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Review Article

Drug delivery of Insulin-like growth factor I

Isabel Schultz, Joel Wurzel, Lorenz Meinel *

Institute for Pharmacy and Food Chemistry, University of Wuerzburg, Am Hubland, DE-97074 Wuerzburg, Germany

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ABSTRACT

This review starts off outlining the control of Insulin-like growth factor I (IGF-I) kinetics in Nature and by virtue of a complex system of 6 binding proteins controlling half-life and tissue distribution of this strong anabolic peptide. In addition, alternative splicing is known to result in IGF-I variants with modulated properties *in vivo* and this insight is currently translated into advanced IGF-I variants for therapeutic use. Insights into these natural processes resulted in biomimetic strategies with the ultimate goal to control pharmacokinetics and have recently propelled new developments leading to optimized pharmaceutical performance of this protein *in vivo*. Aside from parenteral administration routes, IGF-I was successfully delivered across various epithelial barriers from liquid as well as from solid pharmaceutical forms opening novel and more convenient delivery modalities. IGF-I decoration yielded effective targeting upon systemic administration expanding the options for optimally deploying the growth factor for therapy. This review summarizes the exciting biotechnological and pharmaceutical progress seen for IGF-I delivery in recent years and critically discusses outcome in light of translational application for future IGF-I therapeutics.

1. Introduction

Insulin-like growth factor-I (IGF-I) is a polypeptide with a molecular weight of 7,649 kDa playing a key role in the regulation of cellular growth and metabolism. The growth factor was discovered in 1957 [2] and renamed as Somatomedin in 1972 [3]. Complete structural characterization was performed in 1978 [4]. IGF-I is a 70 amino acid peptide in a single chain with three disulfide bonds and classified into four domains (A, B, C, D; Fig. 1). The "Insulin-like" characteristics of IGF-I are structurally reflected by the homology of its A and B chains with those of Insulin [5]. In spite of these structural similarities, Insulin binds the Insulin receptor with 100 fold better affinity as compared to IGF-I [6–8]. The specific IGF-I transmembrane tyrosine kinase receptor is composed of two extracellular α-subunits (~130 kDa), containing a cysteine-rich domain for ligand specificity with two transmembrane β-subunits (~95 kDa) [9,10]. IGF-I binding to its receptor activates PI3K (phosphatidylinositol-3kinase) and MAP (mitogen-activated protein) kinase pathway [6]. IGF-I receptors are found nearly ubiquitously including cells of the immune system (T-cells, human monocytes and B-cells), musculoskeletal tissues (chondrocytes, osteoblasts, osteocytes, osteoclasts, myocytes) the reproductive system (e.g. uterus, ovaria, placenta, testis), endocrine cells (thyroid cells and adrenal cells) as well as in neural cells, fibroblasts, endothelial cells, hepatocytes, or keratinocytes [11,12]. The extent to which IGF-I receptors are found in tissues has been correlated with systemic IGF-I levels [13]. Approximately 80% of the IGF-I in blood are produced in the liver (endocrine) and 20% by local production (autocrine/paracrine) both of which resulting in quite distinguishable pharmacological roles [5,14]. IGF-I activity is further modulated by six IGF-binding proteins (IGFBP-1–6) modulating the pharmacokinetics including tissue distribution, transport across biological barriers, and IGF-I pharmacodynamics [15]. IGF-I stimulates the cellular activity increasing glucose uptake, oxidation and incorporation into glycogen, as well as protein synthesis [12,16]. It is for these anabolic activities that IGF-I has been suggested for the treatment of atrophic musculoskeletal diseases, including sarcopenia, cachexia, osteoporosis, growth failure, treatment of cartilage lesions, or for fracture repair [17–25]. Other potential applications include the treatment after myocardial infarction [26], or neurodegenerative diseases [14]. The delicate control of IGF-I activity *in vivo* is translating into diverse delivery modalities, driven by the intended pharmacological intervention. This article reviews localized delivery strategies and systemic delivery approaches with the ultimate goal to provide guidance for effective IGF-I delivery.

* Corresponding author. Tel.: +49 931 318 54 71; fax: +49 931 318 46 08.
E-mail address: l.meinel@pharmazie.uni-wuerzburg.de (L. Meinel).

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2. Pharmacokinetics and safety of IGF-I

IGF-I pharmacokinetics are modulated by six IGF-binding proteins [27]. Approximately 99% of plasma IGF-I is bound to IGFBPs, particularly to IGFBP-3 [7,13,16,28,29], forming a ternary complex consisting of IGF-I, IGFBP-3 (46–53 kDa protein) and the acid labile subunit (ALS; 88 kDa glycoprotein). This ternary 150-kDA complex increases the plasma half-life of IGF-I from 10 min in free form [6,30] to 12–15 h [6,30]. These insights were therapeutically translated by administering IGF-I together with IGFBP-3 (*vide infra*) in an effort to address the challenge of the short plasma half-life of free IGF-I. The formation of a ternary complex is known for IGF-I, ALS and IGFBP-5, but not for IGFBP-1, -2, -4, or -6 [31]. The A domain and B domain of IGF-I (Fig. 1) are mainly responsible for interactions with all IGFBPs [28,32]. For example, the affinity of IGF-I to its binding proteins was strongly decreased by substitution of the B domain or the mutation of amino acids such as Phe49, Arg50, and Ser51 (located on A domain). IGFBPs participate with their N-terminal and C-terminal domain in IGF-I binding [33]. It was previously demonstrated that Leu^{77}, Leu^{80} and Leu^{81} as well as Gly^{217} and Gln^{223} of IGFBP-3 were critically involved in interactions with IGF-I [34]. Apart from IGFBP binding forming a sink for

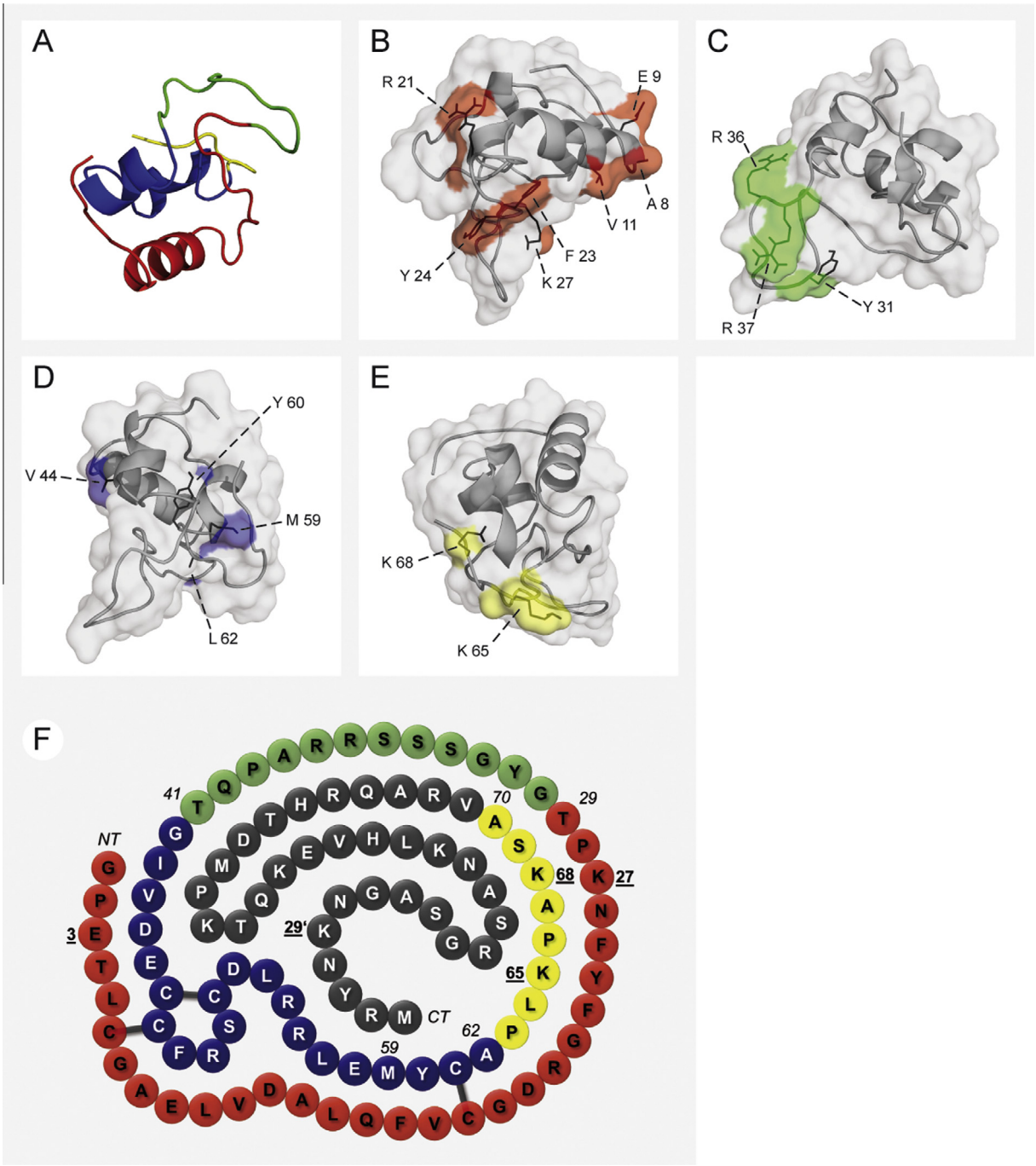

Fig. 1. (A) 3D structure of human IGF-I with B domain (red), C domain (green), A domain (blue) and D domain (yellow). (B–E) The transparent cloud indicates the simulated molecular surface. The essential amino acid residues for receptor binding [28] are highlighted for the (B) B domain (red), (C) C (green) domain, (D) A domain (blue) and (E) D domain (yellow). The pictures were derived from 2GF1 (solution NMR (nuclear magnetic resonance spectroscopy)) [1] using PyMOL molecular graphic system (Version 1.5.0.3. Schrödinger, LLC). (F) Amino acid sequence of human IGF-I [4] with Ea-peptide [107] (dark-gray). Disulfide bonds are represented as bold lines between cysteine residues. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)