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Editorial

Bone morphogenetic proteins (BMPs): From morphogens to metabologens

Among the many tissues in the human body bone has the highest potential for regeneration. What is the molecular basis of this regenerative prowess in bones? Bone is composed of an organic matrix that is principally collagenous and is mineralized with inorganic crystals of hydroxyapatite. Demineralization of the bone results in a demineralized bone matrix. The demineralized bone matrix is a bioactive, biodegradable, biomaterial that induces bone morphogenesis in the extraskeletal ectopic sites. The bioactive signal is bone morphogenetic protein (BMP). There are twenty genes in the human genome that encode functional BMPs [1–3]. Bone morphogenesis is a sequential multistep biological chain reaction and the key steps are chemotaxis of progenitors/stem cells, proliferation of cells and differentiation of true endochondral bone formation. It is well known that regeneration is in part recapitulation of embryonic development and therefore it is not surprising that recombinant BMPs 2 and 7 are currently approved by the Food and Drug Administration (FDA) for spine fusion, fracture healing and oral surgery [4,5]. This is indeed remarkable that recombinant morphogens BMPs are in everyday clinical use all over the world.

This issue of the journal presents the emerging recent advances in the basic science of BMPs and its implications for regenerative medicine. The three key elements for optimal regenerative medicine are inductive morphogenetic signals, responding stem/progenitor cells and a scaffolding of extracellular matrix. The rules of architecture for regenerative medicine and tissue engineering are an imitation of the rules and principles of developmental biology and morphogenesis. The overall organization of the reviews for this special volume is based on the trinity of regenerative medicine, signals, stem cells and scaffolds. The BMP receptor signaling is ably reviewed by Knaus and colleagues. The symphony of developmental regulation is an integration amongst the signaling families of morphogens such as BMPs, Fgf family, Hedgehogs and the Wnts. The integration of BMP and Wnt signaling is incisively covered by De Robertis and coworkers. The BMP receptor dynamics and assembly play a critical role in morphogen actions and interactions and is critically dealt with by Nickel and collaborators. The role of Smads as intracellular effectors of BMP signaling in chondrogenesis is expertly reviewed by Lyons and coworkers.

One of the emerging themes in the BMP field is that these morphogens regulate metabolism in many unexpected and surprising ways. The iron metabolism is regulated by BMPs. This is superbly discussed by Lin and coworkers. We define metabologen as a morphogen (molecule) that can initiate, promote and maintain metabolism and homeostasis. Thus the morphogens may masquerade as metabologens in not only iron homeostasis but also in brown fat adipogenesis and energy metabolism. Tseng has made the exciting discovery that BMP 7 plays a role in adipogenesis and in energy metabolism.

The intricate signaling by the BMP receptor pathways can go awry in certain clinical conditions. Kaplan and Shore and their team identified the mutations in the type I BMP receptor, ACVR1/ALK2 which results in an ossification syndrome Fibrodysplasia Ossification Progressiva (FOP) by ligand-independent activation of the BMP receptor and attendant increased bone formation. The rational synthesis and screening of small molecular weight inhibitors of these BMP receptor kinases is the topic of the exciting article by Hong and Yu.

A clutch of four reviews by Caplan, Peault, Nakashima and Vukicevic are focused on stem cells. The exciting recent work demonstrated that pericytes of the vascular tree in a wide variety of tissues have are the mesenchymal stem cells. The regulation of stem cells by BMPs is an exciting frontier. The scaffolding of the microenvironment plays a critical role as the stem cell niche. The extracellular matrix is the purveyor of contextual information from the outside to the cells and the nucleus. This relay is critically reviewed by Nelson and coworkers. The role of TGF Beta signaling in stem cell lineages is reviewed by Huylebroek and colleagues.

The classic bioassays for bone induction and morphogenesis permitted the isolation, purification and cloning of BMP 2 and BMP 7. In view of this the first clinical utility was sought in bone regeneration. The articles by Rosen and Einhorn are excellent demonstrations of the role of BMP 2 in regeneration of bone and fracture healing.

The alveolar bone and the associated periodontium are critical for tooth anchorage to maxilla and mandible. Ripamonti has reviewed this burgeoning area of BMPs and periodontal regeneration. He has extensively investigated the role of BMPs in subhuman primates. There is potential excitement in developing novel newer BMPs that may function more potently and in lower doses and this topic is explored by Alaoui-Ismaili and Falb.

In addition to its role in bone healing BMPs may have a role in cartilage regeneration. By definition all BMPs are inducers of chondrogenesis therefore cartilage morphogenetic proteins. Therefore BMPs can be expected to play a role in cartilage regeneration. Lories and Luyten have reviewed the potential role of BMPs in joint development and homeostasis.

The regulation of micro RNA biogenesis by members of the TGF Beta signals is the subject of Hata's article. Finally, the

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increasing evidence implicating the role of intronic noncoding DNA in long-range regulation of members of the BMP family is becoming abundantly clear. Mortlock has identified a osteoblast specific Bmp 2 enhancer about 156 kb away in the 3′ region. This exciting review emphasizes the need to investigate the long-range regulation of exons by distant intergenic enhancer sequences.

In conclusion, BMPs have come of age from bone morphogenetic proteins to the body morphogenetic proteins and more recently as regulators of iron and energy metabolism. Thus, the morphogens are masquerading as metabologens! As students of BMPs it is truly astonishing to witness the wide-ranging functions and versatility of roles of BMP family from pattern formation, morphogenesis, cell differentiation, organogenesis, homeostasis, regulation of iron and energy metabolism and finally in regenerative medicine by directing the lineage of the stem cells.

Acknowledgements

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