# *Bone Morphogenetic Proteins (BMPs), satellite cells and Sarcopenia:*

## *Perspective in translational medicine*

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**Disclosure/Conflict of Interest**

There are no potential conflicts of interest relating to the manuscript (for each authors), and there were no extramural sources supporting this research (excluding sources already declared). The study is original and the manuscript has not been published yet and is not being considered for publication elsewhere in any language either integrally or partially except as an abstract. All authors have agreed with the submission in its present (and subsequent) forms.

## Editorial

The term sarcopenia was used for the first time by Rosenberg [1,2] to refer to the loss of lean body mass with aging. More in general, sarcopenia is an aging-induced generalized pathological condition characterized by loss of muscle mass and function related to aging. Muscle wasting in elderly patients is due to myofiber atrophy and loss caused by increased inflammation leading to proteosomal degradation, apoptosis, altered autophagy and decreased myogenic potential [3]. In addition, profound metabolic changes occur in myofibers during aging, included reduced mitochondrial dysfunctions, which contribute altering cell anabolism and reducing contractile force generation, thus leading to loss of muscle mass and strength [3].Concerning the social economic impacts, sarcopenia is strongly associated to reduction of the global physical strength and poor quality of life¸ and, as reported in a multicenter observational study that involved 770 in-hospital patients, it is represent a prevalent condition among older adults admitted to acute care wards and it is associated with increased short- and long-term mortality in hospitalized older adults [4]. Recently, the European Working Group on Sarcopenia in Older People has expanded the definition and suggested criteria for diagnosis including the presence of muscle weakness, a lower muscle mass and the presence of impaired performance [5].

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At every stage of life, the homeostasis of skeletal muscle is linked to the bone function and metabolism especially in osteoporotic patients [6]. Thus, the bone muscle crosstalk must be considered an important element in the patho-physiogenesis of sarcopenia [6]. In detail, Osteoporosis (OP), osteoarthritis (OA) and sarcopenia are considered the most frequent musculoskeletal disorders affecting older people. Indeed, aging process is a factor involved in the loss of the functionality of both bone and muscle [6-7]. The identification of molecular and cellular determinants involved in the pathogenesis of sarcopenia and its relationship with both OP and OA can open new prospective for the development of drugs able to prevent/treat the muscle impairment that occur in elderly. In this context, emerging evidence suggests that Bone Morphogenetic Proteins (BMPs) may play an important role in both muscle and bone homeostasis. The BMPs are molecules of transforming growth factor-β (TGF-β) family that orchestrates various biological processes linked to cell proliferation, differentiation, morphogenesis, cell homeostasis and regeneration [8]. BMP signaling is mostly known for its roles in embryonic development and in bone/cartilage formation [9]. One of the tissues that are under the control of the morphogenetic actions of the BMPs is the embryonic muscle. In fact, during myogenesis the specific levels of BMP signalling and the localized expression of Noggin (a BMP antagonist) determine when and where muscle formation will occur within the somite. In adult skeletal muscle, activation of BMPs has been associated with ectopic bone and cartilage formation and with diseases such as fibro-dysplasia ossificans progressive [9]. Recently it has been demonstrated that BMP signalling has also a role in controlling satellite cell function of adult [10]. During activation and proliferation, satellite cells express high levels of BMPRIa (ALK3) and of activated P-Smad1/5/8 [8]. Exogenous BMP4, acting through BMPRIa, exerts a pro-proliferative function and reduces differentiation by inhibiting MyoD. Conversely, blocking the BMP pathways at different levels leads to a premature differentiation [8]. Among BMPs family have been identified numerous molecules with positive and/or negative effects on muscle cells [11]. As concern BMP-7, recent study demonstrated their ability to block/reduce muscle atrophy after denervation [11]. In the canonical signaling pathway,

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they initiate the signal transduction cascade by binding BMP-receptors and activating Smads proteins. The Smads involved in BMP signaling are Smad1, Smad5, and Smad8 (Smad1/5/8) [11]. Activated Smads then associate with the Smad4, and translocates to the nucleus where it functions as a transcription factor regulating the expression of gene involved in muscle homeostasis, such as MyoD [12]. We and others groups have shown that the BMPs expression has a role in controlling adult skeletal muscle mass and regeneration [11,13,14]. In particular, we found a strictly association between BMP-2, BMP-4 and BMP-7 expression and the activity of satellite stem cells [13,14]. Specifically, we found a correlation between BMPs expression and the number of myogenin and CD44 positive satellite cells [13, 15]. The self-renewing proliferation of these cells not only maintains the stem cell population but also provides numerous myogenic cells, which proliferate, differentiate, fuse, and lead to new myofiber formation as demonstrated *ex vivo* both at histological and ultrastructural level [15]. However, a recent study of Lee et al. shed new light about the role of satellite cells in muscle regeneration in response to mechanical overload in aged mouse [16]. In particular, the authors have shown that the overload influences the muscular composition of the fibers independently of the abundance of pax7 positive satellite cells, suggesting that the biological significance of the increase in the number of satellite cells, due to resistance training, could be to limit fibrosis, thus promoting muscle growth and remodeling [16]. Likewise, Fry and colleagues demonstrated that in a mouse model lifelong reduction of satellite cells neither accelerated nor exacerbated sarcopenia and that satellite cells did not contribute to the maintenance of muscle size or fiber type composition during aging, but that their loss may contribute to age-related muscle fibrosis [17]. In the human subjects, controversy remains on the actual contribution of satellite cells to the development of sarcopenia in later life, this clearly requires further research. Therefore, the monitoring of satellite cells storage and function could provide essential information for the understanding of cellular mechanisms of sarcopenia development and it may become a powerful tool management of sarcopenic and, more in general, frailty patients.

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In this context, it is important to note that the BMPs signaling can induce satellite cells to differentiate in osteoblasts contributing to important physio-pathological phenomena such as fracture healing. In particular, has been demonstrated that under BMPs stimulation muscle close to bone fracture sites is capable of supplying osteoprogenitor cells in cases where the periosteum is insufficient and the muscular osteoprogenitors possess similar osteogenic potential to those derived from the periosteum [18]. Thus, the cellular and molecular impairment that occur in the sarcopenic muscle tissues contributes to delayed healing of the fracture.

In the elderly patients, the BMPs signaling in muscle tissues is frequently counteract by myostatin signaling [12]. Myostatin is a member of the TGF-β superfamily and acts as a potent negative regulator of skeletal muscle growth [13]. It is known to affect muscle mass by negative regulation of myogenesis [15]. *In vitro* experiments have shown that myostatin blocks myoblast proliferation and satellite cell proliferation and self-renewal by down regulation of MyoD [15]. Also, myostatin induced the blocks of muscle regeneration competing both for the binding with BMP-receptor and activation of Smad4. Thun, the balance between myostatin and BMP signaling, as well as the number and the activity of satellite cells, can strongly influence the development of sarcopenia (Fig.1) opening interesting perspectives in the management of sarcopenic patients. Indeed, to date, diagnostic assessment and pharmacological interventions have shown limited efficacy in counteracting the effects of sarcopenia. Nevertheless, data concerning the role of these molecules in the biology of sarcopenia can provide the scientific rationale for the use of BMPs and myostatin as serum biomarkers or for development of new therapeutic protocols based on the use of human recombinant BMP-2/7 and/or anti-myostatin antibodies. In the last years, genetic engineering allows the production of large amounts of BMPs for clinical use, and clinical trials have shown the benefits of FDA-approved recombinant human BMPs 2 and 7, especially for the treatment of delayed fracture healing [19]. Moreover, the possibilities offered by new carries such as bioactive membranes doped with BMPs are promising options that could act to accelerate and enhance their *in situ* biological activity in several districts including muscle tissue. Specifically, the capability of

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BMPs to activate myogenesis by satellite cells function revealed a promising future for the fields of bioengineering and regenerative medicine. Instead, as concern the use of anti-myostatin antibodies, several pre-clinical investigations showed that treatment of mice with an anti-myostatin antibody increased muscle mass and strength in both young and old mice [20]. In addition, in old mice, was demonstrated that increase in muscle mass was accompanied by an improvement in muscle insulin sensitivity providing support for myostatin inhibition as a potential therapeutic strategy for aging-associated sarcopenia and insulin resistance.

The scientific dissertation here reported highlights the multifaced aspects of sarcopenia occurrence and development. A growing understanding of cellular e molecular mechanisms of sarcopenia can speed up the achievement of a personalized medicine that takes into account the uniqueness of the human being.

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**References**

1. Rosenberg IH. Summary comments. Am J Clin Nutr 1989;50:1231-3;

2. Rosenberg IH. Sarcopenia: origins and clinical relevance. J Nutr 1997;127(5 Suppl):990S- 991S;

3. Zembroń-Łacny A, Dziubek W, Rogowski Ł, Skorupka E, Dąbrowska G. Sarcopenia: monitoring, molecular mechanisms, and physical intervention. Physiol Res. 2014;63(6):683-91. Epub 2014 Aug 26.

4. Vetrano DL, Landi F, Volpato S, Corsonello A, Meloni E, Bernabei R, Onder G. Association of sarcopenia with short- and long-term mortality in older adults admitted to acute care wards: results from the CRIME study. J Gerontol A Biol Sci Med Sci. 2014 Sep;69(9):1154-61.

5. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. Age Ageing. 2010 Jul;39(4):412-23.

6. Tarantino U, Piccirilli E, Fantini M, Baldi J, Gasbarra E, Bei R. Sarcopenia and fragility fractures: molecular and clinical evidence of the bone-muscle interaction. J Bone Joint Surg Am. 2015 Mar 4;97(5):429-37.

7. Tarantino U, Baldi J, Celi M, et al. Osteoporosis and sarcopenia: the connections. Aging Clin Exp Res.2013 25 Suppl 1:S93-5;

8. Walsh DW, Godson C, Brazil DP, Martin F. Extracellular BMP-antagonist regulation in development and disease: tied up in knots. Trends Cell Biol. 2010 May;20(5):244-56.

9. Yu, P.B. et al. BMP type I receptor inhibition reduces heterotopic ossification. Nat. Med. 14, 1363–1369 (2008);

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10. Sartori R, Schirwis E, Blaauw B, Bortolanza S, Zhao J, Enzo E, Stantzou A, Mouisel E, Toniolo L, Ferry A, Stricker S, Goldberg AL, Dupont S, Piccolo S, Amthor H, Sandri M. BMP signaling controls muscle mass. Nat Genet. 2013 Nov;45(11):1309-18;

11. Sartori R, Sandri M. BMPs and the muscle-bone connection. Bone. 2015 Nov;80:37-42.

12. Scimeca M, Piccirilli E, Mastrangeli F, Rao C, Feola M, Orlandi A, Gasbarra E, Bonanno E, Tarantino U. Bone Morphogenetic Proteins and myostatin pathways: key mediator of human sarcopenia. J Transl Med. 2017 Feb 15;15(1):34. doi: 10.1186/s12967-017-1143-6.

13. Tarantino U, Scimeca M, Piccirilli E, Tancredi V, Baldi J, Gasbarra E, Bonanno E. Sarcopenia: a histological and immunohistochemical study on age-related muscle impairment. Aging Clin Exp Res. 2015 Oct;27 Suppl 1:S51-60;

14. Tarantino U, Baldi J, Scimeca M, Piccirilli E, Piccioli A, Bonanno E, Gasbarra E. The role of sarcopenia with and without fracture. injury. 2016 Aug 2. pii: S0020-1383(16)30365-5;

15. Scimeca M, Bonanno E, Piccirilli E, Baldi J, Mauriello A, Orlandi A, Tancredi V, Gasbarra E, Tarantino U. Satellite Cells CD44 Positive Drive Muscle Regeneration in Osteoarthritis Patients. Stem Cells Int. 2015;2015:469459.

16. Lee JD, Fry CS, Mula J, Kirby TJ, Jackson JR, Liu F, Yang L, Dupont-Versteegden EE, McCarthy JJ, Peterson CA. Aged Muscle Demonstrates Fiber-Type Adaptations in Response to Mechanical Overload, in the Absence of Myofiber Hypertrophy, Independent of Satellite Cell Abundance. J Gerontol A Biol Sci Med Sci. 2016 Apr;71(4):461-7.

17. Fry CS, Lee JD, Mula J, Kirby TJ, Jackson JR, Liu F, Yang L, Mendias CL, Dupont-Versteegden EE, McCarthy JJ, Peterson CA. Inducible depletion of satellite cells in adult, sedentary mice impairs muscle regenerative capacity without affecting sarcopenia. Nat Med. 2015 Jan;21(1):76-80.

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18. Davis KM, Griffin KS, Chu TG, Wenke JC, Corona BT, McKinley TO, Kacena MA. Muscle-bone interactions during fracture healing. J Musculoskelet Neuronal Interact. 2015 Mar;15(1):1-9.

19. Carreira AC, Zambuzzi WF, Rossi MC, Astorino Filho R, Sogayar MC, Granjeiro JM. Bone Morphogenetic Proteins: Promising Molecules for Bone Healing, Bioengineering, and Regenerative Medicine. Vitam Horm. 2015;99:293-322.

20. Camporez JP, Petersen MC, Abudukadier A, Moreira GV, Jurczak MJ, Friedman G, Haqq CM, Petersen KF, Shulman GI. Anti-myostatin antibody increases muscle mass and strength and improves insulin sensitivity in old mice. Proc Natl Acad Sci U S A. 2016 Feb 23;113(8):2212-7.

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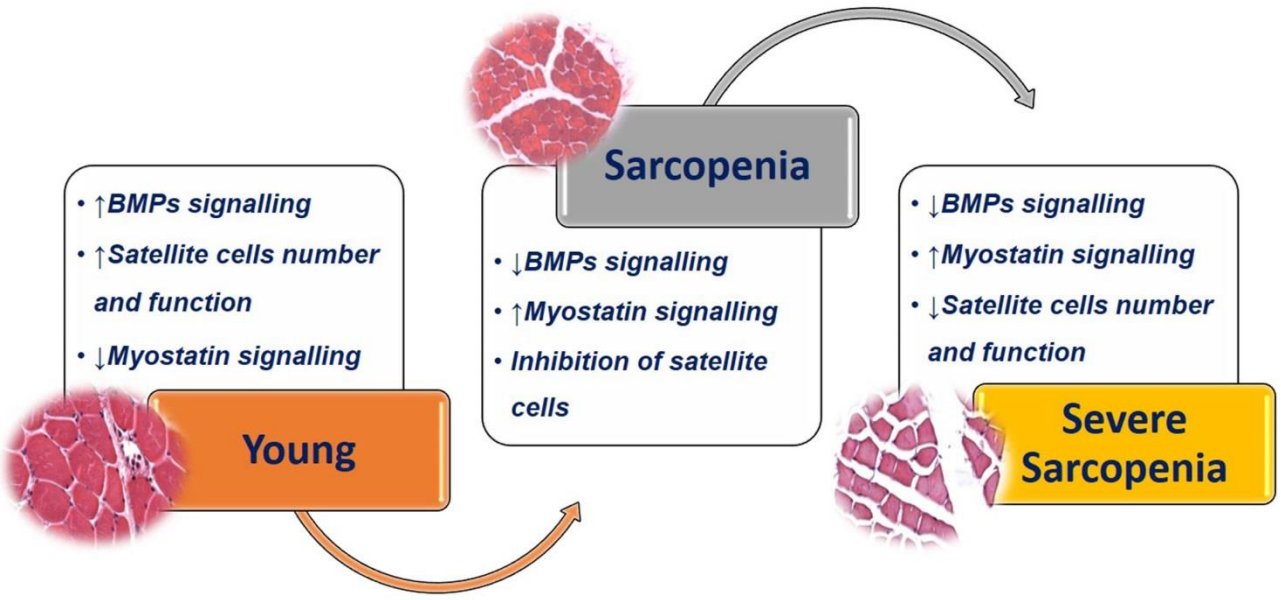
**Figure legend**

**Fig.1 schematic figure of relationship among BMPs and myostatin signaling, satellite cells activity and sarcopenia occurrence.**

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