Chapter 6

Mannose-6-Phosphate/Insulin-Like Growth Factor 2 Receptor (M6P/IGF2-R) in Growth and Disease: A Review

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Abstract

This work aims to summarize the current knowledge about Mannose-6- Phosphate/ Insulin-like Growth Factor 2 Receptor (M6P/IGF2-R) in the regulation of growth and development, and its involvement in tumor progression. M6P/IGF2-R binds both molecules sharing M6P signals and IGF2. The studies showed that M6P/IGF2-R is involved in the trafficking of mannnose-6-phosphorylated enzymes from the Trans-Golgi Network (TGN) to lysosomes and the uptake of secreted proenzymes from the plasma membrane to the lysosomes via clathrin-coated vesicles for their maturation. The M6P/IGF2-R acts as a scavenger that binds IGF2 and transports it to lysosomes for its degradation since IGF2 exerts its biological effects on cell proliferation and development by binding with lower affinity on IGF1 receptor, which is structurally similar to insulin receptor and different from the M6P/IGF2-R. The M6P/IGF2-R has also been studied in human cancer, and frequent losses of heterozygosity (LOH) at the 6q25-27 gene region with mutations in the remaining allele have been described. These results led to consider M6P/IGF2-R gene as a putative tumor suppressor and its potential prognostic value has been suggested.

Keywords: M6P/IGF2-R, genomic imprinting, cell growth and development, loss of heterozygosity (LOH), human cancer, tumor suppressor

1. Introduction

Two mannose-6-phosphate receptors (M6PRs) have been described: the mannose-6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2-R) binds both M6P ligands and IGF2 [1, 2] and the cation-dependent mannose-6-phosphate receptor (CD-M6PR), which needs

divalent cations to bind M6P ligands but does not bind insulin-like growth factor 2 [3]. The M6P/IGF2-R is also called cation-independent M6P receptor (CI-M6PR) because it does not need ions to bind its ligands. In comparison to their molecular weight, the CD-M6PR (46 kDa) and the CI-M6PR (250 kDa) are, respectively, called "Small" and "Big" M6P receptor.

Historically, the insulin-like growth factors have been predicted by studying the action of the pituitary growth hormone (GH) on the growth. GH is a pleiotropic hormone secreted by the pituitary gland, which acts as a growth factor on bone and muscle tissues, or as a differentiation factor and a metabolic regulator in liver, fat, and muscle tissues. GH has been historically proposed to act by using intermediates, the somatomedins, which were able to exert growth hormone-like effects on the skeletal cartilage and other tissues [4]. Further analyses revealed two molecules sharing high homology with proinsulin that were consequently called IGF1 and IGF2 [5, 6].

The insulin-like growth factors 1 and 2 have similar biological effects, but there are nevertheless differences in their expression. In mammals, IGF1 is preferentially expressed after birth and is almost exclusively produced in the liver, whereas IGF2 is preferentially expressed in early stages of embryonic and fetal development in many tissues. In adults, IGF2 is expressed not only in liver but also in other tissues such as the brain (essentially the meninges) and choroid plexus [7]. IGFs play an important role in the regulation of normal cell growth and proliferation, or in malignant transformation [8, 9].

The growth hormone's receptor is a single transmembrane protein sharing similarities with the prolactin receptor and, to a lesser extent, with some members of cytokine receptor family. The binding of GH to its receptor induces signaling pathways in most target cells to transduce hormonal message to the nucleus, which results to activate the transcription of a variety of genes coding for IGFs or several other proteins such as transcription factors, hormones, hormone receptors, prolactin receptor, c-fos, cytochrome P450 IIC, and various enzymes. Several studies reported that M6P/IGF2-R is involved in tumor development in human [9].

This chapter discusses the role of the M6P/IGF2-R in the regulation of growth and its involvement in tumor progression.

2. Structure of the M6P/IGF2-R

The mannose-6-phosphate/insulin-like growth factor 2 is a single-chain transmembrane protein, of 250–300 kDa that functions as a multifunctional receptor by binding molecules sharing M6P signals and IGF2 [1, 2]. The M6P/IGF2-R contains 2451 amino acids with a large extracellular domain made of 2264 residues, a short transmembrane domain of 23 residues, and a small cytoplasmic domain of 164 residues. The extracellular domain of M6P/IGF2-R consists of a 40-residue amino acid signal sequence and 15 conserved repeat domains. Each repeat contains an average length of 150 residues and 13–37% amino acids identity rich in cysteine residues, which make it highly conserved throughout species, with 60–90% homology (**Table 1**). The repeat number 13 contains a 43-amino acid sequence homologous to the

collagen-binding domain type 2-region of fibronectin. The mannose-6-phoshate signals bind to repeats 3 and 9, whereas IGF2 binds to repeat 11 [10–12]. The M6P signals bind to residues R^{435} and R^{1334} localized, respectively, in domains 3 and 9 [10], and the residues (Q^{392}-S^{431}-E^{460}-Y^{465}) localized in repeat 3 and (Q^{1292}-H^{1329}-E^{1354}-Y^{1360}) localized in repeat 9 play an essential role in M6P recognition [13] (**Figure 1**). Further studies showed that domain 5 also steps in mannose-6-phosphate signal binding. The amino acid residues 1508–1566 localized in repeat 11 are needed for IGF2 binding [14]. Moreover, the affinity of IGF2 binding is enhanced by the fibronectin type 2-like insert of domain 13, though the biochemical mechanisms of that enhancement are unknown [9]. However, mannose-6-phosphate receptor does not bind to IGF2 in oviparous [15].

	Human	Bovine	Chicken	Mouse
Human	100	90	60	89
Bovine	90	100	60	87
Chicken	60	60	100	–
Mouse	89	87	–	100

The M6P/IGF2-R amino acid sequences have been compared. Results, expressed in percentage, showed high homology throughout species including human and varies from 60 to 90%.

Table 1. Sequence homology of M6P/IGF2-R in animals.

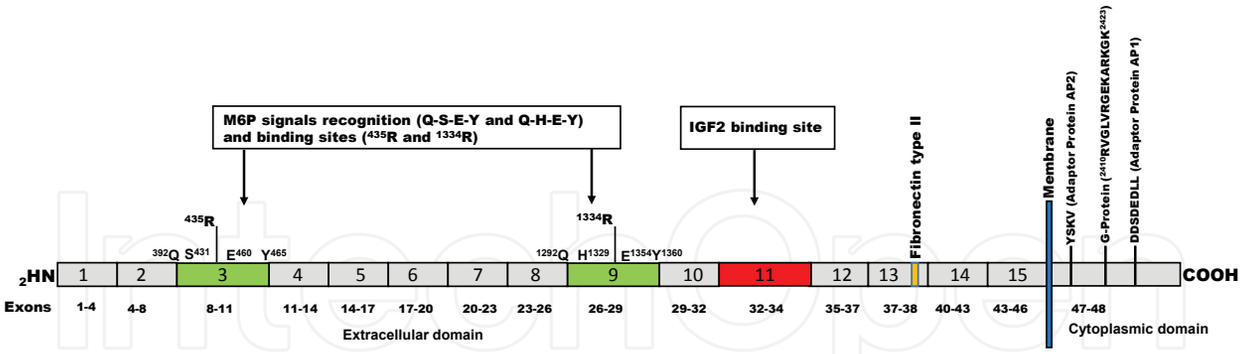

Figure 1. Structure and gene organization of mouse M6P/IGF2 receptor. Numbers in boxes (1–15) symbolize the repeat domains. Binding sites are indicated in repeats 3 and 9 (for M6P signals) and in repeat 11 (for IGF2). M6P/IGF2-R gene consists of 48 exons encoding for the full-length receptor. Amino acid sequences of cytoplasmic domain have been suggested to interact with adaptor or G proteins.

The M6P/IGF2-R has been shown to be shed from the cell surface and secreted in the culture medium in Michigan Cancer Foundation 7 (MCF7) cancer cell lines [16] Moreover, other studies described the M6P/IGF2-R as a circulating protein in rat [17] or in human serum and urine [18]. Subsequent studies showed that the serum form of M6P/IGF2-R is truncated or altered in its cytoplasmic domain with a molecular weight of less than 230 kDa [19].

2.1. Genomic organization and gene imprinting

In mice, M6P/IGF2-R is coded by chromosome 17 [20]. The gene contains 48 exons (**Figure 1**) and spreads on 93 kb [21]. M6P/IGF2-R is imprinted in mice. Genomic imprinting is a developmental gene regulation whereby only one of the parental alleles is expressed [9].

In mice, the M6P/IGF2-R is exclusively expressed from the allele inherited from the mother, while IGF2 is expressed from the allele inherited from the father [9]. The imprinting of M6P/IGF2-R is regulated by the intron 2-region in paternal allele, which contains an antisense transcript mediating the silencing of the paternal M6P/IGF2-R allele. Deletion of that intron 2-region disrupts the silencing and leads to biallelic expression of M6P/IGF2-R inherited from the father [22]. Mice inherited from a disrupted M6P/IGF2-R gene from their mother do not express the receptor in tissues and show malformations in lungs and cardiac muscle. By contrast, when the same gene is inherited from the father, no abnormality was observed in the development confirming the paternal imprinting of the M6P/IGF2-R gene [23].

The oppositely imprinting of IGF2 and M6P/IGF2-R genes supposes that M6P/IGF2-R produced from the mother acts as a scavenger, which neutralizes IGF2 produced from the father before it reaches the signaling from IGF1 or insulin receptors to exert its biological effects [9].

In human, the M6P/IGF2-R gene was previously described to map on chromosome 6q25–27 [20]. Kalscheuer et al. [24] reported that M6P/IGF2-R is not imprinted in human. Others hypothesized that such an imprinting has been probably lost during evolution [25]. Studies reporting M6P/IGF2-R imprinting as being polymorphic in human are controversial as the 3'-untranslated region (3'UTR) polymorphisms used are difficult to amplify and are subject to misinterpretation.

The consensus retained is that the receptor expression is biallelic in most humans and only less than 10% of individuals exhibit imprinting of M6P/IGF2-R [26].

3. Functions of the M6P/IGF2-R

The M6P/IGF2-R mainly and continuously circulates and cycles between endomembrane compartments and cell surface. At a steady state, it is majorly localized in trans-Golgi network (TGN) and endosomal compartments and poorly present on the plasma membrane.

3.1. Mannose-6-phosphorylated ligand binding and lysosomal enzyme routing

The mannose-6-phosphate signals bind to domains 3 and 9 [10, 12], whereas IGF2 binds to domain 11 [10, 14]. The binding affinity of M6P/IGF2-R for M6P ligands varies from Kd = 10^{-10} to 10^{-6} M and depends on phosphorylated ligand structures [27, 28]. The arginine residues ^{435}R and ^{1334}R, respectively, localized on repeats 3 and 9 are needed for M6P signal binding.

The M6P/IGF2-R is involved in the intracellular trafficking of newly synthesized mannose-6-phosphorylated lysosomal enzymes from the trans-Golgi network to the late endosomes [29,

30] and cellular uptake of secreted lysosomal enzyme precursors [31]. Lysosomal enzymes are recognized by their M6P signals and bind to M6P/IGF2-R. Adaptor proteins AP1 interact with guanosine triphosphate (GTP)ase adenosine diphosphate (ADP) ribosylation factor (ARF) and a specific sequence DDSDEDLL localized in the cytoplasmic domain of the M6P/IGF2-R [32, 33]. GTP hydrolysis-released energy is used for clathrin molecule recruitment. Lysosomal enzymes are then transported, *via* clathrin-coated vesicles, to acidified endosomal compartments where the low pH (3–5) leads to the dissociation of the enzyme from the receptor [29]. Enzymes are then released to their lysosomal final destination, the lysosomes, whereas the M6P/IGF2-R are recycled to the cell membrane or headed back to the trans-Golgi network to accomplish other transport cycles (**Figure 2**) [29].

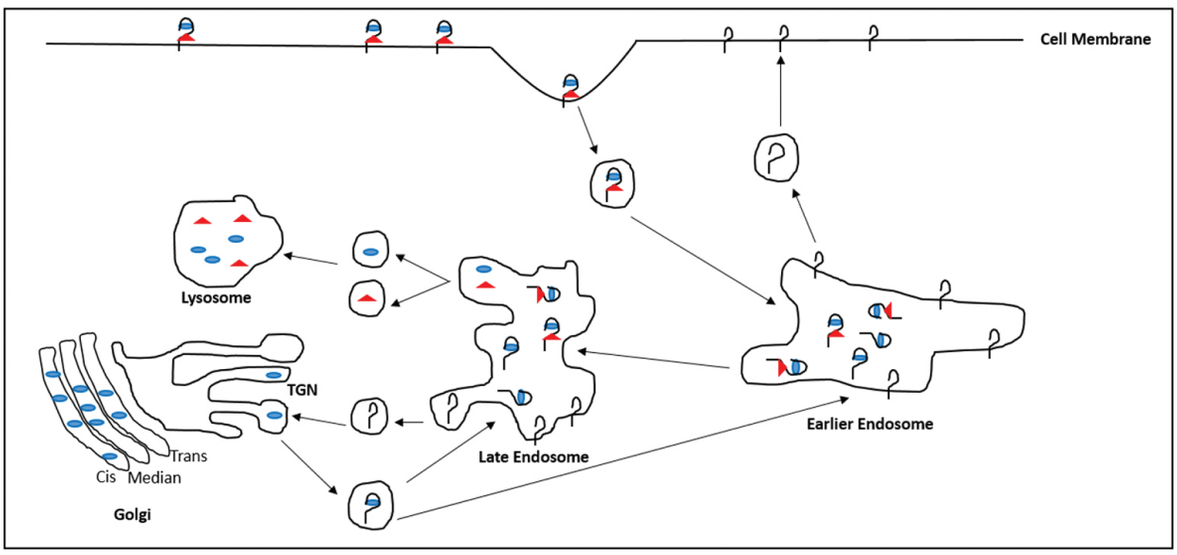

Figure 2. Endocytosis and lysosomal enzymes trafficking by the M6P/IGF2-R. Lysosomal enzymes are synthesized in endoplasmic reticulum and transported in the Golgi where they acquire M6P signals (). Mannose-6-phosphorylated enzymes bind to the M6P/IGF2-R () in the trans-Golgi network and are routed to the late or earlier endosomes. The receptors bound to secreted enzymes and to IGF2 () at the cell membrane level () are endocytosed and directed to endosomes. Enzymes and IGF2 are directed to the lysosomes and the receptors () are recycled to the cell membrane.

3.2. Endocytosis of receptors and secreted proenzymes

About 10% of M6P/IGF2-R are found at the plasma membrane level and they can be internalized and recycled independently of the binding of ligand [34], whereas most of membrane receptors are internalized after the binding of their specific ligand. Secreted proenzymes are uptaken by the membrane M6P/IGF2-R and the proenzymes/M6P/IGF2-R complexes are internalized in clathrin-coated vesicles *via* an interaction between the receptor and adaptor proteins AP2 [33], which recognize cytosolic signals ^{26}YSKV^{29} of M6P/IGF2-R [35, 36]. Enzyme/receptor complexes are transported to early endosomes, the enzymes are then released and transported to late endosomes, then to lysosomes for their maturation into active enzymes, whereas the M6P/IGF2-R are recycled to cell membrane or to the trans-Golgi network [29].

3.3. Binding and regulation of IGF2 mitogenic effects

M6P/IGF2-R binds to IGF2 with higher affinity, Kd = 0.1–1 nM [37, 38] and has a lower affinity for IGF1 [39]. By contrast, it does not bind to insulin [40].

The mitogenic effects of IGF2 are exerted by its binding with lower affinity to the signaling receptors such as the IGF1 receptor or insulin receptor isoform A [9]. M6P/IGF2-R acts as a scavenger by mediating internalization and degradation of IGF2 as described previously in cell cultures including rat adipocytes [41] mouse L-cells [42]. In vivo, studies provide evidence that M6P/IGF2-R regulates IGF2 circulating and tissue amounts, as shown by gene deletion experiments in mice [43, 44]. These studies reported that in mice-deficient M6P/IGF2-R, IGF2 levels were two- to threefold increased than wild type. Moreover, the lack of M6P/IGF2-R increased levels and induces tissue proliferation and hypertrophy that is produced by IGF2 acting on the IGF1 receptor [45].

3.4. Binding to mannose-6-phosphorylated molecules

3.4.1. Transforming growth factor β1

The M6P/IGF2-R is involved in proteolytic activation of the transforming growth factor β1 (TGFβ1), a potent growth inhibitor, that regulates the differentiation and growth in most cell types [46]. *TGFβ1* is a mannose-6-phosphorylated protein synthesized as a single inactive propreprotein, which is secreted and stored in extracellular matrix. Inactive *TGFβ* binds to M6P/IGF2-R and it is then cleaved in mature and active form by extracellular plasmin [47]. This activation mechanism of *TGFβ* by M6P/IGF2-R has been described in cell culture model but not in vivo [46, 30]. Moreover, several studies suggested a role of plasmin-mediated activation of inactive *TGFβ* following its binding to the M6P/IGF2-R [46, 48, 49].

M6P/IGF2-R is known to bind to domains DII and DII of urokinase receptor [50]. So, other studies suggest the binding of plasminogen to the complex M6P/IGF2-R/urokinase plasminogen activator receptor, leading to the generation of active plasmin that activates receptor-bound latent *TGFβ* [51, 52].

3.4.2. Retinoic acid

Retinoic acid plays an important role in development, cellular metabolism, and regulation of cell proliferation. The retinoic acid binds to a specific signaling nuclear receptor. Kang et al. [53] reported that the retinoic acid binds to the cytoplasmic domain of M6P/IGF2-R. Retinoic acid has been shown to stimulate M6P/IGF2 receptor-mediated internalization of IGF2 and to increase lysosomal enzymes sorting [30]. M6P/IGF2-R has been proposed to play a role in mediating retinoid-induced apoptosis/growth inhibition [29].

3.4.3. Leukemia inhibitory factor

M6P/IGF2-R is involved in the internalization and degradation of the cytokine leukemia inhibitory factor (LIF) leading to its regulation [54].

3.4.4. Proliferin

Proliferin is a paracrine factor related to prolactin glycoprotein involved in endothelial cells, angiogenesis during fetal development [55, 56], and a mitogen-regulated protein previously described in mouse 3T3 fibroblasts [57, 58]. Its signaling pathway suggests a G protein-coupled receptor [59] but remains unclear.

3.4.5. Prorenin

The prorenin is a proenzyme secreted by juxtaglomerular cells of kidney. The renin catalyzes the activation of angiotensin I into angiotensin II that regulates blood pressure and extracellular fluid volume [60]. Mannose-6-phosphorylated prorenin [61] binding to M6P/IGF2-R leads to its internalization and proteolytic activation into renin.

3.4.6. Thyroglobulin

Studies showed that radiolabeled thyroglobulin binds to M6P/IGF2-R [62]. Moreover, thyroglobulin can be endocytosed by the M6P/IGF2-R but the receptor fails to direct it to the lysosomes for its degradation in the thyroid gland [63].

4. Does the M6P/IGF2-R interact with G-proteins?

The function of M6P/IGF2-R as a signaling receptor is poorly understood and controversial. Several studies reported that M6P/IGF2-R lacks intrinsic kinase activity, contrarily to insulin and IGF1 receptors. The authors suggested that M6P/IGF2-R is coupled to G-protein via a 14-amino acids sequence (^{2410}RVGLVRGEKARKGK^{2423}) localized in the cytoplasmic domain of the M6P/IGF2-R (**Figure 1**) that is similar to the third cytoplasmic loop of G-protein-coupled seven transmembrane region receptors [64]. Nishimoto et al. [65] showed that IGF2 binds to M6P/IGF2-R and stimulated calcium channel in mouse Balb/c3T3 cells. Moreover, this action of IGF2 on calcium influx was abolished by *Bordetella pertussis* toxin or by using antibodies directed against M6P/IGF2-R, suggesting a G protein-mediated biological effect of M6P/IGF2-R [66]. By contrast, others showed that mice L-cells expressing wild or mutated M6P/IGF2-R and treated to *B. pertussis* toxin were capable to block toxin-inhibiting activity. These last results showed an absence of coupling between M6P/IGF2-R and G-protein [67]. Recent studies using HEK293 cells suggested a novel mechanism of IGF2-mediated G-protein activation. In that model, IGF2 binding to M6P/IGF2-R leads to activation of sphingosine kinase and production of extracellular sphingosine 1-phosphate (S1P), the ligand for G protein-coupled S1P receptors [68]. Others suggested that mannose-6-phosphorylated ligands of M6P/IGF2-R also used that pathway [59]. However, there is no direct evidence involving the binding of these ligands and sphingosine kinase activation. Most of biological effects of IGF2 are mediated by IGF1 receptor and insulin receptor [30]. This pathway probably occurs in chicken since IGF2 stimulates protein synthesis and fibroblast mitosis in that species, whereas mannose-6-phosphate receptor does not bind to IGF2 [15].

5. Role in human cancers

The study of M6P/IGF2-R in the targeting of newly synthesized mannose-6-phosphorylated lysosomal enzymes, such as cathepsin D, in human breast cancer lines showed that pro-cathepsin D is secreted from cancer cell lines, suggesting a possible alteration of M6P/IGF2-R [69].

Studies on M6P/IGF2-R gene localized on 6q chromosome (6q25–27 region) in human mammary cancers showed losses of heterozygosity (LOH) in 48% of tumors [70, 71].

Further studies showed that M6P/IGF2-R gene exhibited LOH in 30% of breast cancer with informative mutations in 2/5 of the remaining allele [72]. The LOH phenomenon has been confirmed in mammary cancers [73] and also described in other human cancers such as hepatocarcinoma [74] and ovarian cancers [75]. Studies at the protein level in mammary cancer showed that M6P/IGF2-R levels were significantly lower in cancer cells than in normal cells in 50% of tumors in which the peritumoral normal glands could be quantified in parallel, agreeing the hypothesis of a tumor suppressor gene for the M6P/IGF2-R [76]. Most of further studies led on M6P/IGF2-R suggested M6P/IGF2-R as being coded by a tumor suppressor gene [72, 77, 78] and its role as a putative prognostic marker in breast cancers has been hypothesized [76].

6. Conclusion

The M6P/IGF2-R is a multifunctional receptor that is known as binding molecules sharing M6P signals and IGF2. Further studies showed that it also binds to many other mannose-6-phosphorylated molecules such as TGFβ, retinoic acid, and so on. The M6P/IGF2-R is a single-chain membrane receptor consisting of a large extracellular domain of 2264 amino acids residues organized in 15 repeats, a short transmembrane of 23 amino acids residues, and a small intracellular domain of 164 residues. The receptor targets newly synthesized mannose-6-phosphorylated lysosomal enzymes by binding M6P signals on specific sites localized in repeats 3 and 9 of extracellular domain and transports them from the trans-Golgi network to lysosomal compartment. The secreted enzymes precursors are internalized by the M6P/IGF2-R localized on the cell membrane and routed to lysosomes for their maturation. IGF2 binds to repeat 11 of the receptor and is transported, after internalization, to the lysosomes for its degradation. IGF2 effects on growth and development are mediated by IGF1 or insulin receptors, although these receptors bind IGF2 with lower affinity. Consequently, M6P/IGF2-R is considered as a scavenger that regulates IGF2 levels before it reaches IGF1 receptor to exert its biological effects on cell proliferation and growth. M6P/IGF2-R would be considered as a "Garbage Receptor," since it does not lead to a known biochemical pathway of signal transduction but transports its ligands to lysosomes for degradation, in opposition to "Signaling Receptor" that induces signal transduction after ligand binding.

The M6P/IGF2-R gene maps on chromosome 6q region and is imprinted in rodents, whereas its expression is mostly biallelic in human. M6P/IGF2-R gene has been suggested as acting as

a tumor suppressor since losses of heterozygosity and mutations in the remaining allele have been frequently described in many human tumors such as mammary, ovarian, and liver cancers. These previous results are supported by the measures of M6P/IGF2-R at the protein level showing significant decrease of receptor levels in cancer cells than in normal cells in about 50% of breast tumors, which led to suggest its potential value as a cancer prognostic marker.

Insulin-like growth factor axis has a critical role in mediating fetal and postnatal growth; thus, alterations in this pathway including changes in the expression of the M6P/IGF2-receptor and impairments in its function could impact somatic growth. Moreover, genetic evidence clearly supports a role for IGF2/M6P receptors in organ development and growth.

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