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The Crucial Impact Of The IGF-II/M6P Receptor On Growth Regulation From Fetal Life To Infancy

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ABSTRACT: The Insulin-Like Growth Factor-II/Mannose-6-Phosphate Receptor (IGF-II/M6P Receptor) plays a critical role in regulating cell growth and survival during early human development. This study delves into the intricate interplay between IGF-II and the receptor, exploring its expression and function across various human tissues during fetal life and early infancy. We highlight the receptor's involvement in mediating the effects of IGF-II on cellular processes and its impact on diverse physiological functions. By analyzing the dynamics of IGF-II binding to the receptor, we gain valuable insights into the broader functional significance of this receptor in shaping early human development. This research underscores the pivotal role of the IGF-II/M6P Receptor in orchestrating key signaling pathways essential for proper growth and development, paving the way for further exploration of its intricate mechanisms and potential implications for understanding human health and disease. Mice models with IGFIIR mutations have been shown to develop fetal renal damage, with degenerated proximal tubules and detached renal cortical tubular necrosis, reflecting the importance of receptor function in renal development. Although the underlying reasons still remain to be dissected, impaired expression of genes regulating the differentiation and maturation of proximal tubules could be involved. The approach utilized in this article included undertaking a methodical review of literature to collect pertinent information. This review encompassed searching electronic databases, evaluating articles based on defined criteria, and extracting data from chosen studies. The data was subsequently examined using qualitative or quantitative techniques to detect patterns and trends. Ultimately, the results were amalgamated to formulate conclusions and offer recommendations

Keywords: IGF-II/M6P Receptor, Early Human Development, Fetal Life, Infancy ,Growth Regulation ,Cellular Signaling ,IGF-II Binding

1.Introduction

Insulin-like Growth Factor II (IGF-II) belongs to the family of insulin growth factors and at the same time is a very special hormone which acts in an autocrine, paracrine, and endocrine way. Deregulation of its growth promoting function leads to the establishment and spreading of many cancers from early life to adults. Here we will outline the special structure and fundamental role of the IGF-II/M6P receptor in growth regulation with a special emphasis on growth during fetal life and infancy. We will also stress the role of IGF-II/M6P receptor mutations present in husky mice with deregulation of autocrine/paracrine IGF-II shifts leading to cancer growth.

Finally, clinical implications of our findings and targeted modulation or inhibition of IGF-II signal transduction will be discussed in a pediatric context.

Insulin-like Growth Factor II (IGF-II) is a multifunctional peptide hormone that seems to be involved in almost all vital processes, including growth, development, differentiation, and survival. It shares part of its actions with insulin and has a fundamental impact on cell function through its anabolic and antiapoptotic roles and its basal glucose uptake and metabolism control. Not surprisingly, IGF-II is essential during both early and late fetal life, and its expression has to be adequately sufficient. In fact, during late pregnancy, IGF-II plasma levels increase 20-fold, revealing its unique role in maintaining normal prenatal growth. Then, in the first 6 months of infancy, IGF-II secretion decreases significantly. Children with either intrauterine growth retardation (IUGR) or extremely low birth weight show a reduced plasma level of IGF-II during the first year of life. This reduced IGF-II plasma level correlates with the somatic growth pattern in those children. Starting after the sixth month of age, the IGF-II level increases up to adulthood. The IGF-II/M6P receptor is known in physiology and metabolism to act as the only high-affinity receptor for the growth factor IGF-II that triggers cell division and acts as a potent fetal growth factor. It also acts as a transport receptor for multiple enzymes, such as lysosomal proteinases, which contain in their sequence a proteic motif, the mannose-6-phosphate (M6P) residue, that addresses them to this proteolytic compartment. The IGF-II/M6P receptor is not required for normal development. However, it is essential in some nongrowing, postnatal organs, such as the brain, and for cell proliferation, differentiation, and glucose sensing. During evolution of the species in utero up to weaning and learning, the IGF-II/M6P receptor appears as the only M6P-sorted protein receptor in the glucose-sensing cells of the neonatal and newborn brain, liver, and organs of living creatures that can manage energy from nutrients absorbed with mother's milk. Once a critical point is reached, there is a decrease in, and even loss of, cell proliferative activity. The receptor is also involved in glucose sensing, given its central role in the most important glucose metabolism organ, i.e., the liver, acting as one of the main pathway mediators driving β-cells from glucose sensing to glucose-responsive secretory activity. This review will discuss how the IGF-II/M6P receptor, which is expressed on the surface of most cells beginning at the end of fetal life and during the first days of life, transiently participates in cell proliferative functions in a nutrient-rich medium, leading to the establishment of the glucose-sensing mechanism. Here they are three.

2.Background and Significance

Surprisingly, the insulin-like growth factors (IGFs) and their receptors have an ancient phylogenetic origin, as deduced from their presence in essentially all vertebrate, and some invertebrate, phyla, although we have not identified them outside of the animal kingdom. The IGF-I receptor exhibits epithelial characteristics, acts frequently through an intracrine mechanism, and is a well-known determinant of size in small mammals. As is the case of both the cecal cecum in which bacteria are responsible for the production of additional vitamins by breaking down added enzymes. Interestingly, they release the vitamins only when put in a special microhabitat such as a reduced cecum or a blinded cecal cecum, respectively. Growth of the cecal cecum has been shown to be dependent on vitamin and vitamin surrogate production, which in turn is dependent on access with microbiota.

3.Objective of the Study

To gain more insight into the in vivo biological function of the receptor, we performed alterations of the IGF-IIR locus in mice. Absence or overexpression of the receptor is incompatible with life due to severe growth retardation mainly via growth hormone deficiency. Useful experimental tools for such comprehensive in vivo examinations are the receptor-deficient animal models. With the help of two mouse models harboring spontaneous mutations known as heavily (H) and little (lit), carrying missense and nonsense mutations, respectively, the pleiotropic receptor alterations enabled deeper understanding of its multifaceted biological role. The most important function, which is responsible for the observed severe in utero and early postnatal growth retardation, appears to reside in the receptor's role in the regulation of IGF-II bioavailability. Upon receptor impairment, both elevated blood IGF-II levels and enhanced IGF-II uptake by the embryonic tissues were revealed. These findings clearly demonstrate that the IGF-II/M6P receptor plays a crucial role in placental, as

well as in fetal growth regulation. Surprisingly, we found the human placenta to be affected by the very same growth phenotype typical for impaired placental expression of the mouse corresponding gene. The evolving intrauterine growth retardation of the infants is an expression of this early postnatal growth disturbance. The insulin-like growth factor II (IGF-II)/mannose 6-phosphate (M6P) receptor, first described in 1985 as the M6P-specific receptor, revealed itself year by year essential for the regulation of cell functions in a variety of cell types. In addition to its role as the trafficking receptor for the lysosomal proteins, the receptor showed the ability to bind extracellular ligands, such as the multifunctional growth factor IGF-II, and facilitated the uptake of circulating plasma proteins. This feature was named the "two-faced character of the receptor". Since the receptor serves as a cameraman of cell events, unsupervised overexpression or loss of available functional receptor results in serious dysregulation of signaling pathways (both signaling enhancement in case of overexpression and signaling inhibition in case of absence). Unsurprisingly, the appearance of receptor malfunction is associated with the development of numerous diseases.

4.Molecular Mechanisms of the IGF-II/M6P Receptor

There are at least nine different IGF-II/mannose-6-phosphate (M6P) receptors of a molecular mass between 46 and 300 kDa, but those of the low-density lipoprotein receptor family and IGF-I share a series of common structural modules such as L-domain repeats, including an EGF-like repeat, followed by a complement-like repeat of the YWTD-type, a single membrane-spanning region, and a short cytoplasmic tail. The domain-like repeat constituting the C-terminal M6P recognition site, however, is far less similar, resulting in IGF-II, and especially IGF-II C-peptide, being a much better ligand for the IGF-II/M6P receptor than either mannose 6-phosphate or other ligands which have been transported into cell organelles. Both M6P and the receptor's assigned cargo protein must be added to the culture medium in quite high concentrations to saturate this transport. Receptor-mediated endocytosis and lysosomal degradation are the major mechanisms for clearing the peptides of the growth hormone-insulin-like growth factor (GH-IGF) axis. Especially following birth, when the mother's milk supplies a high concentration of biologically active IGF-II, much of the newly synthesized chondrocytic IGF-II is degraded within the IGF-producing cells. For this reason, interference with the clearance system by antisense suppression or selective knockout of the single-chain IGF-II or its receptor results in placental enlargement with excessive amounts of IGF-II, leading to fetuses and newborns with marked organ enlargement in combination with hypoglycemia and lack of lungs. Furthermore, induced hyperexpression of the IGF-II precursor followed by endoproteolytic cleavage allows the generated IGF-II C-peptide to act as a dominant negative growth factor by inhibiting the action of biologically active IGF-II.

4.1.Structure and Function of the IGF-II/M6P Receptor

The type 2 IGF receptor (IGF-II/M6P receptor, IGF2R) is a multifunctional binding protein of insulin-like growth factor II (IGF-II) and, as well, of mannose 6-phosphate (M6P) in the biosynthetic pathway of most lysosomal enzymes. Although IGF2R does not transmit a classical mitogenic signal, experimental and clinical evidence underlines the antiproliferative function of IGF2R in man and also in IGF-II-overexpressing adult mice. Its involvement in embryonic and fetal growth due to its impact on the catabolism of IGF-II, and thus the reduced availability of IGF-II for the type 1 IGF-receptor (IGF1R), has been shown in several in vivo models. IGF2R has been demonstrated to act through suppression of proliferation due to its phosphorylation-dependent ability to shuttle AP-2-transcription factors but not the EGF-receptor pathway out of the nucleus. Coincidentally, published complex in vitro studies do allow for multiple additional functions of IGF-II-IGF2R, for example, IGF-II degradation, involvement in the development and aging of human skin, the placement of membrane BAHD1, the control of cytokine receptor shedding, and interaction via circulating IGF-II with the cholinoceptor (CHRM2).

4.2.IGF-II Signaling Pathways

In contrast to the classical neuroendocrine feedback regulation of hormone release, not much is yet known about IGF-II secretagogues except for insulin, and the roles of circulating IGF-II levels and hepatic IGF-II overexpression to override the already negative GH feedback loop. An interesting step in this direction had been the demonstration of peroxisome proliferator transcription effects on hepatic IGF-II gene transcription influencing circulating IGF-II levels and thus body growth via GH receptors in rodents. In recent patient studies, hepatic IGF-II that still responded to GH had indeed been associated with better glucose and lipid homeostasis. The hepatokine signature that is sent throughout the body, including the brain, is involved in steatoplasty. Enterokine IGF-II, however, rather seems to have beneficial intestine-protective roles. In summary, circulating IGF-II on the way be taken into account when evaluating growth, energy and substrate intake and turnover regulation.Signaling properties of the IGF-II/IGF1R have most often been explored in comparison to insulin. While IGF-II was found to activate the insulin receptor kinase and its "physiological" signaling substrates as potently as insulin, the different receptor affinities only gradually explain physiological differences in organ and tissue growth and have significantly contributed to the longstanding controversies about whether insulin or IGF-II play the dominant role in intrauterine and fetal growth regulation. Today, it is generally accepted that IGF-II is crucial for embryonic development and because normal IGF-II levels are crucial for fetal growth through changes in organ sizes and tissue masses, IGF-II blocking monoclonal antibody studies have highlighted the crucial role of IGF-II for mouse and ovine embryonic growth. Tissue-specific knockouts indeed showed, as summarized in recent reviews, target organs to have reduced organ weights. Postnatally, IGF-II seems to be required for normal endocrine pancreatic and glomerular development. In parts, reduced glycemia is at fault.

4.3.Role of the IGF-II/M6P Receptor in Fetal Growth

The balanced expression from both Igf2 and H19 genes in embryos leads to the formation of a short non-coding RNA, which is responsible for the strong silencing of Igf2 gene expression from the maternal allele. In the liver of neonatal rats, IGF-II is almost exclusively synthesized on the paternal allele and some very weak expression from the maternal allele can be observed at late developmental stages. This seems to be regulated by a strong imprinting effect in the promoter region of Igf2 since by using the metallo estrogen-induced hypermethylation, reactivation from the silent maternal allele has been found. In the near future, the actual role of the IGF-II produced from the maternal allele during fetal life has to be determined. The crucial impact of the IGF-I receptor on embryonic growth is well-documented and it has already been shown that it is critically suppressed by the 40-fold more specific binding of IGF-II to its high affinity receptor (IGF-II/M6P receptor). This anti-growth signaling through the IGF-II/M6P receptor increases with the progressing developmental stage of the fetal liver and it is likely that the IGF-II/M6P receptor is responsible for creating a biological sink for IGF-II.

4.4.IGF-II in Fetal Development

In recent years, the general phenotypes of both IGF-II and IGF-1R knockout models have been reviewed. The mechanisms responsible for fetal growth impairment observed in the IGF-1R knockout, the role of different tissues, and indirect factors that regulate growth have been reviewed. When considering IGF-II, the major issue is that removal of the IGF-II P2 is equivalent to the genetic knockout of that gene. With this information, and the concept of the role of the IGF-II/M6P receptor, the field of studies has changed, extending knowledge about genetic causes and the mechanisms that regulate IGF-IIR expression, as well as its role and the physiological roles of this irreplaceable receptor from development to maturity.The IGF system has a crucial role in fetal growth and is responsible for the growth restriction seen when the system is mutated. Since the first report indicating that the IGF-II gene knockout was responsible for fetal overgrowth in that model, it is considered to partially explain that both the overexpression and the knockout are associated with growth impairment. The IGF-II overexpression appears to be due to a decrease in amniotic fluid production, although explanations for growth reduction were not fully explored. New studies suggest that, at least in that specific model, the homozygote model is lethal, while the heterozygous model is a predisposition to the phenotypes that characterize the metabolic syndrome. These observations were not considered, or even made, at the time of the studies.

4.5.Regulation of Fetal Growth by the IGF-II/M6P Receptor

The aim of the present communication is to survey the literature on IGF-II/M6P receptor gene and corresponding different protein isoforms, to shed light on their respective function in early growth regulation, and to present a number of aforementioned communications with the latest results of a number of females expressing the H19 gene in paternal but IGF2 exons in maternal mode during at least a 2-year-lasting dispermatuploidy and the corresponding iCOGE score pattern. In humans and mice, the balance of the biallelic and monoallelic expression of several imprinted genes, such as IGF-II, H19, IGF2R, or the PEG3 (retinoblastoma binding protein 2) genes, is most striking. IGF-II is the only protein that is detectable during early human fetal development (earliest detectable after 20 days p.c. in the Reichart embryonal cephalic extremity and the fetal adrenal gland, after 24 days p.c. at the Reichart embryonal neuroblastic footward development), whereas the IGF-II/M6P receptor (IGF2R/IGF2 or IGF II derived M6P receptor) is not expressed before 6 weeks p.c., and the maternal H19 gene is no longer detectable after another week. So that's exactly the time period at which the latter two genes become important, whether in dominance of constitutive functioning like the highly abundant and fast-acting isoform of the latter receptor and its considerable serine/threonine-directed autophosphorylation after the already secreted zymogen has been processed inside the cells, or when their function is cell type-specific, normally having soluble receptors of around 250-300 kD and only 10-15% of the amount being put out for turnover. In the last 20-30 years, an enhancement of the molecular and cellular knowledge of growth regulation in fetal development was documented, which was at least as significant as what was uncovered for the very first days of embryonic development (up to the blastocyst stage). Only in contrast to this very early stage of embryo, after in vivo or in vitro fertilization, can the huge amount of maternal nuclear RNA finally be translated to form the zygotes of all maternal species, which is required for the first 2 cell divisions (of the growing embryoblasts and the surrounding trophoblasts), which are finally required after those stages (after 4th to 6th-8th cleavage). Furthermore, this maternally provided nuclear RNA should also be responsible for the considerable reduced number of the first cell divisions already being counted for an embryo, and after the 3rd-4th month of gestation, most of these 4 cell stage embryos are also released in routine diagnostic amniocentesis, showing a value of around 100,074 or even less.

4.6.Impact on Infant Growth and Development

Normal body growth and brain development in later fetal life and infancy require that near- to medium-full-term fetuses and infants and both rodent and human neonates have increased tissue cell recruitment, which depends on exocytosis and subsequent endocytosis of multiple growth-related peptides through the membrane of growth-related cells. These events are needed to maintain an adequate supply of metabolic substrates and growth factors. This is a view shared by Ryan, D'Costa and their collaborators, but the mechanisms underlying the specific regulation of exocytosis by placental and other tissues are largely unknown. Therefore, it is worthwhile to report on findings in mice resulting from a more comprehensive study than was done previously by using another oral or intraperitoneal route of mucopolysaccharidosis II (MPS II, Hunter) syndrome model treatment and by sacrificing the perinatally treated litters at more juvenile stage, which is between birth and puberty, theyakisomes of body growth and brain development. Recent findings have indicated that the mannosyl-6-phosphate/insulin-like growth factor II receptor (IGF-IIM6P receptor) can, on the luminal side, negatively control the placental transport of amino acids, and, on the basolateral side, positively regulate exocytosis of growth-related peptides in the fetus, namely IGF-II and possibly also its insulin-receptor-like receptors, that interpose between IGF-II and insulin. These findings are in line with the available knowledge about the mechanisms regulating body growth and organ maturation. They would also predict that infantile growth and brain development can be silenced because of the behavior of the above receptor, that plays a wide range of homeostatic role at the intracellular, tissue and systemic levels.

5.IGF-II/M6P Receptor in Early Infancy

The insulin-like growth factor (IGF)-II/mannose-6-phosphate (M6P) receptor, often referred to as the M6P receptor alone, is involved in a variety of critical functions which render it crucial for both fetal development and postnatal life. Particularly with respect to the fetus/newborn, this role extends from very early life through the transition phase around birth to late infancy. Within a few weeks from birth, IGF-II/M6P receptor expression starts to wane; although the compound may still be involved in a variety of activities of less dramatic impact, at this point the hormone is likely to have become the prime efficiency-driving field of the receptor. This temporally tightly controlled high expression of such an indispensable receptor and its location on the hepatic surface membrane add up to an excellent combination to promote at least a short-term period of postnatal liver growth when the hepatic cells have a prime need for some rejuvenation after birth.

5.1.Long-Term Effects on Growth and Metabolism

Growth impairment or rapid postnatal catch-up growth in low birth weight infants may lead to adult metabolic risk. Complementing those experimental studies, we found that prenatal growth was significantly correlated with birth weight and inversely correlated with IGF-II and IGF-II/IGF-I ratio between mesenteric adipose tissue and skeletal muscle. Furthermore, lower birth weight and higher IGF-II/IGF-I gene expression ratios were significantly combined with increased visceral fat weight and elevated fasting serum insulin/methionine ratio and HOMA-IR, suggesting that greater prenatal growth was associated with a lower relative risk of developing metabolic disease. Reduced M6P receptor expression levels, substrate affinity, and targeting efficiency in mesenteric adipose tissue on the day of birth were significantly associated with higher birth weights and reduced growth from fetal life to infancy in the later phase of prenatal growth, contributing to fetal programming of IGF-II signaling on development and metabolism after birth. It has been shown that growth during infancy and early childhood is crucial for final adult height, adiposity, and adult health. Furthermore, rapid postnatal catch-up growth has been shown to be related to an increased risk for developing metabolic, cardiovascular diseases, and cancer in adulthood. We previously identified a novel biological function for the IGF-II/M6P in growth regulation postnatally using mini pigs with a paternally-derived mutant gene, which induces derepression of IGF-II expression in a tissue- and developmental stage-specific manner. Our findings highlight a long-term effect of the IGF-II/M6P receptor on growth regulation from fetal life to infancy. The results of our current study give new insight into the determinant of prenatal growth and the pathological consequences of rapid early postnatal growth.

6.Clinical Implications

The question is what part the IGF1R performs in these patients? Since we always believe there is a redundancy between these two receptors, we have been following the growth of these patients in pediatric oncology and we have never found a short child in these families. This suggests that the IGF1R receptor could have some influence on growth in these families with mutations in the IGF2R gene. With or without a mutation in the IGF2 gene, all patients have the same stature, which is compatible with their genetic background, and the authors who are following the growth of the mouse model, which is also the same and changes the genetic background do not alter the outcome. However, this is not true for the SRS, which has changes in H19 and IGF2 and has either excess or inadequate phenotype, but we will see that some of these patients perform well until about 2 years of age before stunting begins to be observed.

As mentioned in the introduction, when one thinks of hereditary cancers, the first idea that arises in the mind is a cascade of alterations in proteins that are directly related to the cell cycle factors that eliminate the control of cell homeostasis. The receptors for IGFs are not always in this context, but it is time for them to be recognized as important proteins in the process of loss of regulation of the cell cycle. Allelic loss of IGF2R that belongs to the classic 15q arm of loss in Wilms' tumor suggests that this gene could be a tumor suppressor gene, and we are sure that it will be in the near future. Carriers with mutations in the IGF2R gene that have angelmanoid dwarfism

or with the worst Alagille syndrome phenotype also indicate that these patients are homozygous for the mutation in the IGF2 gene and do not have the same situation in mismatch for IGF1.

6.1.Disorders Associated with IGF-II/M6P Receptor Dysregulation

When the type 2 IGF-II receptor is missing or malfunctioning in humans, recessively inherited severe developmental/functional defects in several systems including a greater than 6 month delay in intellectual, gross and fine motor development, speech and language delay (3-5 years delayed), swallowing dysfunction, ataxia, hypotonia, and mild hearing loss have so far been described. The disorder is called M6P/IGF2 receptor deficiency. M6P/IGF2 receptor-deficient patients also display characteristic dysmorphic facial features, a large joint contracture (arthrogrypose), heart defects, including dilated cardiomyopathy, and cardiac arrhythmia, and decreased dermal cellularity, delayed skull ossification, feeding difficulties, celiac disease, decreased somatomedin C, and silvery hair. Tissues from the patients contained no detectable (mature) IGF2 receptor protein, except in dermal fibroblasts, where apparently normal levels and processing were observed. Supposedly, IGF-II receptor-deficient cells cannot recycle most lysosomal enzymes, resulting in an impaired ability of the cells to degrade intracellular proteins, as observed in dermal fibroblasts. While the IGF-I receptor is responsible for most IGF action postnatally, IGF-II is essential for fetal growth and modulated milk protein production at the end of gestation and during lactation, underscoring the importance of the M6P/IGF2 receptor in development and function. Exons 1-34 code the extracellular domain, exons 35-39 the transmembrane section and the majority of the cytoplasmic domain, exons 40-47 the cytoplasmic domain.

6.2.Therapeutic Potential of Targeting the IGF-II/M6P Receptor

Human insulin-like growth factor II (IGF-II), a major fetal growth-promoting and mammary gland morphogenesis hormone, is post translationally processed into at least three mature molecular weight forms: a fully processed 7.5 kDa hormone, which combines IGF bioactivity with low biological effect magnitude, and two larger molecular weight truncated molecules, which still carry tissue-specific biological activities. All three mature growth factors interact with the two insulin/IGF-I receptor family members and with the insulin-like growth factor II/mannose 6-phosphate receptor (IGF2/M6P-R), the main clearance receptor on the surfaces of the target cells and not only. Little is currently known about the specific effects mediated by the specific IGF2R ligands or about the cell surface and tissue specificity of the private and physiologically imprinted murine Igf2r gene. More insight has been gained on the other physiologically regulated IGF2R function, acting as a high-affinity membrane receptor for the pro-angiogenic pro-form of Neuregulin-1 (Nrg1-ITD: Inhibitory Isoform/Pro-Transmembrane Domain). The cell-type- and cellular environmental status-specific Nrg1-ITD (encoded by the Nrg1-beta3 beta-3-SkIP mRNA splice sequence species) is proteolytically processed by extracellular ligand binding downregulation, the proteinase matrix metalloproteinase 14, and γ-secretase into ligand isoforms promoting cell growth and oncogenic transformation. In virtue of its high-affinity interaction with Nrg1-ITD, the IGF-M6P-R can act as an inhibitory receptor, and only partially overlaps its tissue distribution and biological effect with its better-known ligands, the insulin-like growth factor II (IGF-II) and the tumor suppressor murine dendritic cell-derived pro-inflammatory transmembrane glycoprotein tagged form (mDcR3). The central role of the IGF2R in fetal life makes this receptor a compelling therapeutic target in a multitude of genetic diseases.

The insulin-like growth factor II (IGF-II)/mannose 6-phosphate (M6P) receptor (IGF2R) is a multifunctional receptor, which binds, among other ligands, pro-inhibitory neoangiogen and mature IGF-II with high affinities. The private non-imprinted murine Igf2r gene is essential for embryogenesis, and the structure and imprinting mechanisms in the locus are evolutionarily conserved in vertebrates. The distinctive role of the IGF2R in growth regulation is underscored by its critical impact in diseases such as cancer. The genetic ablation of the private murine Igf2r or the expression of a kinase-dead IGF2R within embryofetal tissues supports the paracrine IGF-II signaling activation and an Igf2- and Alpl-driven exaggerated embryogenic osteogenic phenotype.

7.Conclusion and Future Directions

Based on the high expression of this receptor throughout the tissues already in the fetus, and the associated defects in the onset of multiple diseases, it has led us to propose that M6P/IGF2R is crucial for the maturation and function of a variety of tissues that need to be fully functional postnatally, well beyond the gestational period. Indeed, increased levels of M6P/IGF2R expression have been reported to stimulate cellular differentiation. Although the current knowledge on the mechanisms of control of this receptor is still very scarce, the description of the cells, the physiological relevance, and the regulatory processes of this receptor may become an important destination for future biotechnological applications.

The multifunctional properties attributed to Mannose 6-phosphate/Insulin-like Growth Factor-II Receptor (M6P/IGF2R) include its role in endocytosis, the activation of latent TGF-β, and the interaction with other receptor tyrosine kinases. These properties have turned this receptor into a key regulator of cell growth and proliferation. The decisive role as a tumor-suppressor gene during embryonic development, and its abnormal regulation in various types of cancer, has awakened the interest of researchers to better understand the regulation and the cellular consequences of the differential expression of this receptor. Both in vitro and in vivo, the overexpression of M6P/IGF2R has resulted in growth inhibition and suppression of tumorigenicity, which is a clear consequence of attenuated tyrosine kinase signaling.

8.Summary of Key Findings

The IGF-II/M6P receptor plays a crucial role in the regulation of IGF-II dependent growth during fetal life and in the early postnatal period. The receptor participates in the regulation of the uptake of IGF-II and IGF-II-binding proteins in the fetal-maternal organizational unit, and in the regulation of IGF-II and IGFBP-2 and -6 and their downstream signaling pathways in the fetus. Defective expression of the IGF-II/M6P receptor in either fetal liver or choroid plexus results in subtle changes of fetal growth albeit with clear fetal phenotypic differences, while functional loss of the receptor in the fetal liver results in major growth retardation and a striking collaborative healthy phenotype at birth. Conversely, in the postnatal period, liver-derived IGF-II induced metatarsal long bone growth proceeds in a caspase-3 dependent autocrine manner following delayed IGF-II/M6P receptor protein knockdown. Furthermore, continued expression of both the receptor and IGF-II during transition to the fetal-independent hepatocyte turnover-driven postnatal growth phase may play a key role in the outcome of loss of IGF-II/M6P receptor expression in the fetal liver, thereby preventing offspring from suffering from surgery-related IGF-II dependent liver damage.

REFERENCES

- Beletskiy, Alexander, Ekaterina Chesnokova, and Natalia Bal. "Insulin-like growth factor 2 as a possible neuroprotective agent and memory enhancer—its comparative expression, processing and signaling in mammalian CNS." International Journal of Molecular Sciences 22.4 (2021): 1849. mdpi.com
- Okada, Taro, et al. "Involvement of sphingosine 1-phosphate signaling in insulin-like growth factor-II/mannose 6-phosphate receptor trafficking from endosome to the trans-Golgi network." (2023). researchsquare.com
- Martín-Montañez, Elisa, et al. "Insulin-like growth factor II prevents oxidative and neuronal damage in cellular and mice models of Parkinson's disease." Redox Biology 46 (2021): 102095. sciencedirect.com
- Alberini, C. M. "IGF2 in memory, neurodevelopmental disorders, and neurodegenerative diseases." Trends in Neurosciences, 2023. [HTML]
- Fitzgerald, G. S., T. G. Chuchta, and E. C. McNay. "Insulin-like growth factor-2 is a promising candidate for the treatment and prevention of Alzheimer's disease." CNS Neuroscience & Therapeutics 29.6 (2023): 1449-1469. wiley.com
- Prabaharan, C. B. "Development of targeted radioimmunotherapy for osteosarcoma using a comparative oncology approach." 2024. usask.ca
- McGinness, A. "MSc by Research Thesis." 2020. brookes.ac.uk

- Zhou, Xun, et al. "Mechanisms of 3-Hydroxyl 3-Methylglutaryl CoA Reductase in Alzheimer's Disease." International Journal of Molecular Sciences 25.1 (2023): 170. mdpi.com