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Review

Promiscuity and specificity in BMP receptor activation

Thomas D. Mueller [a,*], Joachim Nickel [b]

[a] Department for Molecular Plant Physiology and Biophysics, Julius-von-Sachs Institute of the University Wuerzburg, Julius-von-Sachs Platz 2, D-97082 Wuerzburg, Germany
[b] Department for Tissue Engineering and Regenerative Medicine, University Hospital Wuerzburg, Roentgenring 11, D-97070 Wuerzburg, Germany

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ABSTRACT

Bone Morphogenetic Proteins (BMPs), together with Transforming Growth Factor (TGF)-β and Activins/Inhibins constitute the TGF-β superfamily of ligands. This superfamily is formed by more than 30 structurally related secreted proteins. Since TGF-β members act as morphogens, either a strict relation between a particular ligand to a distinct cellular receptor and/or temporospatial expression patterns of ligands and receptors is expected. Instead, only a limited number of receptors exist implicating promiscuous interactions of ligands and receptors. Furthermore, in complex tissues a multitude of different ligands can be found, which signal via overlapping subsets of receptors. This raises the intriguing question how concerted interactions of different ligands and receptors generate highly specific cellular signals, which are required during development and tissue homeostasis.

1. Complexity of an organism correlates with cytokine superfamily size

For their development, maintenance and survival multicellular organisms require constant intercellular communication to regulate all aspects of cellular life such as differentiation, proliferation, migration or apoptosis. No matter whether these are paracrine, endocrine or eventually autocrine stimuli the regulatory mechanisms although not exclusively but very frequently involve protein–protein interactions between a cell surface-located transmembrane receptor and a protein hormone also termed ligand. As nature seems to recycle "successful" protein scaffolds/structures and to develop new functionalities by duplicating genes rather than inventing de novo structures for each function, ligands and their receptors often form superfamilies with the number of members rising with increasing complexity of the organism [1] (the degree of complexity can be correlated with the number of different specialized cell types [2,3]). The Transforming Growth Factor (TGF)-β superfamily is no exception to this observation, with five potential ligand members in worm (*Caenorhabditis elegans*) [4], seven ligands in fly (*Drosophila melanogaster*) [5], 12 in fish (*Danio rerio*), 16 in amphibia (*Xenopus laevis*) and more than 30 ligand members in mammals (see online resources in [6]). Consistent with the hypothesis above, it seems that ligands having essential functions during early development have orthologs in all of the aforementioned phyla. For instance, orthologs of BMP-4, which is essential during early embryonic development of vertebrates [7], can be found in fly (Decapentaplegic, Dpp), in zebrafish (zBMP-4) as well as in amphibia (xBMP-4) sharing similar functions and mechanisms for dorsoventral patterning [8]. Only *C. elegans* does not seem to have a direct ortholog of the mammalian BMP-4, the genes encoding for the four ligand members, of which *daf7*, *dbl1*, and *tig2* are mapped to the human TGF-β ligands GDF-11, BMP-5 and BMP-8. The two factors Daf-7 and Dbl-1 are involved in the so-called Dauer larval development pathway regulating the body size of the larvae based on environmental conditions [4]. The function of orphan worm TGF-β member Tig-2 is unclear and Unc-129 mutant animals have been described to exhibit defects in axon outgrowth [9,10]. Thus the ligands present in worm seem to have functionalities other than patterning as is observed in other invertebrates and vertebrates [10]. Other TGF-β members have likely evolved later and exhibit functions restricted to higher organisms; e.g. GDF-9/BMP-15, which are involved in ovarian follicle development [11], the Anti-Muellerian Hormone (AMH), which plays an important role in male sex differentiation [12].

2. The TGF-β superfamily comprises four subfamilies

On the basis of their biological functions and phylogenetic analyses the more than 30 TGF-β ligands in mammals can be arranged in four main subfamilies (Fig. 1A). The Activin/Inhibin subfamily has initially been identified to regulate the expression of the pituitary Follicle-Stimulating Hormone (FSH) in the gonads ([13] for

* Corresponding author. Fax: +49 931 31 86158.
E-mail address: mueller@biozentrum.uni-wuerzburg.de (T.D. Mueller).

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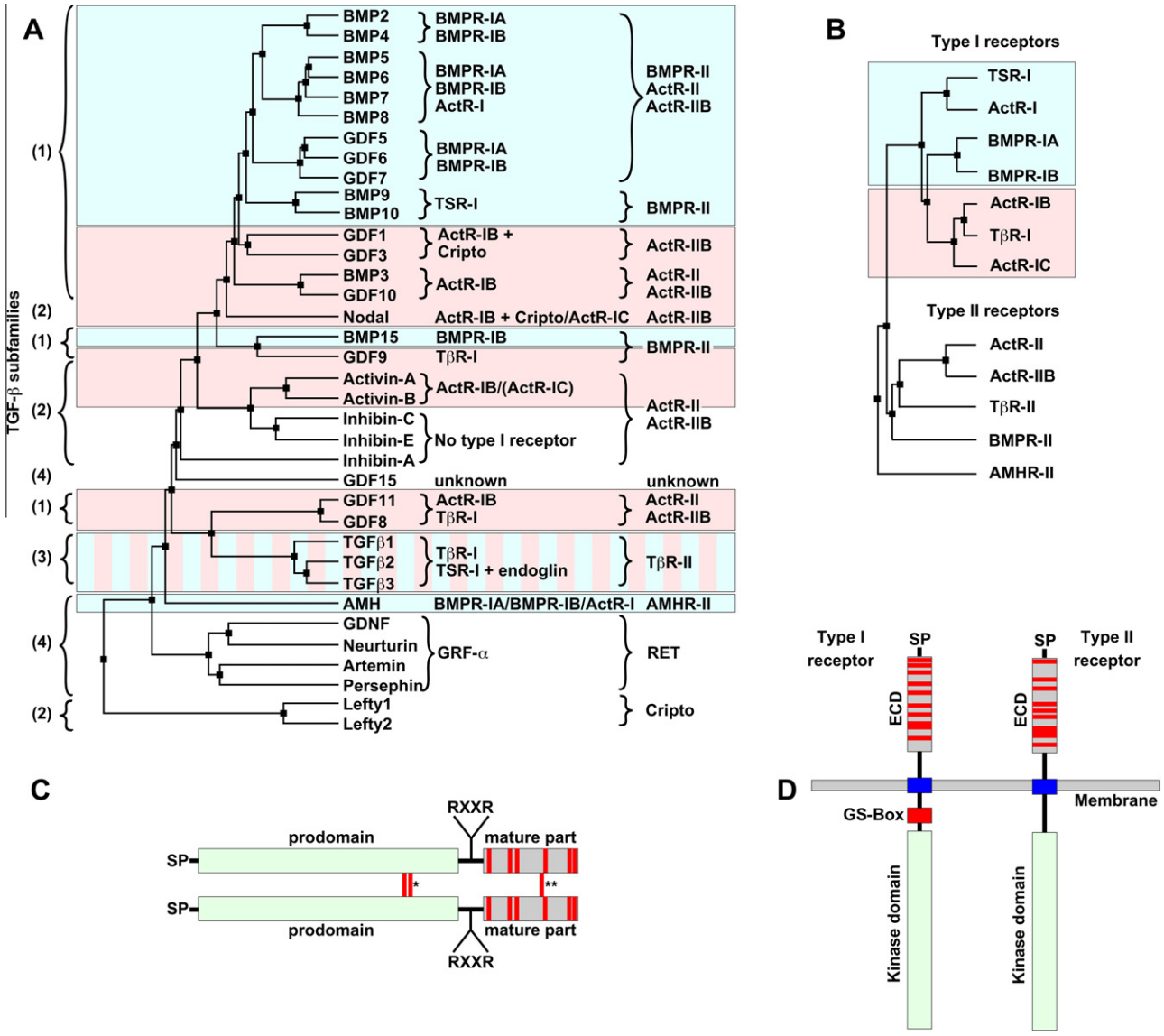

Fig. 1. (A) Phylogenetic analysis of the TGF-β ligand superfamily (only the mature region was used) showing the existence of four subfamilies as indicated on the left: BMP/GDF (1), Activin/Inhibin/Nodal (2), TGF-βs (3) and others (4). Type I and type II receptor usage is indicated next to each ligand and deduced from biophysical interaction or in vitro pulldown and crosslinking analyses. Light-blue shaded boxes emphasize SMAD 1/5/8, whereas light-red shaded boxes highlight SMAD 2/3 downstream signaling. (B) Phylogenetic tree (kinase domains were used for analysis) of TGF-β receptors highlighting type I and type II subgroup classification. Color usage for type I receptors indicates the SMAD pathway utilized (as in A). (C) TGF-β ligands are synthesized as dimeric proproteins including an N-terminal signal peptide (SP), a large prodomain and a C-terminal mature part with a characteristic cystine-knot motif. Cysteine residues are illustrated by red bars. Proteolytic processing by furin proteases occurs at the RXXR motif. Indicated by the single asterisk are the two intermolecular disulfide bonds, which are exclusive to TGF-β1/2/3 and covalently link the prodomain dimer. The intermolecular disulfide bond in the dimer of the mature part is marked by two asterisks (Lefty-1, -2, GDF-3, GDF-9 and BMP-15 lack this disulfide bond). (D) The architecture of TGF-β type I and type II receptor architecture consists of an N-terminal extracellular ligand-binding domain (EC), a single span-transmembrane and an intracellular kinase domain. The extracellular parts comprise ten cysteines in both receptor subtypes, but with a distinct sequential arrangement. An intracellular glycine/serine-rich domain (GS-box) characteristic for type I receptors is essential for kinase and downstream SMAD pathway activation.

recent review see [14]). However outside the gonads, Activins have additional functions, e.g. mesoderm induction, which is important for early body pattern determination and organogenesis (for review [15]) or in inflammation and immunity (for review [16]) (Fig. 1A). The subfamily members Nodal together with the more distant factors Lefty-1/-2 (that act as inhibitor to Nodal) are required for establishing left-right asymmetry [17] and Nodal itself is possibly also involved in maintaining embryonic stem (ES) cells in an undifferentiated state [18]. The subfamily of the TGF-β factors is the likewise smallest with only three members in mammals: TGF-β1, TGF-β2 and TGF-β3 (Fig. 1A). The TGF-βs are pleiotropic factors controlling proliferation and differentiation of many different cell types, thus TGF-β functions have been implicated in the control of immunity (e.g. by inducing FoxP3-positive regulatory T-cells a.k.a. iTregs) [19], in wound healing (e.g. promoting fibrosis through induction of extracellular matrix synthesis in different tissues and organs) [20] or for embryonic development [21]. However, best known is their dual role in the development and progression of cancer. Normally, TGF-β inhibits growth of most cell types including epithelial, endothelial and hematopoietic cells by blocking the cell cycle in the G1 phase thereby acting as tumor suppressor. But as a potent inducer of the epithelial-to-mesenchymal transition required for TGF-β's function in wound sealing, it enables carcinoma cells to spread and metastasize into normal