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Survey

The multiple facets of the TGF-β family cytokine growth/differentiation factor-15/macrophage inhibitory cytokine-1

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ABSTRACT

GDF-15 (also MIC-1, NAG-1, PLAB, PTGFB) is a member of the TGF-β superfamily, which is widely distributed in mammalian tissues and has been shown to play multiple roles in various pathologies, including inflammation, cancer, cardiovascular diseases, and obesity. GDF-15 serum levels are a highly reliable predictor of disease progression. Both the anti-tumorigenic potential of GDF-15 and its capacity to promote metastasis have been documented for a large variety of cancers, yet its opposing functions, which are typical for members of the TGF-β superfamily, have only partly been resolved on the molecular level. Knowledge on physiological functions in the non-diseased organism is scarce. In the nervous system GDF-15 knockout analyses have revealed that GDF-15 is essential for the postnatal maintenance of various neuron populations. When applied exogenously GDF-15 is a powerful factor for promoting survival of developing and lesioned neurons in vitro and in vivo. Receptor activation by GDF-15 has only been partially resolved.

Contents

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1. Introduction – discovery of GDF-15

Growth/differentiation factor-15 (GDF-15) was discovered and cloned as a divergent member of the TGF-β superfamily in the late 1990s independently in at least seven different laboratories. Names were given based on relationship to TGF-β members or different cloning strategies applied. Using a subtraction cloning approach designed to identify genes related to macrophage activation, Bootcov et al. [1] identified macrophage inhibitory cytokine-1 (MIC-1). They found MIC-1 to be upregulated in macrophages by a variety of stimuli including IL-1β, TNF-alpha, IL-2, and TGF-β. The dimeric protein of Mr 25 kDa expressed in CHO cells inhibited lipopolysaccharide-induced TNF-alpha production in macrophages indicating that it might serve as an autocrine regulator of macrophage activation. Hromas et al. [2] isolated a molecule, supposed to be a novel member of the bone morphogenetic protein (BMP) TGF-β subfamily, from placenta and called it placental bone morphogenetic protein (PLAB). PLAB was shown to inhibit proliferation of primitive hematopoietic progenitors and introduced as a putative placental mediator of embryonic development. In a gene discovery effort targeting transcripts in placenta Lawton et al. [3] identified a novel TGF-β family member, which they named "Placental Transforming Growth Factor Beta" (PTGFB). Two transcripts, one of 1.2 kb, predominant in placenta, and another one of 1.9 kb that is predominant in adult skeletal muscle were identified. Selecting for cDNA clones encoding secretory proteins from a human full-length cDNA library Yokoyama-Kobayashi et al. [4] discovered one clone which encoded a novel TGF-β superfamily protein. Targeting putatively novel members of BMPs Paralkar et al. [5] also cloned the factor. They found it highly expressed in placenta and prostate, but also in cartilaginous tissue of the developing skeleton and in skin. We found GDF-15 by screening EST data bases for conserved TGF-β sequences and used subsequent cloning and a human placental cDNA library [6,7]. In an approach to identify genes regulated by cyclooxygenase (COX) inhibitors Baek et al. [8] identified a cDNA from a human colorectal cell line, HCT-116, treated with nonsteroidal anti-inflammatory drugs (NSAIDs) and named the gene NSAID activated gene, NAG-1. They characterized NAG-1 as a potent anti-tumorigenic and proapoptotic protein. In summary, despite the heterogeneity of strategies used several of the initial analyses already documented the wide distribution of the novel TGF-β family member, its prominent expression in macrophages and exocrine glands including prostate gland, and its anti-inflammatory, anti-proliferative, and anti-tumorigenic capacity.

2. Gene structure, regulation of expression and tissue distribution

Initial analyses of the rat, mouse and human GDF-15 genes revealed that they are composed of two exons, and contain one single intron that interrupts the coding sequences at identical positions within the pre-pro-domain of the corresponding proteins (Fig. 1) [3,6]. The predicted proteins contain the structural hallmarks of members of the TGF-β family, i.e. the seven conserved carboxy-terminal cysteine residues that form a cysteine knot

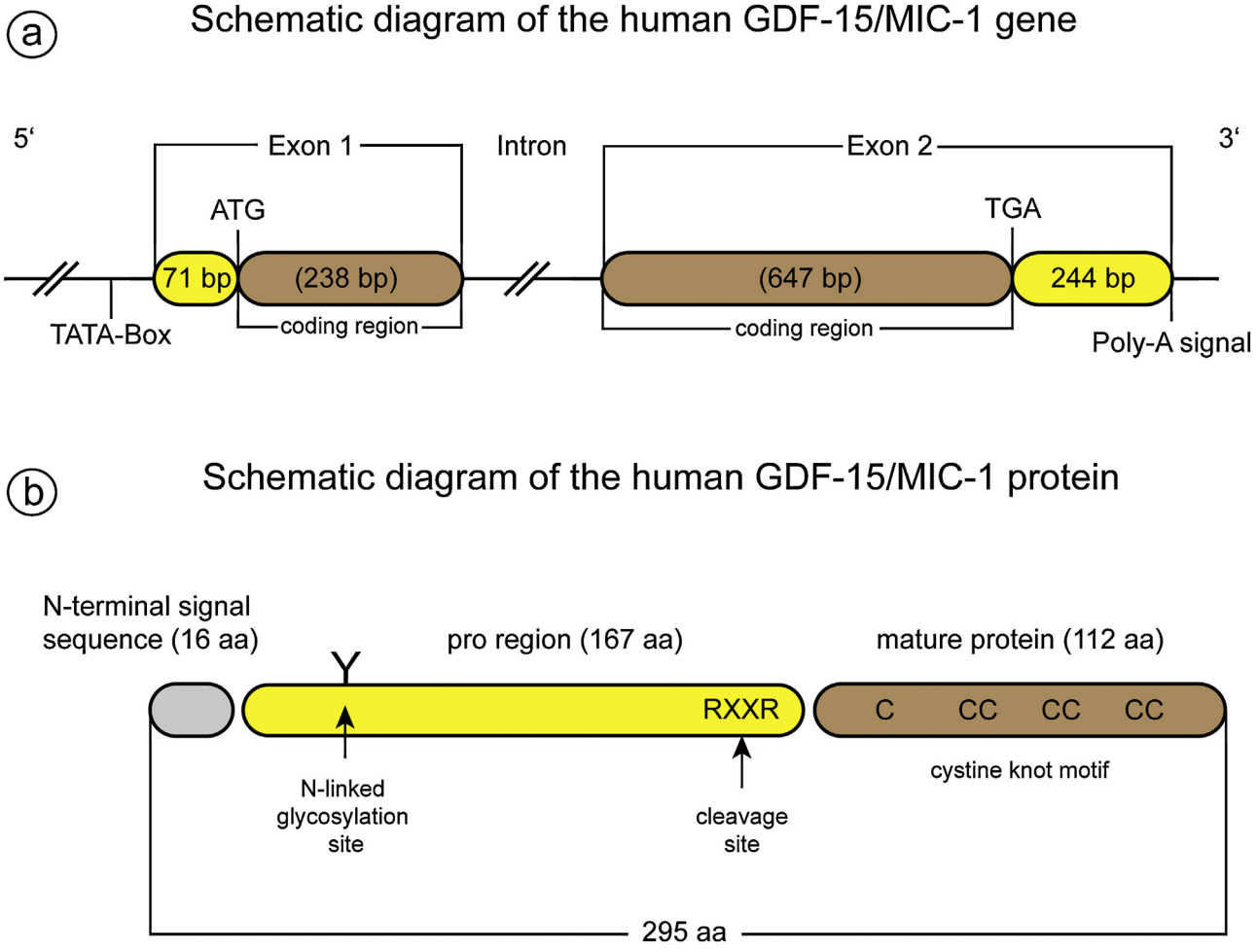

Fig. 1. Structure of the GDF-15 gene and protein. Courtesy of Dr. A. Schober.