Austin Biomarkers & Diagnosis

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Editorial

The Imperative Balance of Agonist and Antagonist for BMP Signalling Driven Adult Tissue Homeostasis

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Received: November 07, 2014; **Accepted:** November 10, 2014; **Published:** November 13, 2014

Editorial

The human body is a complex adaptive system that has the innate capacity to overcome changing conditions through the modularity of signalling cues. It has been shown that the adaptability of Bone Morphogenetic Protein (BMP) regulated adult tissue homeostasis often disintegrates in degenerative diseases [1,2]. Thereby, pathophysiological conditions, including impaired regenerative diseases of the muscle, bone and adipose tissue illustrate the functional interdependency of the BMP agonist with its antagonists [1,3]. In this context, complimentary expression has often been suggested to be imperative for healthy adaptability and regeneration of adult tissue homeostasis [1-5].

Up to date, more than 15 human BMPs have been characterized, all belonging to the TGF-β super family of metabologens that constitute pivotal morphogenetic signals and orchestrate local and systemic tissue homeostasis [6]. It has been shown, that BMPs take part in basic adult tissue-physiology through the regulation of the respective stem cell niche integrity [7]. In order to mediate it's function, BMPs bind distinct transmembrane BMP type I and type II receptors which initiate intracellular SMAD and non-SMAD signalling cascades that regulate transcriptional as well as non-transcriptional responses, necessary for stem cell and progeny fate decisions including proliferation, migration and differentiation [1,2,6].

The function of BMPs as determinant of intra-tissue homeostasis has recently been broadened through the discovery that a sub-group of BMPs, namely BMP4, BMP6 and BMP9 are detectable in the circulating system [8]. Thereby, it was shown that up to 10pg/ml BMP6 is present in human sera of healthy individuals, suggesting that BMPs putatively also act as endocrine factors that take part in the regulation of inter-tissue homeostasis [9]. Indeed, an integrated functional genomic screening program revealed that in particular the circulating BMPs act as adipokines that take part in the regulation of glucose homeostasis [10-12]. Since, systemic treatment of mice with BMP9 revealed micro-vesicular changes and necrosis in the liver; it is still under debate whether BMPs are suitable for the treatment of diabetes [13]. Interestingly, further studies on the role of BMPs in the liver identified that-through the recruitment of the BMP co-receptor hemojuvelin-BMP6 becomes the key endogenous regulator of hepcidin which in turn regulates iron metabolism [14-16]. Thereby, ongoing research needs to clarify whether BMP6 is locally produced in the liver, or whether it also derives from other sources and might become measurable in the serum of hemochromatosis patients.

It becomes apparent, that predominantly the BMP (co)-receptors and the extracellular BMP antagonists fine-tune the BMP signalling cascade and thereby directly couple immediate and long-term environmental changes with the operating mode of the cytokine [1-3,6,17]. Based on their structural integrity, BMP antagonists are classified into three subfamilies: (i) the DAN family; (ii) Twisted Gastrulation and (iii) Chordin and Noggin. As secreted glycoproteins, the BMP antagonists show distinct tissue specific expression patterns but share functional similarity through direct association with BMPs and prohibition of BMP binding to their cognate receptors [3-5]. Thereby, it is suggested that the 'so formed' functional inactive complex attenuates SMAD signal transduction in order to constrain BMP activity locally [1-5,17].

In order to understand the causal relation of how local BMP signal adaptation affects systemic adjustments in the body it is of value to identify common mechanism in BMP driven rare hereditary and frequent acquired pathophysiological conditions. Here, research on the impact of BMP regulated muscle-, skeletal- and adipose-tissue homeostasis revealed that imbalanced BMP signalling is often causative for diseases with indications in gain or loss if tissue volume and structure, hence tissue plasticity [1-3,6].

In this context, mainly the BMP antagonist Noggin has been characterized as crucial BMP regulatory factor [3-5]. Noggin is a pleiotropic factor which is present during gastrulation and tissue development. The presence of Noggin in mouse ectodermal and endodermal tissues has been shown but its BMP/SMAD antagonizing function has been mainly investigated in mesodermal tissue derivatives namely bone, cartilage, muscle, fat and dermis [3]. In Noggin null mice a series of developmental abnormalities, including failure of neural tube formation, hair-follicle retardation, dysmorphogenesis of the axial skeleton and joint lesions have been described [3,18]. Counterintuitive to the proposed dogma, the absence of Noggin in these mice did not lead to hyper-ossification of bone due to excessive BMP signalling but rather delayed and even abrogated bone ossifications [18]. Similarly, it has been described that in these mice late stages of myogenesis were delayed and lead to reduced muscle mass [18]. This is in particularly interesting since it was recently shown that the BMP/SMAD pathway is a hypertrophic signal in adult mice controlling muscle maintenance, growth and mass [19]. Furthermore, it has recently been shown that higher Noggin levels were measured in mesenchymal stem cells (MSCs) of adult obese mice [20]. Interestingly, obese mice demonstrated a reduced bone mineral density, suggesting a switch of MSC differentiation to enhanced adipogenesis whereas a Noggin knockdown resulted in increased osteogenic differentiation of adipose-derived stem cells [21,22].

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How important Noggin is in humans has been shown through Noggin heterozygous missense mutations which lead to deregulation of apoptotic processes in the interphalangeal joints as seen in proximal symphalangism (SYM1) and multiple synostosis syndrome 1 (SYNS1) [3-5]. Besides implications in cancers such as schwannoma or prostate cancer metastasis, current knowledge on Noggin's role in humans is primarily based on *ex vivo* cell culture experiments [23-25]. Inconsistent with the published dogma, these studies demonstrate that Noggin plays a key role in the process of hMSC osteogenic differentiation, suggesting an anabolic effect of Noggin [26]. Interestingly, elevated circulating Noggin levels in obese humans suggest that Noggin plays a putative role in human energy balance and body weight regulation [20]. Therefore, it has been suggested that Noggin may serves as a novel biomarker for obesity [20].

In conclusion, it will be of value to establish BMPs and its respective antagonist as (i) distinct and (ii) complimentary clinical biomarkers of the depicted adult tissue degenerative diseases to ascertain early identification of disease onset and progression. Interestingly, the combinational use of BMP6, Noggin and SOST (an additional BMP/WNT antagonist) has been suggested to significantly predict the progression of esophageal squamous cell carcinoma [27,28]. In the future, this combinatory usage of BMP agonist and BMP antagonist as clinical biomarkers might facilitate precise identification of onset and progression of imbalanced BMP signalling driven disorders such as muscular atrophy, osteopenia and obesity which might allow for precautious intervention to acquired consecutive systemic implications such as osteoporosis or diabetes.

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