International Journal of Technical Research and Applications e-ISSN: 2320-8163,
www.ijtra.com Special Issue 36 (September, 2015), PP. 17-20

IMPACT OF DRUGS ON STEM CELL TO TREAT BONE DISEASES

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Abstract— **Brittle bone disease or osteogenesis imperfecta is a disease of defective collagen- induced inadequate bony matrix, weak bones, frequent and numerous fractures, progressive deformities of limbs and spine, retarded growth and short stature. Induce differentiation of tissue-derived mesenchymal stem cell pursue treatment of Osteogenesis imperfecta. This paper addresses critical review over the drugs that have an ability to differentiate bone marrow stem cell as well present effects of drugs on the said disease. The author conducted on extensive review of published literature on stem cells using general search engines and meta search engines through two key search strategies; medical subject heading (mesh) and text word searching. Once the 'key article' was identified, authors used the 'related article' features and further reference list harvesting. As series of research suggest that steroid, dexamethasone, statin like Imatinib mesylate, Desatinib and zoledronic acid are effective drugs for stem cell differentiation by varying mechanism. In conclusion author can say that the embryonic stem cell therapy has a lot of ethical dilemma because of its source as embryo. Better option is to use adult stem cell and increase its differentiation by using natural drug which is more cost effective, having low side effect and solves related ethical concerns as well. Also author advocate in concentrating further researches and funding in this field more on finding natural drug which can give good adult stem cell differentiation like to be embryonic so that society can be served with global acceptance.**

Index Terms— ***Natural drug, Ontogenesis imperfecta, Stem cell differentiation.***

I. INTRODUCTION

Stem cells are biological cells found in all multicellular organisms, which can differentiate and self-renew to produce more cells of their like. Osteogenesis Imperfecta (OI) is a genetic disorder results from mutations in the collagen I gene, causing abnormalities in bone structure and strength. Over 150 mutations are responsible for the OI outcome, involving collagen precursor genes such as COL1A1 and COL1A2. Extracellular matrix and bone strength builder protein is collagen; patients with OI suffer from defective collagen- induced inadequate bony matrix, weak bones, frequent and numerous fractures, progressive deformities of limbs and spine, retarded growth and short stature. Therefore, the disease is commonly known as 'brittle bone disease'. Transforming growth factor-b1 (TGF-b1), interleukin- 1b (IL-1b) and tumor necrosis factor-a (TNF-a) in inducing differentiation of human tissue-derived MSCs [1]

Spatial cascade process of bone formation immerse bone marrow MSCs differentiation into osteo-progenitor cells lengthened to preosteoblast and osteoblast follow to matrix maturation to matrix mineralization [2]. Bone resorption and formation balance governs regulation of extremely mineralized tissue. New bone formation shows concurrent process related to promotion or inhibition of MSCs to osteoblast. Anything which can stimulate or increase this process may promote the bone formation followed to treat bone diseases.

Here we are going to take in consideration of bunch of drugs as stimulator for bone formation like Dexamethasone, Dasatinib, Imatinib, Lithium, Zoledronic acid, Immunosuppressant, Icaritin, Medthylsulfonyl methane, Amelogenin, Poncirin, Silk fibroin, Conjugate linoleic acid, Phorbaketal A and geranyl geranyl transferase inhibitor-298.

II. METHODS

An extensive review of published literature on stem cells and the related drugs which assure stem cell differentiation on assorted manner by using general search engines and meta search engines through two key search strategies; medical subject heading (mesh) and text word searching. Once the 'key article' was identified, authors used the 'related article' features and further reference list harvesting.

III. DISCUSSION

A. Dexamethasone

Parathyroid hormone (PTH) and PTHrP exert anabolic effect on bone to treat osteoporosis which may induce by glucocorticoid as adverse drug reaction. PTHrP stimulate preosteoblast differentiation and improve mature osteoblast and osteocyte survival rate by combining with G-Protein coupled receptor as PTH1R common of PTH and PTHrP cause cAMP and diacylglycerol second messenger accumulation result protein kinase signaling pathway activation [3] follows the osteoblast specific transcription factor Cbfa1 phosphorylation [4] express osteocalcin (OCN) gene appear OCN marker differentiate preosteoblasts, osteoblasts (fibroblast) and osteocytes express bone sialoprotein (BSP) and osteocalcin produce osteoid matrix consist of type 1 collagen which mineralized by zinc, copper and sodium. Dexamethasone increase the expression of the PTH1R receptor and osteoblast

marker as well as enhance alkaline phosphatase activity and bone mineralization [5] Dexamethasone initially reduce the osteocalcin expression by 50% but later increase tremendously [6] hence Dexamethasone plays an important role to direct the stem cell towards terminal maturation [3]

B. Dasatanib

Src proto-oncogene perform a role in cell survival and its differentiation [7] control by cytokines [8] and maintained by 527 Tyr phosphorylation [9] Src kinase shows an absolute effect over osteoclast [10] even for its survival. But exert opposing effect on osteoblast maturation by inhibiting Runx 2(Runt Related Transcription Factor 2) expression [11] Encode Runt DNA-binding domain of RANKL protein (neuclear protein) mendetory element of osteoblast differentiation [12] . Dasatinib is a new dual Src/Bcr-Abl tyrosine kinase inhibitor [13]. Plays a dual role in bone metabolism as inhibit 527 Tyr phosphorylation follow post translational Src inhibition enhance osteoblast differentiation and also reduce RANKL mRNA expression and RANKL protein as well as decrease OPG\RANKL ratio [14]

C. Lithium

MSCs differentiation can also be control by translational or post translational level. In Translational level enhancement in osteogenic genes activation transcription factor 4 (ATF4) [15] and EDNI [16] expression but decrease TWIST1 and ITGA2 [17] expression exert positive effect over osteogenesis. ATF 4 found to be a major gene as it can also stimulate expression of extracellular matrix protein and bone mineralization [18]. In post translational level downregulatation of Rho-Rho kinase pathway enhance osteoblast differentiation as well as Wnt-7 signaling also promote differentiation [19] which can be inhibited by by glycogen synthase kinase-3b (GSK-3b) by phosphorylation [20] Lithium 5 mM enhance collagen I synthesis which upregulate ATF4 and osteoblast markers RUNX2, ALP, BSP and GTP binding protein RRAD inhibit Rho-Rho kinase signaling follow increase osteoblast differentiation. Lithium is a potent inhibitor of GSK-3b and hence mimics Wnt-7 signaling. Lithium induces ATF4 and CLEC3B promote mineralization. But higher concentration then the 5mM may be severe inhibitory because of the disturbance in cellular homeostasis. [21]

D. Zoledronic Acid

Strict molecular control mechanism governs differentiation of MSCs into respective lineage. Zinc finger containing transcription factor Osterix (OSX) belongs to kruppel like family of transcription factor with characteristic of three zinc finger DNA binding domain directing carboxy terminus of the protein [22] OSX mediate expression of osteoblast genes like osteocalcin, osteonectin, osteopontin, bone sialoprotein (BSP) and type I collagen [23] methylation is important for heritable gene expression cellular memory [24] During osteoblast differentiation promoter region of OSX become hypomethylated which directly alter gene expression of osteoblast genes which then follow affect over osteoblast differentiation [25]. Zoledronic acid is a nitrogen containing bisphosphonate [26] and potent bone resorption inhibitor leads bone loss. Zoledronic acid show high affinity at the site of bone turnover and bone mineral specially calcium. Zoledronic acid treatment with osteoblast cell may improve differentiation [27]. Zoledronic acid control methylation and render hypomethylation of OSX during osteoblastic differentiation and promote smooth gene expression of osteoblast gene.[26]

E. Immunosuppressant

FK 506, Rapamycin and Cyclosporine are the significant immunosuppressant drugs which have assertive attitude towards MSCs differentiation and bone diseases. Immunosuppressant drugs enhance the collagen III and XII, samad 2, metalloproteinase 2, annexin V, EGF receptor and osteonectin expression modifies cellular differentiation [28]. FK 506 is best in all that only it can show higher ALP activity, calcium and osteocalcin content without the presence of any differentiation hormone As well as increase BMP activity by phosphorylation of BMP dependent SAMAD [29] Rapamycin plays a specific role in upregulation of early osteogenic markers, BMP-2 and Runx-2 but continuous exposure may improve late osteogenic marker like osteocalcin, osteoprotegerin and osteonectin [30]

F. Methylsulfonylmethane (MSM)

MSM is a sulphur containing organic compound and also the dimethyl sulphoxide oxidative metabolite have an ability to reduce arthritic degenerative alteration [31]. MSM as single or with combination with estrogen or GH compound can be effective for osteoarthritic diseases and also prevent the bone loss. Normally to acquire normal bone growth and bone mass longitudinally, Growth hormone (GH) compound regulate homeostasis and remodeling of bone by combining with growth hormone receptor (GHR) Phosphorylate janus kinase 2(Jak 2) is a GHR associated tyrosin kinase which then phosphorylate signal transducers and activators of transcription (STAT) protein and stimulate GH regulated gene (IGF 1) transcription [32] GH exert its effect due to activation of STATs 1, 3, 5a, and 5b. Osteosarcoma cell line UMR-106 expresses Jak2/STAT5 signaling system as well 1,25-(OH)2D3 facilitate Jak2/STAT5 mediated GH signaling into osteoblast like cells MSM proliferate osteoblast like cell by stimulating the GH induced Jak2 and STAT5b and also enhance IGF-1R, p-IGF-1R, STAT5b, p-STAT5b, and Jak2 into osteoblast like cell (MG-63 and UMR-106) even in absence of GH; MSM trigger STAT5 DNA binding with

promoter site of IGF-1 and IGF-1 R and increase their expression as of GH signaling. On the other hand MSM also improve ALP, ON, BSP, OCN, Osterix, and Runx2 gene expression [33]. Mimicking action of MSM with GH intensifies osteoblast differentiation and bone growth.

G. L-Ascorbic acid

L-Ascorbic acid in vital concentration increase differentiation of osteoblast as well collagen biosynthesis and mineral deposition in mesenchymal stem cell turn to mature extra cellular matrix [34] hence gives mechanical strength to bone cell.

IV. Conclusion

The embryonic stem cell therapy has a lot of ethical dilemma because of its source as embryo. Far more good option is to use adult stem cell and increase its differentiation by using natural drug which is more cost effective, having low side effect and solves related ethical concerns as well. We include many of drugs basic mechanism of action for stem cell differentiation in different viable cell form to emphasize correct step of mechanism suitable for drug action and also provide a port to decide drug regimen for adequate needed differentiation. We open up the bunch of drug with similar work in different way in one roof to facilitate researcher good choice of drug podium. Also we advocate in concentrating further researches and funding in this field more on finding natural drug which can give good adult stem cell differentiation like to be embryonic so that society can be served with global acceptance of such therapy.

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