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Minireview

Growth factor receptors in helminth parasites: Signalling and host–parasite relationships

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Abstract Parasitic helminths remain major pathogens of both humans and animals throughout the world. The success of helminth infections depends on the capacity of the parasite to counteract host immune responses but also to exploit host-derived signal molecules for its development. Recent progress has been made in the characterization of growth factor receptors of various nematode and flatworm parasites with the demonstration that transforming growth factor beta (TGF-β), epidermal growth factor (EGF) and insulin receptor signalling pathways are conserved in helminth parasites and potentially implicated in the host–parasite molecular dialogue and parasite development.

Keywords: Parasite; Helminth; Receptor kinase; Growth factor; Signalling; Host–parasite relationship

1. Introduction

Reversible protein phosphorylation regulates most of the basic cellular functions and energy metabolism in all eukaryotes. In metazoan organisms, protein phosphorylation also coordinates cell and organ differentiation as well as communication between cells or with the external environment. Transmembrane receptors with serine/threonine kinase (RSTK) or tyrosine kinase (RTK) activity are activated by specific growth factors and induce the phosphorylation cascades essential for growth and development.

Wide similarities exist between growth factor signalling pathways in vertebrates and invertebrates and extensive studies from invertebrate model organisms, such as the fly *Drosophila melanogaster* and the nematode *Caenorhabditis elegans*, have allowed many important advances in the understanding of the function of different growth factor receptors like transforming growth factor-beta (TGF-β) [1,2], epidermal growth factor (EGF) [3,4] and insulin [5] receptors in the regulation of development. In the helminth *C. elegans*, both TGF-β and insulin pathways have been demonstrated to regulate reproductive development by controlling dauer formation and life span extension under suboptimal living conditions [6,2].

Although parasitic helminths still remain major pathogens causing debilitating diseases in both humans and animals throughout the world, very little is known about the mechanisms that control their reproduction and their survival in the host. These parasites are remarkably well-adapted to their hosts and can survive for very long periods (up to 25 years in the case of schistosomes) while evading the host immune response. The success of helminth infections is critically dependent on specific host–parasite interactions as well as on the receipt of appropriate host-derived signals by the parasite. During recent years, members of the TGF-β, EGF and insulin receptor families have been characterized from parasite nematodes (filarial species) and flatworms (trematode and cestode species). Structural and functional studies have demonstrated that these molecules show extensive similarity with other invertebrate and vertebrate orthologues and the conservation of their ligands and signalling pathways. Results suggest the potential implication of growth factor signalling in host–parasite relationships and raise interesting questions about the impact of parasitism on the co-evolution of ligand and receptor molecules in helminth parasites.

2. Conserved TGF-β signalling in parasitic helminths

TGF-β belongs to a large family of structurally related proteins including activins/inhibins and bone morphogenetic proteins (BMP) that control a wide range of key events in growth and development of many organisms and regulate immune response against infectious agents. TGF-β plays a pivotal role in a large spectrum of intracellular protozoan infections by downregulating host cellular responses against parasites [7]. In helminthic infections, its role in the inhibition of macrophage cytotoxicity has also been demonstrated [8]. Besides the importance of host TGF-β signalling in the regulation of host–parasite interactions, much evidence has been provided that helminth parasites might directly influence TGF-β dependent pathways via the expression of TGF-β receptor and ligand homologues.

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Abbreviations: TGFβ, transforming growth factor beta; EGF, epidermal growth factor; BMP, bone morphogenetic protein; RSTK, receptor serine threonine kinase; RTK, receptor tyrosine kinase; IR, insulin receptor

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TGF-β initiates signalling at the cell surface through its interaction with two receptor serine threonine kinases (RSTKs). The type II receptor (TβRII) binds the ligand and recruits the type I receptor (TβRI) to form a heteromeric complex. The constitutively active domain of TβRII phosphorylates a glycine/serine (GS) region in the juxtamembrane domain of TβRI and activates its kinase domain. TβRI then interacts with and phosphorylates a subset of receptor-regulated Smad proteins (R-Smad) promoting their association with a common Smad protein (Co-Smad) and the translocation of the Smad complex to the nucleus where it can regulate gene transcription [9,10]. In *C. elegans*, a TGF-β pathway involved in regulating dauer formation comprises the daf-7 ligand, the daf-1 type I and the daf-4 type II receptors, and different Smad proteins (daf-8, daf-14 and daf-3). An alternative TGF-β pathway involved in the regulation of body size and male tail patterning comprises the ligand dbl-1 and the receptors SMA-6 and daf-4 [2].

Several components of this pathway have been characterized and shown to be conserved in helminth parasites. In the filarial parasite *Brugia pahangi*, the gene *Bp-trk-1* encodes a protein homologous to TGF-β receptors and is transcribed during each of the stages of the parasite cycle [11]. By overall sequence similarity, Bp-trk-1 appears to be related to TβR1 and close to the *C. elegans* SMA-6 receptor (Fig. 1). In the cestode parasite *Echinococcus multilocularis*, two R-Smads (EmSmadA and EmSmadB) were shown to functionally interact with human BMP receptors [12] but it is in the schistosome trematode that the TGF-β pathway has been the most intensively studied.

A homologue of TβR1 (SmTβR1 or SmRK1) has been described in the trematode parasite *Schistosoma mansoni* (Fig. 1) and shown to be expressed at the surface of the parasite following its entry into the mammalian host [13]. Using a heterologous expression system, SmTβR1 was shown to interact with human TβRII and to activate Smad2 signalling molecules in response to human TGF-β [14]. Two R-Smads (SmSmad1 and SmSmad2) as well as a Co-Smad (SmSmad4) have been identified as downstream partners of SmTβR1 [15–17]. The existence of a conserved TGF-β signalling pathway in *S. mansoni* was further confirmed by Knobloch et al. [18] who demonstrated an

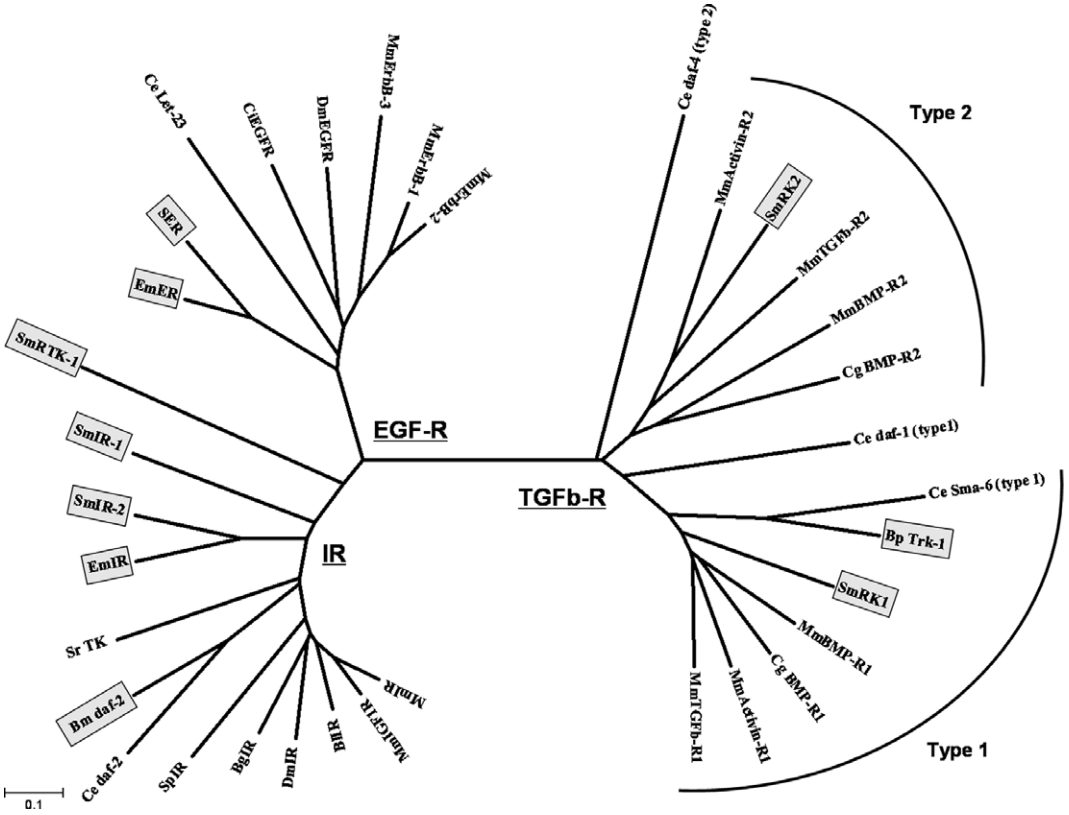

Fig. 1. Phylogeny of IR, EGF-R and TGFb-R. Phylogenetic analyses of kinase domains showing the relationships between IR from helminths (*Schistosoma mansoni*, SmIR-1 AAN39120 and SmIR-2 AAV65745; *Echinoccocus multilocularis*, EmIR CAD30260; *Brugia malayi*, Bm daf-2 AAW50597; *Caenorhabditis elegans*, Ce daf-2 AAC47715), from sponge (*Sycon raphanus*, Sr TK CAC14729), from insect (*Drosophila melanogaster*, DmIR AAC47458), from mollusc (*Biomphalaria glabrata*, BgIR AAF31166), from echinoderm (*Strongylocentrotus purpuratus*, SpIR ABC61312), from prochordate (*Branchiostoma lanceolatum*, BlIR O02466) and from mammal (*Mus musculus*, MmIR NP_034698 and MmIGF1R Q60751), EGF-R from helminths (*Schistosoma mansoni*, SER AAA29866; *Echinoccocus multilocularis*, EmER CAD56486; *Caenorhabditis elegans*, Ce Let-23 P24348), from insect (*Drosophila melanogaster*, DmEGFR P04412), from prochordate (*Ciona intestinalis*, CiEGFR BAE06394) and from mammal (*Mus musculus*, MmErbB-1 AAA17899, MmErbB-2 P70424 and MmErbB-3 Q61526), and TGFβ-R from helminths (*Schistosoma mansoni*, SmRK1 AAC16404 and SmRK2 AAQ23043; *Brugia pahangi*, Bp Trk-1 AAC47801; *Caenorhabditis elegans*, Ce daf-1 P20792, Ce daf-4 P50488 and Ce Sma-6 AAD12261), from mollusc (*Crassostrea gigas*, Cg BMP-R1 CAE11917 and Cg BMP-R2 CAD20574), and from mammal (*Mus musculus*, MmBMP-R1 P36895, MmBMP-R2 O35607, MmActvin-R1 P37172, MmActvin-R2 P27038, MmTGFb-R1 Q64729 and MmTGFb-R1 Q62312). Catalytic domain of *Schistosoma mansoni* SmRTK-1 was also added (AAL67947). Sequences were aligned (232 unambiguously aligned residues) using Clustal W (Mega 3.1) and used for construction of a phylogenetic tree by the neighbour joining bootstrap resampling method with 100 000 replicates.