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Newly Discovered Molecules as Potential Candidates for Treating Osteoporosis

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Introduction

Osteoporosis is one of the most common age associated comorbidity affecting more than 40 million worldwide and the complications are as severe as other disorders like heart failure and hypertension. Although the frequent diagnosis of this metabolic disorder was observed in women, presence of it in men is not an outlandish phenomenon. Two out every three women over the age of 50 are likely to face osteoporosis related fractures in their lifetime. To maintain the structural and functional integrity and to provide the load bearing flexibility, bone undergoes a continuous dynamic process called bone remodelling. This process is controlled by two major bone cell types-osteoblasts, the bone forming units and the osteoclasts that function as bone resorbing cells. Imbalance in this process would lead to bone disorders such as osteoporosis, osteopetrosis and Paget's disease. Osteoporosis can be broadly divided into two types- primary osteoporosis which include age related and post-menopausal osteoporosis; and secondary osteoporosis which are caused mainly due to metabolic imbalance of essential molecules or concomitant effects of medicines as in case of long-term glucocorticoid administration. By far, the only most effective anabolic treatment used in clinics is intermittent injections of parathyroid hormone. Thus, the challenge remains to find molecules that can work at par or better than the existing treatment. In the present review we have briefly summarised the potential candidates for osteoporotic treatment.

Inhibitor of Gut Derived Serotonin

Serotonin (5-hydroxytryptamine) is one of the most important neurotransmitters, which also acts as a hormone in the periphery. The two most crucial steps in the multistep pathway of serotonin synthesis are the conversion of L-Tryptophan to L-5OH-Tryptophan by Tryptophan Hydroxylase (Tph) and L-5OH- Tryptophan to Serotonin by an aromatic L-amino acid decarboxylase. There are two isoenzymes of Tph in mice - Tph1 and Tph2. While circulating serotonin is synthesised by Tph1 which is mostly expressed in the Enterochromaffin cells, the Serotonin in brain is produced from serotonergic neurons that exclusively express Tph2 [1].

These serotonins from two different sources have completely different functions; gut- derived serotonin (GDS) acts as a hormone, while brain derived serotonin (BDS) functions as a neurotransmitter. Recent evidences from literature suggest the role of GDS in bone mass regulation. GDS acts as a strong inhibitor of osteoblast proliferation and bone formation without perturbing the bone resorption [2]. Yadav et al. [3,4] showed that decreasing the GDS synthesis using Tph1 inhibitor (LP533401) increases the bone mass not only in wild type mice but also in the mice and rat models of postmenopausal osteoporosis [3-5]. This oral administration of LP533401 is not only very specific but also a very effective alternative to the present osteoporotic therapies.

Vitamin B12 and its downstream molecules

Vitamin B12 (B12) is a vital water-soluble vitamin that serves as a cofactor for the enzyme's methionine synthase and L- methylmalonyl–coenzyme A mutase [6], which in turn synchronize the fundamental metabolic cellular processes. Mammals are incapable of synthesizing B12 and are therefore dependent on their diet for the supplement. B12 was first associated with osteoporosis and fractures in individuals with pernicious anaemia. While in one study Kim et al showed a direct effect of B12 on osteoblastic proliferation [7], another contrary

study ruled out any direct effect and implied in vitro stimulation of osteoclastogenesis through elevated homocysteine and methylmalonic acid levels [8].

Recently, Roman Garcia et al. [9] corroborated the negative effect of vitamin b-12 deficiency on bone development and maintenance. To delineate this phenomenon, they used a stomach specific protein Gif – gastric intrinsic factor, whose insufficiency led to vitamin B12 deficiency. The second progeny of Gif−/− had imperceptible serum levels of B12 accompanied by severe growth retardation. Two independent studies have shown reduced bone mineral density in individuals with low levels of B12 [10,11]. The heterogeneity of methodologies and experimental conditions emphasise on further studies to elucidate the mechanism of action of B12 in prevention and cure of bone metabolic disorders.

Senolytic molecules

Senescence cell accumulation in different tissues with aging is a well-known phenomenon and these cells along with their secreted factors are collectively known as senescence associated secretary phenotype (SASP). These senescent cells stop dividing and undergo distinct phenotypic alternation which helps them to remain metabolically active [12-14]. Targeting

these SASP specifically has been increasingly recognized as the most promising therapy to prevent age related degenerative diseases. Recent studies on the identification of senescent cells in the aged osteoporotic bones, and specifically targeting them in-vivo by inducible expression of Caspase8, demonstrates the role of these cells in age-associated bone loss and generates avenue for many senolytic drugs to prevent osteoporosis [15]. Contemporary studies have shown that the combination of senolytics like Dasatinib and Quercentin prevent age related bone loss by specifically killing senecencse cells without hampering the physiology of proliferating and differentiating cells in mice [16]. These pharmacological molecules are promising candidates that have both anabolic and anti-resorptive effects on bone.

Melatonin

Melatonin is a bio-amine produced by pineal gland and other peripheral sites. It regulates many physiological and metabolic functions. It is synthesized by tryptophan by series of enzymatic reactions. Melatonin exerts its effects mainly through two receptors MT1 and MT2 [17]. From almost last two decades scientists have been hypothesizing the role of melatonin in bone health. Circulating melatonin is known to decline with age, which gives the correlative support to its possible involvement in post-menopausal and senescence osteoporosis. Melatonin augments proteins like procollagen type I c-peptide which is incorporated into the bone matrix and Osteoprotegerin that inhibits the differentiation of osteoclasts [18]. The direct evidences came from the recent study where it has been demonstrated through genetic and pharmacological methods that Pineal Derived Melatonin (PDM) regulates the bone mass specifically through MT2 receptor [19].

Melatonin also regulates the expression of osterix protein and its stability which ultimately helps in promoting osteoblast differentiation [20]. Worldwide instances of osteoporosis have been on an alerting rise mainly due to poor lifestyle and insufficient nutrition. This brings us to an urgency of finding new affordable and efficient drugs with minimum side-effects. The above-mentioned molecules show promising results in rodents and further experiments are needed in human cohorts to assess the effectiveness of these molecules to treat osteoporosis.

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