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The role of bone morphogenetic protein 2 in the reprogramming of cancer stem cells.

Muhammad Fawwaz Abdullah[1,2,3], Mudiana Muhamad[2], Sharaniza Ab-Rahim[2*]

[1]Institute for Medical Molecular Biotechnology, Universiti Teknologi MARA, Cawangan Selangor, Kampus Sungai Buloh, Sungai Buloh, Selangor, Malaysia

[2]Department of Biochemistry and Molecular Medicine, Universiti Teknologi MARA, Cawangan Selangor, Kampus Sungai Buloh, Sungai Buloh, Selangor, Malaysia

[3]Advanced Medical and Dental Institute, Universiti Sains Malaysia, Kepala Batas, Pulau Pinang, Malaysia

Abstract

Bone morphogenetic protein 2 (BMP-2) is a family member of the transforming growth factor-beta (TGF-β) superfamily and firstly recognized in early embryonic and postnatal development. BMP-2 has been reported to have crucial role in bone and cartilage formation, tissues and organs development, regulate cell differentiation, proliferation, angiogenesis, morphogenesis, chemotaxis, cellular survival and apoptosis. The BMPs are also identified as factors in tumor development and propagation; distinctly associated to diverse sides of carcinogenesis. The theory of cancer stem cells (CSCs) hypothesized that only a small hierarchical organization of cells is assisting tumorigenesis and inheriting cellular heterogeneity throughout long-life primary tumor. Reprogramming of CSCs using induced pluripotent stem cell (iPSC) approach possibly benefits in identifying the CSCs-related oncogenes, tumor-suppressor genes, and interactions between CSCs-related genes and the cancer microenvironment. Moreover, the reprogramming technology may provide crucial information related to cancer initiation and progression. This review will be focusing on BMP-2 signaling in modulating normal cells, human diseases, and cancer progression and suppression. Furthermore, this review will provide summary of updated reports on the role of BMP-2 in the developments of CSCs and its possible role as therapy through reprogramming technology by BMP-2 as an important regulatory factor in modulating the proliferation and aggressive properties of CSCs.

Keywords: Bone morphogenetic protein 2 (BMP-2), Reprogramming, Stem cells, Cancer stem cells (CSCs), Differentiation, Development.

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Introduction

Bone morphogenetic proteins (BMPs) are well established as multi-functional cytokines; a family member of the transforming growth factor-beta (TGF-β) superfamily and firstly recognized in early embryonic and postnatal development. It was discovered in the late 1980s by Wozney et al. [1] based on the previous study which reported the activity of BMPs [2]. Following studies have reported BMPs to have crucial role in the formation of bone and cartilage. Furthermore, BMPs have been known to be part of tissues and organs development, regulate cell differentiation, proliferation, angiogenesis, morphogenesis, chemotaxis, cellular survival and apoptosis [3-5]. The BMPs are also identified as factors in tumor development and propagation; distinctly associated to diverse sides of carcinogenesis [6].

BMPs are categorized into four subgroups based on the structure, amino acid and the similarity of the nucleotide. Its phylogenetic comprises of BMP-2 and BMP-4, BMP-5, BMP-6, BMP-7 and BMP-8, BMP-9 and BMP-10, and BMP-12, BMP-13 and BMP-14 (GDF-5, GDF-6 and GDF-7) [7]. BMP-2 is known as osteogenic BMP which is based on its strong bone-inducing activity [8] and essential for endochondral bone formation [9]. BMP-2 is previously reported to promote the transformation process of undifferentiated cells at the beginning state [10]; induce bone and cartilage formation *in vivo* [11]; involve in cell differentiation, proliferation and apoptosis [5]; and the more recent studies regarding BMP-2 centering around regulation on tumorigenesis in several cancers [12-15].

Stem cells are undifferentiated cells, have self-renewal capability and can differentiate into specific matured cell types. Embryonic stem cells (ESCs) are pluripotent stem cells that able to differentiate to generate all types of tissues during embryonic development, whereas the adult stem cells (ASCs)

are crucial in replacing and repairing specific adult tissues [16]. Induced pluripotent stem cells (iPSCs) are reprogrammed somatic cells using specific measurements into stem cell-like cells, which have similar properties with embryonic stem cells [17]. Another important stem cell-like cell is the cancer stem cells (CSCs) which considered as a subpopulation of such stem cells. As the CSCs are found within tumors, their characteristics are similar to both stem cells and cancer cells. Uniquely, their asymmetrical cell division and alteration in gene regulations differentiate them from the normal stem cells [18,19].

The term reprogramming, in biology, refers to the reversing process of differentiated cells back into embryonic state. This biological reprogramming technology started to emerge in 2006 when Takahashi et al. demonstrated that by altering four genes, octamer 4 (*Oct4*), SRY box-containing gene 2 (*Sox2*), Kruppel-like factor 4 (*Klf4*) and oncogene c-Myc (*OSKM*) in adult mouse cells, a reprogrammed induced pluripotent stem cells (iPSCs) can be created, thus could be used in human medicine [17]. This reprogramming method has been used for reprogramming many types of cells including cancer cells due to similarity between CSCs and normal stem cells.

This review aims to provide an inclusive understanding of BMP-2 signaling in modulating normal cells, human bone-related and non-bone diseases, and importantly cancer progression and suppression. Additionally, this review also emphasizes updated research reports on the role of BMP-2 in the developments of CSCs alongside normal stem cells and the possible future therapies utilizing reprogramming method on BMP-2 as an important regulatory tool in modulating the development of CSCs.

Role of BMP-2 in Normal and Disease Cellular Progression

Signaling pathways involving BMPs progression are divided into canonical and non-canonical pathways. In general, BMPs signaling pathway is functioning when a heterotetrameric signaling dimer complexes of type 1 and type 2 receptors is formed. All receptors have a short extracellular domain, a single transmembrane domain, and an intracellular domain. Type 1 receptor consists of seven receptors, activin A receptor like type 1 (ACVRL1), activin A receptor type 1 (ACVR1), activin A receptor type 1B (ACVR1B), activin A receptor type 1C (ACVR1C), bone morphogenetic protein receptor type 1A (BMPR1A), bone morphogenetic protein receptor type 1B (BMPR1B) and transforming growth factor beta receptor 1 (TGF-βR2), and five type 2 receptors, activin A receptor type 2A (ACVR2A), activin A receptor type 2B (ACVR2B), anti-Mullerian hormone receptor type 2 (AMHR2), bone morphogenetic protein receptor type 2 (BMPR2) and transforming growth factor beta type 2 (TGF-βR2) [20]. The heterotetrameric signaling complex mechanisms can be altered depending on what type of BMPs is initiated hence can activate different pathways. The signal transduction cascade triggered by the canonical pathway by binding to cell surface receptors and creating a heterotetrameric dimer complexes of type 1 and type 2 receptors [21]. For example, BMP-2 and BMP-4 are preferred to bind to type 1 receptors and only enlisted type 2 receptors, while BMP-6 and BMP-7 interact with type 2 receptors and recruit type 1 receptors [22]. On the other hand, non-canonical pathways such as mitogen-activated protein kinase (MAPK) and Smad-independent signaling pathway are led to regulation of gene expression. Moreover, BMP signaling is also being regulated by intracellular (PKBP12, microRNAs, phosphatases, and I-Smads), extracellular (Noggin), and membrane (Endoglin) modulators [23]. Such example of non-canonical pathway of BMP-2 is reported in development of the dental epithelium where TGF-β signaling initially triggered the activation of Smad1, Smad5 and Smad8 in this tissue. The report mentioned that the levels of P-Smad1, P-Smad5, and P-Smad8 are maintained in both dorsomorphin-treated dental epithelium of the tooth germs and the dental epithelium of Msx1 mutant, in which BMP-2 expression is decreased [24].

BMPs are considered as powerful stimulators for both bone formation and other related cellular functions. BMPs activities are controlled by specific molecular proteins at specific molecular levels. These activities can be either a list of BMP antagonists bind BMP ligands and inhibit BMP functions, the binding of Smad6 to type 1 BMP receptors prevents the binding and phosphorylation of Smad1 and 5 [25], or a selectively binding of tob (an anti-proliferative protein) to Smad1 and 5, thus blocks BMP signaling in osteoblasts [26], or even interaction of Smurf1, an E3 ubiquitin ligase (Smad ubiquitin regulatory factor 1) together with Smad1 and 5, mediates the degradation of the Smad proteins [27].

BMP-2 has been shown to have physiological function in both bone formation and development. This role had been demonstrated by Chen et al. by injecting BMP-2 around the calvariae of mice's surface, hence inducing the formation of periosteal bone locally without an initial cartilage step [28]. BMP-2 has been demonstrated to regulate proliferation and osteogenesis, and lacking of BMP-2 will results in serious defects in repair sites of the osteoblasts [29,30]. Moreover, BMP-2 can inhibit the differentiation of osteoprogenitor cells originated from multipotential mesenchymal cells into osteoblasts [31]. Inadequate level of BMP-2 will also slow down the process of bone healing and repair.

BMP-2 also has been associated with osteoarthritis (OA). OA is a disease which affects synovial joints, like knee, hip and hand due to degeneration of articular cartilage. Degeneration of cartilage of OA tissues [32] and chondrocyte hypertrophy might be due to dysregulation of BMP-2 response [33]. Some indicators of disease severity and joint arthroplasty is higher level of BMP-2 and BMP-4 serum, but there was no association of BMP-2 and BMP-5 in OA progression [34,35].

The BMP-2 antagonist's mutations have unveiled the importance of BMPs that is being modulated in a specific system. For instant, proximal symphalangism and multiple synostoses syndrome caused by heterozygous mutations of the human noggin gene, have the same symptoms. Proximal symphalangism, is a disorder which has an autosomal-dominant with conductive deafness, carpal and tarsal bone

fusion, and ankylosis of the proximal interphalangeal joint [36,37], while multiple synostoses syndrome is a disorder of joint morphogenesis [38]. In these disorders, noggin protein will bind and inactivated BMP-2, 4 and 7. In addition, 3D crystal structure clearly demonstrates the function of noggin which mainly targets BMP-2, 4 and 7, hence inhibits them [39]. Furthermore, BMP-induced and Smad-dependent transcription in osteoblasts were inhibited by Tob and associated with Smad1 and Smad5 proteins [40]. The Tob consists of Tob, Tob2, BTG1, BTG2 and BTG3 are belonging to an anti-proliferative protein family [41]. The study of Tob in knockout mice has demonstrated that the higher level of BMP-2 effects on osteoblast proliferation, differentiation and the local bone formation [42].

In general, BMPs have multifunctional cytokines. Not only BMPs regulate the development of both bone and cartilage, but BMPs also take part in many non-osteogenic development processes. BMPs play crucial roles in maintaining adult's tissue homeostasis and depletion of BMP production of functionality normally causes marked defects or severe pathologies. Ectodermal cell fates for example, are determined by neural induction [16] and BMPs perform as indicator of epidermal induction [43]. BMP-2 in focus, administers neuronal phenotypes developmental from neural crest cells [44]. The process of myogenesis is being inhibited by BMPs when they direct the somite development. For example in the limb bud, when BMP-2 interacts with the fibroblast growth factor 4 and sonic hedgehog, the expansion is inhibited, and the chondrocytes and osteoblast precursors formation is induced [45,46].

The BMP-2 potential in inducing bone and cartilage formation can also be used to understand the mechanism of certain diseases, hence using recombinant human BMP-2 (rhBMP-2) in disease treatments is applied. Such in cleft palate (CP), an observable birth defect that has multiple etiologies, BMP-2 is involved in palate morphogenesis in development, and syndromic CP is associated with haploinsufficiency of BMP-2 [47]. In embryogenesis, deletion of BMP-2 may results in embryonic lethality and previous report had shown that the malfunction of amnion/chorion and cardiac development happened in BMP-2 deficient mice [48]. Meanwhile, BMP-2 also modulates cartilage development, and for chondrocyte proliferation and maturation, BMP-2 is considered as a main factor in endochondral bone development [9]. BMP-2 also may results in a serious chondrodysplasia phenotype, a congenital disorder of bone and cartilage development [49]. Additionally, BMP-2 is important in homeostasis and fracture healing. BMP-2 initiates the fracture healing and limb-specific BMP-2 knockouts, a down-regulated of BMP-2 results in sudden fractures and fails to start the healing process [50].

The BMP-2 signaling is also required for normal growth and morphogenesis of the developing gastrointestinal tract [51]. Additionally, BMP-2 homozygous mutants caused abnormalities in the development of the heart, results in malformation of the amnion, chorion and embryo death [48]. BMP-2 is expressed in both extraembryonic mesoderm and myocardium, and the BMP-2 signaling in myocardium is crucial for the formation of endocardial cushion (EC). Moreover, the regulation of BMP-2 signaling triggers underlying endothelium forming ECs is depending on an epithelial-mesenchymal transformation (EMT) [52]. ECs finally produce the differentiate heart septa and valves, and allow the development of a mature heart with four chambers. Specific deletion of BMP-2 in cardiac progenitors block the formation of the four-chambered heart causing the heart valve region turns differentiated chamber myocardium. Further study has confirmed the function of BMP-2 in EC EMT when deletion of BMP-2 in atrioventricular (AV) happened, plus in development of cardiac jelly and AV myocardium [53].

Looking at molecular levels of every cells, a single individual of cell must have some very small differences in their genetic materials, DNA. Such differences might occur in either by programmed differences in specialized cells, random mutation and stability of DNA or chimerism and colonization. There are many factors can cause continuous alteration of DNA segments such as environmental damage, chemical degradation, genome instability, and small but significant errors in DNA replication and DNA repair [16]. There were so many studies of mutations of BMPs show the crucial roles of BMPs in various kinds of inherited diseases. Dysfunction of BMP-2 regulations is also being associated with the oral epithelium [54] and prostate cancer cells malignancy [55]. Moreover, further investigations have been done in the embryonic development and postnatal life, to investigate on how BMP ligands, receptors and signaling proteins are functioning by using the null mutations of these factors in animal models. For instant, inadequate BMP-2 in mice reduced their ability to survive independently after birth. Homozygous BMP-2 mutant embryos had cardiac developmental defect which demonstrated by the heart development abnormality in the exocoelomic cavity and die between 7 and 11 days period [48]. In hypertropic cartilage of BMP-2 null mutant mice, BMP-2 might functionally silent BMP-6, since BMP-2 and 6 are co-expressed in hypertropic cartilage [56,57].

BMP-2 as Potential Diseases and Cancer Therapies

BMP-2 in cancers can have either positive or negative effects in tumorigenesis and metastasis. BMP-2 can either act as tumor suppressors or tumor promoters through different mechanisms. BMP-2 can activate oncogenes, and initiate metastasis progression in tumor microenvironment. Evidence of BMP-2 and signaling components as a novel biomarker for cancer treatment with significant therapeutic implications remains controversial. Due to significant reduction of BMP-2 in prostate cancer compared to benign prostate tissue, it may functions as a marker of poor prognosis [58]. Moreover, the low expression of BMP-2 in epithelial ovarian cancer tissue also proposed that it probably obtain indigent prognosis of ovarian cancer patients.

Besides that, BMP-2 has negative modulation on miRNAs. miRNAs structures are short, non-coding RNAs of 18 to 25

nucleotides long that important in variety tumorigenic processes [59]. miRNAs profiling on C2L12 mesenchymal cells (a BMP-2-stimulated osteogenesis) distinguished two miRNA representatives and demonstrated miR-133 directly triggers Runx2, that essential for bone formation, and miR-135 may target SMAD5 (a signal osteogenic transducer of BMP-2) [60]. Furthermore, BMP-2 also relates to the study of drug resistance of cancer cells. For example, knockdown of BMP-2 increased chemo-resistance of the MCF-7 in breast cancer cell line [61], while BMP-2 treatment in *in vivo* models increased tumor development and chemotherapy resistance [62]. On the other hand, Persano et al. demonstrated that based treatment using BMP-2, escalated the temozolomide response in glioblastoma multiforme (GBM) cells with hypoxic drug-resistant and this chemotherapy resistance is reported as one of the leading factors for poor GBM among the most aggressive tumor types [63].

BMP-2 has been shown to have the osteoinductive capabilities in clinical trial studies. Variety of animal models such as mice, rabbits, dogs, sheep and other laboratory animals are used to evaluate and demonstrated the capability of BMP-2 to treat bone deformity in major-sized defects [64]. Such animal models, massive bone errors are not curable without a therapeutic interference, thus eases analysis of the BMP-2 abilities in inducing bone. Among the studies are BMP-2-gene therapy studies where they showed that the implantation of transfected BMP-2-bone marrow mesenchymal stem cells with a bioresorbable polymer mixture, healed the bone defects [65]. Additionally, recombinant human BMP-2 (rhBMP-2) that has been systemically administrated in mouse models, had shown positive regulation of mesenchymal stem cell activity and overturn the loss of age-related bone and ovariectomy-induced [66]. Therefore, BMP-2 might be useful in treating osteoporosis. Moreover, rhBMP-2 also demonstrated as an enhancer of bone healing in a rat femoral bone defect model and a rabbit ulna osteotomy model by delivering rhBMP-2 using a carrier such as calcium phosphate or liposome [67,68]. More clinical studies have shown the utilization of rhBMP-2 as a complete bone graft replacement in spinal fusion surgery [69,70] and several studies have demonstrated that the induction efficacy of BMP-2 in fusion is much way better than autogenous bone graft [69,71], and very useful in intervertebral and lumbar posterolateral fusion [72]. In dentistry, BMP-2 also can induce the formation of new dentine, plus has likely to be a substitute for root canal surgery and a very effective bone inducer for periodontal reconstructive implantation [73].

Stem Cell Differentiation and BMP-2

Stem cell biology has contributed a vantage point in addressing the problems in developmental biology. The development of human obeys the predetermined dogma from fertilized egg until it becomes a complete complex, multi-cellular organism. Stem cells are unspecialized cells, self-renewal and capable to differentiate into variety of specialized cell types. There are three types of germ layers developed from the fertilized egg: endoderm, ectoderm, and mesoderm. From these primitive cell types, they develop into all tissues of organism [74]. Several studies have showed that BMP-2 mediated osteogenesis from mesenchymal stem cell (MSC) precursors. For instance, improvement of the osteogenic differentiation of stem cells was triggered by the boost of BMP-2 binding efficiency [75,76]. Moreover, BMP-2 also has been demonstrated to activate WNT/β-catenin signaling and promote the differentiation of human dental pulp cells (HDPCs), which then mediate by p38 MAPK *in vitro* [77]. BMP-2 antagonist noggin has also been reported to regulate human ESCs differentiation and induce the novel cell types that give rise to neural precursors [78].

Several cancers originate from blood, brain, breast, skin, and gut, are derived from a minor group of stem cells from specific tissues, which function mainly for development, conserve their proliferation potential and to minimize DNA replication errors [79]. Adult stem cells are somatic cells that have self-renewal ability and able to differentiate into specialized cells. Normal stem cells must possess those two unique abilities as mentioned before. A normal stem cell is said to be self-renewal due to its property of producing more identical stem cells with similar replication potential and development. This ability enables mass production of the stem cells in response to intracellular and extracellular environments, hence initiate the proliferation and regulation of those cells in tissue and organs. In addition, a normal stem cell must also able to differentiate into tissue-specific specialized cells. Hematopoietic stem cells for example normally produce both myeloid and lymphoid progenitor cells which then give rise to variety of differentiated cells such as macrophages, monocytes, basophils, neutrophils, eosinophils, platelets, and erythrocytes (myeloid); T cells, B cells and natural killer cells (lymphoid) [80,81]. Such ability has brought attention for scientists to study the growth potential of stem cells *in vitro* and *in vivo* [82,83]. Stem cells also have a longer lifespan compared to matured cells. In the blood system for instance, terminally differentiated stem cells such as macrophages and basophils have a short lifespan because they generally die after normal tissue maintenance or cellular damage [84]. Therefore, stem cells are higher probability to cause the mutation rather than the matured cells.

Mutations resulted from aberrant mitoses in the regulatory systems that suppress abnormal proliferation. This might happen during mitotic division when a parent stem cell is self-renewing itself continuously. Majority of the mutations are benign because the abnormal cells are usually eradicated from the normal pool of dividing cells. However, at several phases, these abnormal cells could get accumulated and might trigger the development of cancer. Most mutations are affecting protein regulations of cell division, DNA damages and repair mechanisms as well as signaling pathways. Stem cells are said to be the target for mutations because they are the only long-lived cells in nearly the entire tissues that are vulnerable to genotoxic stresses compared to their specialized progeny [85]. From stem cell and cancer studies, CSCs emerged and believed to originate from normal stem cells or progenitor cells, which promote tumors when encountering specific genetic mutation or environmental alterations [86]. The study of genetic

alterations in differentiation of stem cells is a crucial approach for regeneration of defective tissue in stem cells therapy. Therefore, adding BMP-2 as a key factor on differentiation of stem cells is something that is worth to be investigated.

Possible Role of BMP-2 in CSCs Reprogramming

Stem cells role in cancer was discovered in 1994, reported by Lapidot et al. [87] followed by identification of CSC proposed by Bonnet and Dick in their research involving human acute myeloid leukemia (AML) [88]. After sample transplantation from patients with AML into severe combined immune-deficient (SCID) mice, they were able to identify an AML-initiating cell population. CSCs were later identified in many common solid tumors, including leukemia [87-89], breast cancer [90], colorectal cancer [91-93], and brain cancer [94].

The theory of CSCs hypothesized that only a small hierarchical organization of cells is assisting tumorigenesis and inheriting cellular heterogeneity throughout long-life primary tumor. CSCs do not really emerge from normal tissue stem cells modification even though they possess unique stem cell properties. Moreover, several observations have shown that cancers are resistant to both chemotherapy and radiation treatment, hence explains the tumor dormancy and metastasis phenomenon [95]. The studies of CSCs have encouraged the advanced treatment strategies for cancers focusing on eliminating CSCs, and not diminishing tumor size [96]. The origin of CSCs has speculated that, are they either really emerged from normal stem cells or normal somatic cells that gone mad over their regulatory and growth mechanisms? Perhaps progenitor or differentiated cells can obtain stem cell properties through mutations and cancer? Either theory speculated another important question is how CSC is functioning? CSCs require specific regulatory networks to exert their carcinogenic functions, such as cytokines from the cancer cell microenvironments. Therefore, novel cancer therapies might be developed through the elucidation of these pathways [97]. Because of the same properties of self-renewal and differentiation shared by both normal and CSCs, they may also share similar regulatory mechanisms relating to cell function stemness. Several pathways including Wnt pathways, Bmi-1, c-myc, Notch and Hedgehog (Hh) are examples of shared pathways in both normal and CSCs [98].

CSC studies have contributed to the search of novel cancer targeted therapies. By targeting the distinct functional and molecular properties of CSCs, it would be improving the efficacy of cancer therapies. Clinically, deciphering mechanisms of chemo- and radioresistance that control in CSCs is vital. Many targeting strategies are being explored within the different aspects of CSCs such as self-renewal pathways, quiescence, radio-resistance and CSC-specific cells surface molecules as reviewed by Batlle et al. [99]. In addition, the discrete molecular and functional properties of CSCs may also represent therapeutic liabilities that could be utilized for other novel combination strategies development. For BMP-2 and TGF-β family in general, there are few strategies of treatment under development that combines both anti-CSCs with chemotherapy. For instance, the self-renewal ability of triple-negative breast CSCs have been improvably inhibited using an anti-proliferative agent named paclitaxel by implicating TGF-β type 1 receptor in *in vivo* models [100]. Besides, the cronic myeloid leukemia (CML) TGF-β-Akt signaling inhibition suppressed imatinib cytotoxicity and apoptosis in CSCs, which sequentially regulated the nuclear localization of FOXO3a [101]. BMP-2 in specific has been demonstrated to sensitize glioblastoma stem-like cells to temozolomide (TMZ) by influencing the stability of hypoxia-inducible factor-1α (HIF-1α) and O6-methylguanine-DNA-methyltransferase (MGMT) expression [102].

Elucidating the problems arise as mentioned before about CSCs may be benefiting for the development of novel cancer therapies. Such problems may require a new methodology. One of the most recent technologies is the use of cancer cell-reprogramming approach using induced pluripotent stem cell (iPSC) technology. The reprogramming technology allows for the discovery of CSC-related oncogenes, anti-oncogenes, tumor-suppressor genes and epigenomes. This method also benefits for studying the associations between CSC microenvironment and its related genes, plus the mechanisms of cancer stem initiation and progression. However, this reprogramming method still faces so many challenges such as the chromosomal aberrations, genetic mutations, and cancer-specific epigenetic. The fundamental knowledge of reprogramming introduced by Takahashi and Yamanaka of using four specific transcription factors OSKM by generating stem cells-like cells provided a stepping stone for more researches to study the functional mutations of cancer-associated genes and genome epigenetic alterations, hence understanding the molecular mechanisms of tumorigenesis in humans [17].

Previously, BMP-2 has been reported as a key regulator in several normal and CSCs [103,104]. The reprogramming of *BMP-2* gene modification of iPSC-MSCs for bone tissue engineering had been done previously. Liu et al. demonstrated BMP-2-iPSC-MSC on Arg-Gly-Asp-calcium phosphate cement (RGD-CPC) enhanced differentiation and bone mineral production [105]. Unfortunately, there is no report about BMP-2 in the reprogramming of CSCs. Therefore, BMP-2 modulation in iPSC-CSCs is worth to be investigated.

Conclusions

In summary, BMP-2 is one of the most important factors in regulating bone and cartilage formation. Additionally, BMP-2 also regulates tumorigenesis in several cancers. The studies of BMP-2 may provide more views and understanding about the signaling pathways and molecular properties of CSCs hence utilizing BMP-2 as a modulating factor. Moreover, a precise approach is needed to deliver the BMP-2 into targeted cells such as reprogramming technology. Better results are expected from using the suitable approach thus providing more conclusive insights on CSCs progression and suppression to benefit cancer therapy.

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*Correspondence to

Sharaniza Ab-Rahim

Department of Biochemistry and Molecular Medicine

Universiti Teknologi MARA

Malaysia