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Survey

BMP signaling in vascular development and disease

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ABSTRACT

Genetic and functional studies indicate that common components of the bone morphogenetic protein (BMP) signaling pathway play critical roles in regulating vascular development in the embryo and in promoting vascular homeostasis and disease in the adult. However, discrepancies between *in vitro* and *in vivo* findings and distinct functional properties of the BMP signaling pathway in different vascular beds, have led to controversies in the field that have been difficult to reconcile. This review attempts to clarify some of these issues by providing an up to date overview of the biology and genetics of BMP signaling relevant to the intact vasculature.

Contents

1. Introduction

Genetic studies in mice demonstrate that the BMP signaling pathway plays a critical role in regulating embryonic vascular development. Many of the same pathways that regulate

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vascular development are reactivated following vascular injury, suggesting that defective BMP signaling also plays a role in vascular homeostasis and disease in adults. Definitive evidence for this derives from genetic studies indicating that components of the BMP signaling pathway are mutated in patients with hereditary vascular diseases. These studies also suggest that defects in BMP signaling play a role in more common vascular diseases not associated with mutations in components of the BMP pathway. However, rapid advances in understanding the biology of this signaling pathway have made it difficult to grasp some of the complexities of these studies. The purpose of this review, therefore, is to provide an overview of the relevant biology of BMP signaling (Section 2) and to summarize current genetic and functional data linking abnormalities in BMP signaling with vascular development and disease (Section 3).

2. Part 1: BMP signaling

2.1. BMP family of ligands

BMPs are secreted TGF-β superfamily ligands first identified in extracts from bone matrix that could induce ectopic bone formation when implanted subcutaneously in rats [1]. It is now known that BMPs play an essential role in the development of nearly all vertebrate organs, including the embryonic vasculature [2,3]. Within the TGF-β superfamily, BMP ligands (some of which are also referred to as growth and differentiation factors (GDFs)) can be organized into clades based on sequence similarity to conserved molecules in primitive organisms (Fig. 1). On this basis, 15 *bona fide* mammalian BMP/GDF ligands that activate typical BMP-dependent responses have been identified. Some of these ligands, including GDF8, GDF11, GDF1 and GDF3 are misnamed,

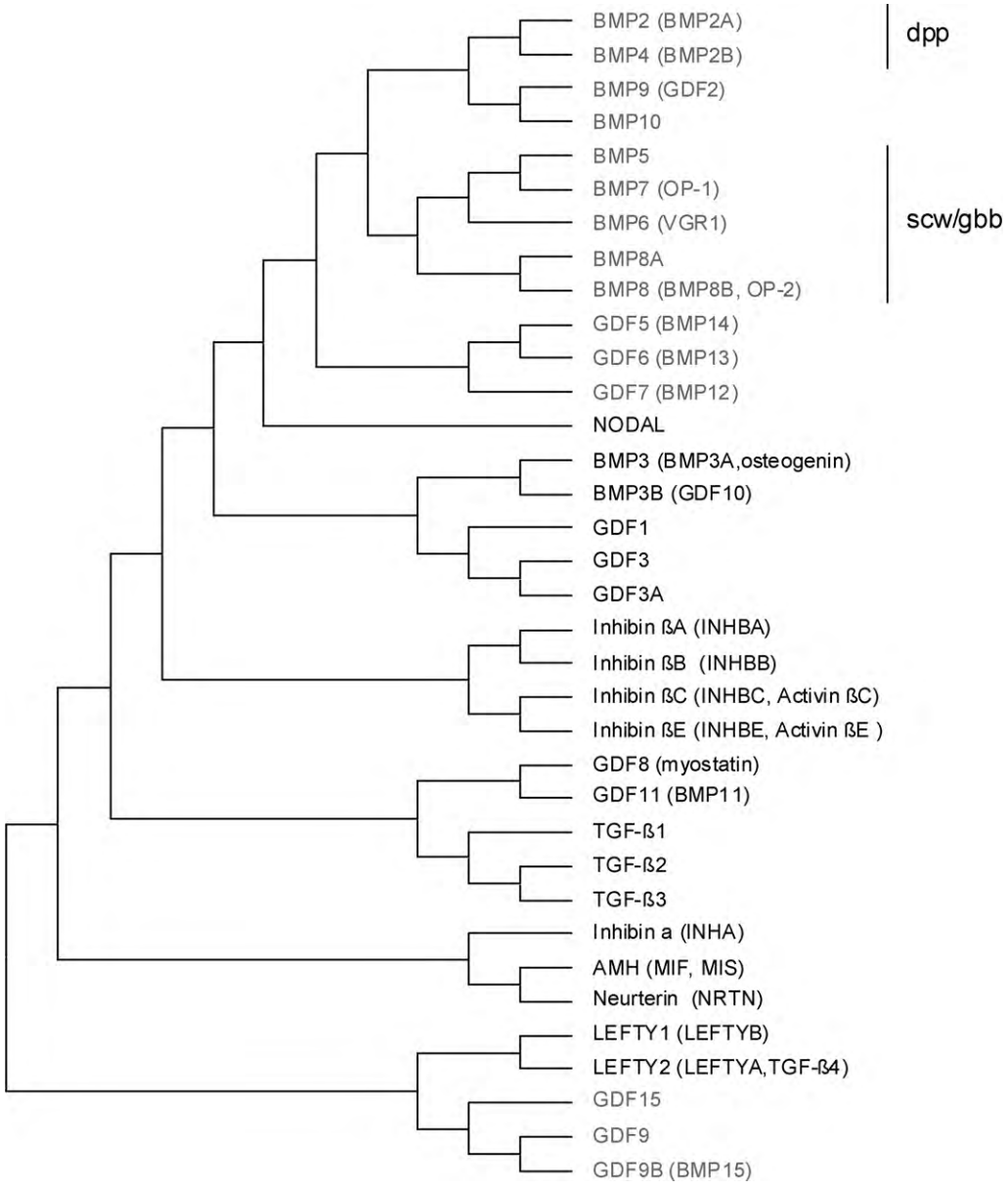

Fig. 1. Phylogenic comparison of TGF-β superfamily ligands based on full length human protein sequences. Sequence similarity to *Drosophila* BMP orthologues is indicated. Alternative names are listed in parentheses. Ligands in grey are *bona fide* BMPs that have been shown to activate BMP-SMADs. Phylogenetic analyses were conducted in MEGA4 [198] using the neighbor-joining method [199].