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 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
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 an 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.

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References


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