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Basics & Beyond : The Implant & Genomic Basis of Osseointegration

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ABSTRACT

The study of implantology has evolved since its introduction into dentistry. Apart from other aspects of an implant, osseointegration has been of prime interest to researchers and practitioners. The study of osseointegration alone has lead to many discoveries regarding the implant's macro and micro design and has been used very advantageously so far. Although peri-implant healing has already been studied in depth, there is little information on the genetic influence on peri-implant bone healing. The purpose of this review is to analyze and sequence the events of peri-implant healing and to identify all the genes and their processes that lead to successful peri-implant healing.

Keywords: Bone Morphogenic Protein, Osseointegration, Bone to Implant Contact, Osteogenesis, Genetic Regulation

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INTRODUCTION

Osseointegration is a term frequently used to describe successful healing between implant surface and bone [1]. Since inception of implantology, mechanism and time frame for osseointegration has been an enigma.

Earlier known as "Bone Bonding"[2], osseointegration still has no exact definition in literature, it has been defined as, "A direct structural and functional connection between ordered, living bone and the surface of a load carrying implant, is critical for implant stability and is considered a pre-requisite for implant loading and long term clinical success of endosseous dental implants"[3]. Zarb and Albrektsson described it as, "A time dependent healing process whereby clinically asymptomatic rigid fixation of alloplastic materials is achieved, and maintained, in bone during functional loading" [3].

Osseointegration is a dynamic complex interaction between the implant surface and peri-implant bed at the cellular/molecular level. Several factors together promote this cellular interaction with implant surfaces. This review will explore the ideal requisites for peri-implant bone healing and the various stages of osseointegration.

Ideal Requisites for Osseointegration-

1. Implant biomaterial.
2. Implant surface topography and energy.
3. Peri-implant bed preparation.
4. Primary stability.

Implant Biomaterial-

Titanium and its alloys can be classified as α-type, β-type and α+β-type.

α-type alloys are those that have certain elements dissolved in titanium matrix and are strong solution strengtheners and produce little change from α to β stage of titanium at its transformation temperature [β transus for pure Ti- 885°C] and β to α on cooling. Such elements are called as α-stabilizers, eg- Al, Sn, Ga and Zr.

β-type alloys are those that contain elements that decrease this phase transformation of titanium on

cooling. Such elements are called as β-stabilizers eg- V, Mo, Nb, Ta and Cr.

α+β-type alloys are those that contain up to 10-50% β phase at room temperature. These have a combination of both α and β stabilizers. E.g. - Ti-6Al-4V [4].

Currently pure titanium and α+β type alloys are used extensively in both medical and dental fields, specifically for dental and orthopedic implants. Following are the titanium and its alloys that are being used today-

1. CpTi-
   Commercially pure titanium comes under the unalloyed grades of ASTM specification; there are five grades of CpTi-
   a. Grade I- 99.5% Ti.
   b. Grade II-99.3% Ti.
   c. Grade III- 99.2% Ti.
   d. Grade IV- 99.0% Ti.
   e. Grade VII- 99.4% Ti.
2. Ti-6Al-4V.
3. Ti-6Al-4V ELI.
4. Ti-6Al-7Nb.
5. Ti-3Al-2.5V.
6. Ti-5Al-3Mo-4Zr.
7. Ti-5Al-2.5Fe.

Implant Surface Topography and Energy-
Response of tissues towards an implant is majorly governed by the implant surface composition and surface characteristics. For an implant to successfully osseointegrate it is important that it elicits a certain biological response from the surrounding peri-implant bed [5-7].
In an effort to elicit a faster biological response and to procure a better BIC several surface modifications have been developed, which can be broadly categorized as-

a. Morphological.
b. Physiochemical.
c. Surface coatings.
d. Biochemical.

These have actually lead to development of new surfaces like TiO_2 Nano-tube Surface [8,9] which is touted to reduce osseointegration time and also greatly increase BIC [10]. Research has shown that doping these TiO_2 Nano-tubes with silicon and silver particles promoted bone proliferation [8, 11, 12].

Surface modifications impart the implant topography with a considerable degree of roughness, composition, and charge. The above stated three factors contribute to surface energy of an implant [5, 13, 14, 15]. This surface energy decides the implant hydrophillicity and allows for adhesion of various cells and proteins that initiate the process of osseointegration [15-18].

Peri-Implant Bed Preparation-
Peri-implant bed/osteotomy site is the area where the actual healing occurs; it is the source for all the factors that contribute to the different stages of osseointgration.

The preparation of the bed should be least violent as drilling can lead to development of frictional heat which is deleterious to the peri-implant bone and will hamper osseointegration.
According to literature, temperature of the osteotomy site should not exceed 47°C for 1 minute above which protein denaturation, osteoblastic death and loss of necessary local factors occurs [3]. Although this phenomenon is still questionable yet it cannot be ignored.

Primary Stability-
Initial stability of an implant is of prime importance for successful healing of peri-implant site [2, 19]. A study in 2005 emphasized that initial stability of an implant allowed successful angiogenesis and osteogenesis [19, 20]. In many ways implant stability and healing of surrounding tissues is comparable to healing of a fracture as immobilization of fractured segments is required to promote union, otherwise chondrogenesis occurs between fractured segments [21].
In case of implants excessive motion promotes fibrous and connective tissue growth over bone growth [22].

Literature states that a micro-motion greater than 150µm leads to fibrous union of an implant [2], whereas some studies suggested that micro-motion less than 25-50µm is beneficial to bone formation [23]. Thus, it can be stated that close contact between the implant and bone is required for adequate primary stability which leads to proper osseointegration.
After considering the four requisites required for osseointegration it becomes imperative to look into the interactions occurring between the implant and its surrounding tissues.

The surgical preparation prior to implant placement allows the implant to first come in contact with blood, which starts a biological response at the molecular level and is a fascinating cascade leading to osseointegration.

The First Contact-
As soon as the implant approaches the osteotomy site, the first tissue it comes in contact with is blood. This results in a cascade of processes that includes- protein deposition, coagulation, inflammation, and tissue formation. These processes are greatly influenced by implant surface chemistry [24].

Protein Deposition-
Within seconds of implant to blood contact a monolayer of proteins gets deposited on the implant surface, it is because of this protein monolayer that platelets and MSCs are able to interact with the implant surface. There are over 200 proteins in blood and only a selective few appear in this monolayer [24, 25]. This selective protein adsorption can be attributed to the surface charge of the implant.

Since proteins are charged molecules they change their 3-dimensional shape to conform their surrounding electrochemical environment, thus the surface charge of an implant plays a major role in selection of specific proteins and their adsorption. Also, this conformation of proteins determines whether specific bioactive peptide sequences will allow attachment of incoming cells [25, 26]. These bioactive peptide sequences are commonly known as "Integrins". The most commonly found sequence is the arginine-glycine-aspartic acid [RGD] sequence that is responsible for cellular binding, signaling and response.

The kind and type of protein adsorbed determines the hosts response to the foreign object and therefore, maybe a deciding factor for successful healing. The first and most common proteins to get adsorbed are fibronectin and vitronectin that contain the RGD sequence and therefore, allow interactions with MSCs [13, 24, 26]. Apart from fibronectin and vitronectin; fibrinogen, von Willebrand factor, complement and IgG are also adsorbed and initiate platelet activation, coagulation and inflammation.

Platelet Activation-
Within five seconds of contact with blood the first cells to interact with implant surface are platelets [27, 28].

Platelets are basically small cells derived from megakaryocytes and get activated on contact with foreign materials, injured endothelium, sub-endothelium and or by factors released from other platelets or cells, this activation results in a number of intracellular processes.

Bioactive molecules within the platelets like ADP, PDGF, histamines and serotonin are released into the peri-implant environment. This leads to expression of a cell surface glycoprotein on the membrane of the platelet called P-selectin. P-selectin expression helps in platelet adhesion to neutrophills, monocytes and leukocytes, meanwhile activated platelets form micro-particles. These micro-particles are pro-coagulants and bind to fibrinogen and fibrin leading to expression of factors tenase and prothrombinase in the cell membrane [28, 29].

Platelet adhesion is mediated by two membrane-bound receptors GP-Ib and GP-2b/IIIa. GP-Ib requires the immobilized von Willebrand factor as a co-receptor and GP-2b/IIIa binds to proteins adsorbed on implant surface [30].

Multiple platelet activation leads to formation of a clot via fibrinogen which supports platelet aggregation through Ca^{2+} dependent binding with the activated GP-2b/IIIa receptors. Simultaneously, conversion of prothrombin to thrombin leads to the growing of thrombus via a stable fibrin polymer in the presence of activated factor XIII. [29, 30]. This leads to formation of a stable clot that allows for osteoconduction. Davies and Hosseini defined osteoconduction as the "recruitment and migration of osteogenic cells" [31]. The clot acts as a provisional matrix with adhesive plasma proteins allowing for cellular adhesion and migration from capillary bed towards the implant, and this occurs because of presence of signaling molecules like cytokines, chemoattractants, mitogens and growth factor [27, 29, 31, 32].

TGF-βI and II are very important signaling molecules found within the platelet and have recently been showed to induce migration of osteoprogenitor cells through the SMAD signaling pathway [33].

Chemoattractants therefore, released from activated platelets influence migration of monocytes, neutrophills and MSCs towards the implant surface, this is why the fibrin clot is essential for mediating both inflammation and osteoconduction [26, 34].

Inflammation-
An inflammatory response occurs simultaneously with coagulation and platelet activation [29]. After platelets the next cells to migrate to the peri-implant space are neutrophills and monocytes that initiate an inflammatory response. Generally neutrophills arrive first with peak levels at 24-48 hours. After 48 hours monocytes transform to macrophages and become the dominant leukocytes [23, 32].

With monocyte transformation and activation of leukocytes within capillaries [cytokine mediated] there is release of inflammatory mediators like IL-I, IL-6, IL-8, TNF-α and macrophage colony stimulating factor [28, 29, 35].

The hematoma in the peri-implant space is similar to a fracture hematoma, with expression of same signaling molecules, relative mRNA expression levels for signaling molecules of fracture hematoma shows variations overtime with various stages of healing [36, 37, 38].

Similarly, with expression of inflammatory mediators, members of TGF-β superfamily are also expressed within 24 hours, these members include BMPs and GDFs. Osteoconductive factors have also shown improved bone formation during implant bed healing in in-vivo animal models [11, 33, 35, 39-42].

Osteogenic cells require blood supply and therefore, angiogenesis is an essential requirement. Expression of angiogenic factors are naturally accompanied with metallomatrix proteinase, which degrades the extracellular matrix of pre-existing capillaries and allows the angiogenic factors to stimulate growing new vessels [43].

A very important angiogenic factor is the VEGF which is released due to destruction of the extracellular matrix of the capillaries. VEGF leads to stimulation of endothelial cells and causes cell division to form new vessels. It also causes differentiation of peri-vascular cells to form endothelial cells and smooth muscles. Since osteoblasts have been found to contain VEGF receptors, it is believed that VEGF also has the capacity to modulate osteoblastic functions [44]. Apart from VEGF; PDGF, angiopoietin, bFGF are also important factors for angiogenesis [43].

The complex interaction within the peri-implant space leads to recruitment, migration and differentiation of MSCs which participate in osteogenesis.

Osteogenesis-

MSCs get recruited from marrow, pericytes and cambium layer of periosteum [45, 46]. These cells travel through the fibrin clot towards implant surface which is mediated by numerous factors released by platelets and leukocytes [34].

Osteoblastic Differentiation- Signal Transduction & Transcriptional Regulation-

Osteoblastic differentiation is an extremely well choreographed process. Recent studies involving gene targeting in mice lead to a better understanding of the factors involved at a molecular level.

Osteoblastogenesis employs MSCs that can differentiate into chondrocytes, adipocytes and myoblasts [47].

There are three stages of osteoblastogenesis-

a) Proliferation.
b) Matrix maturation.
c) Mineralization.

These three stages involve use of distinct osteoblastic markers, which are [48, 49]-

a) ALP.
b) Colla I.
c) OPN.
d) BSP.
e) OCN.
f) PPR.

The cytokines that control this process are [50]-

a) TGF β.
b) BMP- 2, 4, 7 and their inhibitors noggin, chordin, gremlin and sclerostin.

Hormones that positively impact osteoblastic differentiation are-

a) IGF I.
b) PTH.
c) PTHrP.
d) 1, 25[OH]2D3.
e) Leptin.
f) Glucocorticoids.
g) Notch Pathway.
h) Members of IL-6 family.

Signaling for Osteoblastogenesis-

Wnt Signaling-

Wnts are a group of GPs with many inhibitors and are ligands for frizzled receptors [FZD]. There are two types of Wnts [51, 52]-

i. Activates Canonical Signaling Pathway.
ii. Non-Canonical Wnt protein that activates heterotrimeric GPs.

Out of the two the canonical pathway is the most important in case of bone biology [53, 54].

In the “On-State” of the canonical pathway the Wnt proteins bind to the FZD / LRP5/6 complex and generates certain signals through Disheveled, Axin and Frat-I proteins to inhibit GSK-III and stabilize the β-Catenin which leads to transcription of target genes by translocating itself into the nucleus [55, 56, 57].

In the "Off-State" the nuclear and cytoplasmic levels of β-Catenin become lowered in the cells but still remains associated with the cadherins of plasma membrane which spares it from degradation [57].

TGF-β Signaling-

BMPs are a group of phylogenetically conserved molecules having potent osteogenic effects and were first identified due to their ability to cause endochondral bone formation [58, 59, 60]

The members of the TGF-β superfamily utilize Type-I and Type-II transmembrane Serine/Threonine Kinase dual receptor system for signaling. This leads to expression of BMP-1, 2, 3, 4, 6, 7, and 9. BMP- 1, 2, 4, 6, 7, and 9 promote bone formation whereas BMP-3 serves as a negative regulator [58, 61, 62, 63, 64].

BMPs act via SMAD-Dependent and SMAD-Independent pathways, which are the major transducers for transmembrane dual receptor systems. There are three kinds of SMADs [65, 66]-

a) R-SMAD.
b) Co-SMAD.
c) I-SMAD.

After stimulation and activation R-SMADs undergo phosphorylation to form complexes with Co-SMADs and start regulating transcription of target genes [earlier activated by Wnt signaling] [67]. BMP does not induce osteoblastic differentiation directly it instead activates SMAD which further activates Runx2 transcriptional factor; this Runx2 transcription further induces osteoblastic differentiation [68-72].

Other signaling pathways involved are, Hedgehog signaling, FGF signaling, Ephrin and Sympathetic signaling.

Genetic Regulation: Transcriptional Factors Regulating Osteoblastogenesis-

The transcriptional factors of osteoblastogenesis are a range of proteins belonging to the homeobox family, which are the Activator Protein [AP] family members [73]-

i. Jun.
ii. Fos.
iii. Fra.
iv. SMADs.
v. CCAAT/Enhancer Binding Protein β [C/EBPβ].
vi. C/EBPd.
vii. Lymphoid Enhancing Factor.
viii. Twist.
ix. ATF4.
x. Runx2.
xi. Osterix.

From the above mentioned genes Runx2, Osterix and ATF4 are master genes involved in osteoblastogenesis. These act as "master switches" that aid in MSCs commitment to tissue specific cell types. One such master switch is the Runx2 transcriptional factor that plays a central role in regulating process of osteoblastogenesis [73]. Runx2 plays a pivotal role but still requires other transcriptional partners that regulate effectiveness of Runx2 expression and activity [73].

Runx2 belongs to the Runt related factors family encoded by specific unlinked genes having common DNA identification pattern TGTGGT and heterodimerise with the omnipresent CBF-β for stable DNA binding [74, 75]. Additionally Runx2 is also rich in residues of glutamine and alanine that activate Osteocalcin and Colla-I genes [76, 77].

Most importantly Runx2 might also act as an inhibitor of osteoprogenitor proliferation; therefore, it regulates transition from growth to post proliferative stage [78].

Other genes facilitating Runx2 activity are MSX2 genes that affect the MSCs commitment to osteoblasts. Another gene Bapx-I aids in activation of Runx2 expression [79-81]. Developmental action of Runx2 is regulated by genes that code the helix-loop-helix transcription, such genes, Twist-I and Twist-II directly code the DNA helix and lead to effective bone formation, this phenomenon is yet to be further researched [82-84]. However, expression of Runt related factors, Cbfa-I, Twist genes and osteoblastic markers has recently been demonstrated to occur in human osteoblasts that were cultured upon sterile Titanium, Steel and Ceramic surfaces [85], implying that osseointegration and osteoblastogenesis of peri-implant site is similar to bone growth at the molecular and cellular level.

Tumor suppressor genes such as p53 tumor suppressor gene act as a negative regulator of osteoblastogenesis, this has been proved in two animal studies. In one study bone metabolism and skeletal structures was examined in mice without p53 gene and in the other study, effects of hyperactive p53 gene was studied in mice, both studies came to the conclusion that p53 suppresses osteoblastogenesis by suppressing Runx2 or Osterix expression [86-88].

Other three main transcriptional partners of Runx2 that positively influence Runx2 activity and osteoblastic differentiation are Osterix, ATF4 and SATB2.

Now the differentiated osteoprogenitor cells colonize the implant surface and begin secreting a matrix. This has been demonstrated to occur within 24 hours of implantation in a porcine model [20]. This initial matrix secreted by osteoprogenitor cells does not contain collagen [24]. This matrix forms the afibrillar interfacial zone and has a varying thickness from 0.2-0.5µm [24].

Davies et al., first described this afibrillar zone to be analogous with the cement line outlining the osteons, this is electron dense and consists of osteopontin and bone sialoproteins and plasma derived osteonectin and α_2HS-Glycoprotein [24, 89, 90, 91].

The non-collagenous proteins, osteopontin and BSP have nucleation sites for mineralization; therefore, the afibrillar interfacial zone forms a non-collagenous, calcified layer on implant surface and a collagenous compartment composed of Type-I Collagen beyond afibrillar zone. Mineralization of afibrillar interfacial zone precedes mineralization of the collagenous compartment [24]. During mineralization the osteoblast move away from the mineralization front however, sometimes few osteoblast fail to escape and get enveloped [22]. This leads to development of osteocyte within a bone lacuna, resulting in formation of immature woven bone, proceeding from implant surface to the prepared osteotomy walls. This process is known as "Contact Osteogenesis"[26].

Formation of bone also occurs in the opposite direction that is from prepared osteotomy walls to the implant surface this is termed as "Distant Osteogenesis"[26].

During osteotomy preparation, due to thermal necrosis and physical injury the osteocytes in the bone will die to a depth of 100-500µm, this dead bone is subject to osteoclastic activity [24, 92]. Osteoprogenitor cells migrate to this surface of bone and form cement like non-collagenous layer similar to that on the implant surface [22, 93], followed by formation of a collagen containing layer by fully differentiated osteoblast. Mineralization occurs same as that in contact osteogenesis. Thus, it can be stated that bone formation occurs in two opposite directions. Flourochrome labeling has revealed that bone formation via contact osteogenesis progresses at a 30% faster rate than distant osteogenesis [24, 31, 94].

As mineralization from distant and contact osteogenesis progresses towards each other and meet midpoint the osteoblasts involved get trapped in lacunae and the mineralizing ends of the contact and distant osteogenesis coalesce and unite, this phenomena is called as "Osseocalescence".

Contact osteogenesis, distant osteogenesis and their coalescence leads to formation of woven bone in the peri-implant space. This provides secondary stabilization to the implant. Thus, it can be said that there is a changeover from primary stability which results from frictional fit between implant and bone to secondary stability that results from formation of woven bone around the implant [95]. It can also be stated that primary stability declines overtime as bone which is in direct contact gets resorbed by osteoclastic activity.

Secondary stability may be stated to arise from bone bonding if the implant surface topography is 3-dimensionally complex i.e; it has macro, micro and nano porosities, this feature of an implant allows for interdigitation and incorporation of bone into the surface of the implant and allows for successful bone bonding, if the implant surface is not complex bone bonding does not take place and bone grows as a result of distant osteogenesis only [1, 13, 18, 20, 26, 96].

Remodeling-

Many consider remodeling of bone to be the last stage of peri-implant healing but in fact it occurs throughout the healing process, the sequence of remodeling is a defined series of events that is - activation of osteoclastic cutting cones, resorption of bone by osteoclasts, angiogenesis, differentiation of MSCs to osteoblasts and bone formation by osteoblasts [97]. This has been called as BMU and is believed to be the cause of formation of a new osteonal system within the existing bone [98]. Remodeling thus first occurs in the host bone and then in the woven bone formed in the peri-implant space.

During implantation the host bone suffers significant micro-damage that may extend 1-2mm into the bone [97], this leads to an enhanced remodeling in the host bone which may last more than six months, along with host bone remodeling there is remodeling of woven bone in peri-implant space, and this results in formation of mature lamellar bone [98].

Since woven bone is formed more rapidly and consists of loosely packed collagen fibers with varying spatial arrangement, whereas lamellar bone has organized and thicker bundles of collagen fibers, therefore, formation

of lamellar bone in peri-implant space is the desired end result as its structure makes it mechanically stronger [99].

Peri-implant bone continues to remodel throughout the life of an implant. This remodeling may allow for increased BIC. Brånemark et al., conducted a study where titanium screws were inserted into the rat tibia and compared histology with the pullout and torsional strength for titanium screws, they found that in the first four weeks as the bone quantity increased, the pullout strength increased, but increase in torsional strength was seen between fourth to sixteenth week period as bone remodeling occurred. Thus, it was concluded that there was a positive correlation between torsional strength BIC and that remodeling improved BIC [100].

In ideal conditions remodeling will always improve the BIC, however, it may not happen always, since remodeling is greatly influenced by the stresses generated in the peri-implant bone.

Julius Wolff recognized this and stated that – "every change in the function of the bone is followed by certain definite changes in the internal structure and external conformation in accordance with mathematical laws" [101].

In healthy bone the BMU activity is balanced that is because of normal loading the osteoblastic and osteoclastic activity occurs at a normal rate. If there is unloading for period of time the osteoclastic activity predominates and leads to loss of bone mass [98, 101].

Similarly, the implant placed into the bone might bring about changes in stress distribution in the bone as it is stiffer than the host bone; this may lead to an unbalanced BMU activity and is called as "Stress Shielding" [102].

CONCLUSION

For a basic understanding of peri-implant healing one needs to know about the dental implant, the biomaterial, the topography and the complex 3-dimensional roughness imparted via various surface treatments.

Out of all the requisites, surface roughness is the most important factor that gives an implant the ability to osseointegrate. It can be argued that surface roughness makes an implant osseoinductive and osseoconductive. This can be described in the way the implant surface allows protein adsorption that induces platelet activation which in turn following a cascade of events allows for bone formation, this can be described to be an osseoinductive behavior and the interdigitation of bone into the roughness of the implant to be osseoconductive behavior.

Primary stability of an implant is also an important factor that cannot be ignored. The frictional fit of an implant with the surrounding host bone allows for the various factors to remain in a constant touch with the implant surface which allows for undisturbed healing. Although primary stability of an implant is eventually lost and is replaced by secondary stability it is still important as it basically allows for most of the healing to occur.

Signaling and transcriptional control of osteoblastogenesis also seems to be an interesting topic for research; several studies have shown involvement of various signaling pathways and genes in healing of fractures or development of bones. It is important to note that all the several pathways and genes involved in the process work together at the same time to get the desired result and malfunction of even a single component can have drastic effects. It can be argued that since the quantity and quality of bone formation is majorly genetically controlled, therefore, osseointegration also might depend upon the genetic makeup of an individual.

In conclusion, the cascade of peri-implant healing till date has been questionable yet a fascinating subject for researchers around the world, with advancement in genetics, more researchers are trying to unmask its genomic basis and are trying to utilize their knowledge to manufacture new surface treatments that can allow for faster biological response and rapid osseointegration.

It is fair to state that several studies in the past decade have almost shown similar results but more clinical and research data is required to unfold this enigma of osseointegration.

Conflicts of Interest- None.

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Abbreviations-
BIC- Bone to Implant Contact
MSC- Mesenchymal Stem Cell
ADP- Adenosine Di-Phosphate
PDGF- Platelet Derived Growth Factor
GP- Glyco Protein
TGF- Transforming Growth Factor
SMAD- Homologs of two Drosophila proteins i.e.; Caenorhabditis Elegans protein SMA and
Mothers Against Decapentaplegic (MAD) protein
IL- Interleukin
TNF- Tumor Necrosis Factor
mRNA- Messenger Ribo Nucleic Acid
BMP- Bone Morphogenic Protein
GDF- Growth Differentiation Factor
VEGF- Vascular Endothelial Growth Factor
bFGF- Basic Fibroblast Growth Factor
ALP- Alkaline Phosphatase
Colla I- Type I Collagen
OPN- Osteopontin
BSP- Bone Sialoprotein
OCN- Osteocalcin
PPR- Pentatricopeptide Repeat
IGF- Insulin-like Growth Factor
PTH- Parathyroid Hormone
PTHrP- Parathyroid Hormone Realted Protein
LRP- Low-density Lipoprotein Related Protein
GSK- Glycogen Synthase Kinase
R-SMAD- Receptor-Regulated Smad
Co-SMAD- Common-mediator Smad
I-SMAD- Inhibitory Smad.
FGF- Fibroblast Growth Factor
EBP- Enhancer Binding Protein
ATF4- Activating Transcription Factor 4
CBF-β- Core Binding Factor subunit β
MSX2- Msh Homeobox 2
CBFa1- Core Binding Factor alplha 1
Bapx1- Bagpipe Homeobox Protein Homolog 1
SATB2- Special AT-rich sequence Binding Protein 2
BMU- Bone Multi-cellular Unit