously express it presents certain limitations

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