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INSULIN-LIKE GROWTH FACTORS (IGFS) SYSTEM AND TUMORS

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BASE CHARACTERISTICS

Insulin-like growth factors (IGF, insulin-like growth factors, formerly named somatomedines) are peptides, that participate on growth regulation, metabolism regulation, cell survival and differentiation. They are regulated by growth hormone (GH). IGFs are synthesized in liver and they occur in other body fluids (Tab. 1). Their extrahepatic production and autocrine and paracrine mechanism has been already described (1).

Tab. 1 IGFs

Growth factor	Molecular weight	Amino acids number	Physiologic function
IGF1	7,464	70	Regulation of growth, metabolism, cell survival and differentiation *In postnatal development*
IGF2	7,400	67	Regulation of growth, metabolism, cell survival and differentiation *In prenatal development*

IGFBPs occur in different body fluids like serum, amniotic fluid and cerebrospinal fluid (Tab. 2). IGFBPs are synthesized in liver or can be also synthesized by cancer cells. IGFBPs increase the half-life of IGFs in serum and inhibit or stimulate IGFs action by binding to the target cells receptors. These binding proteins serve as storage of IGFs in intercellular space (2).

Effect of IGF1 and IGF2 on cell is mediated by receptors. IGFs receptors belong to the group of receptor protein tyrosine kinase (PTK). They phospohorylate its substrate proteins on residual tyrosine (3). This group involves receptors for majority peptide growth factors, which participate on cellular growth and differentiation (Tab. 3).

Signal transduction follows the successful binding to the receptor via signal intracellular pathway – i.e. cascade of enzymes and its substrates (Fig. 1).

Two main cascades activate after IGF1R activation via adaptor protein insulin receptor substrate (IRS1). First signal pathway PI3K/PKB (fosfatidylinositol-3-kinase / proteinkinase B) and the second cascade is ERK pathway (extracellular signal regulated

kinases). This pathway belongs among several MAP kinase pathways (MAPK mitogen activated protein kinases) (4).

Tab. 2 IGFBPs

Binding protein	Molecular weight	Binding affinity	Occurrence
IGFBP1	34,000	IGF1, IGF2	placenta, amniotic fluid
IGFBP2	27,000	IGF2	cerebrospinal fluid
IGFBP3	53,000	IGF1, IGF2	serum
IGFBP4	26,000	IGF1, IGF2	osteoblasts
IGFBP5	23,000	IGF1, IGF2 low affinity	kidney, osteoblasts
IGFBP6	22,800	IGF2	cerebrospinal fluid

Tab. 3 Receptors for IGFs

Receptor	Structure	Binding affinity	Signal transduction
IGF1R	dimer 2α, 2β subunits	IGF1, IGF2	YES
IGF2R	Monomer	IGF2	NO
IR (IR-A, IR-B)	dimer 2α, 2β subunits	IGF1, IGF2	YES
IR/IGF1R (IR-A/IGF1R, IR-B/ IGF1R)	dimer 2α, 2β subunits	IGF1, IGF2	YES

IGFs SIGNAL PATHWAYS

Mechanism of IGF1 action: The biological effect of IGF1 is mediated by IGF1 receptor (IGF1R). IGF1 binds to the extracellular domain of IGF1R. Tyrosine kinase receptor autophosphorilates after activation of the cytoplasmic domain and the adapter protein via activation of the insulin receptor substrate (IRS1/2) are activated by two major signaling cascade. Phosphatidylinositol-3-kinase (PI3K) / Protein kinase B (PKB, also known as Akt) signaling pathway, and Extracellular signal regulated kinase (ERK) pathway, which is one of multiple Mitogen activated protein kinase (MAPK) pathways.

Signal pathway PI3K/PKB is particularly important intracellular signal pathway. It is integrated into many normal cellular processes related to the proliferation, metabolism, growth and survival of cells. Abnormality of this pathway caused by isoforms and mutations of different components will result in different forms of cancer diseases. Central component of this pathway is formed by PI3K heterodimer formed by regulatory subunit p85 and by catalytic subunit p110. They are commonly found to be altered by mutations in cancer diseases (5). PI3K activation results in blockage of inhibitory effect of regulatory subunit p85 followed by activation of catalytic subunit p110. It changes immediately membranous fosfatidylinositol-3,5-biphosphate (PIP2) into triphosphate form (PIP3).

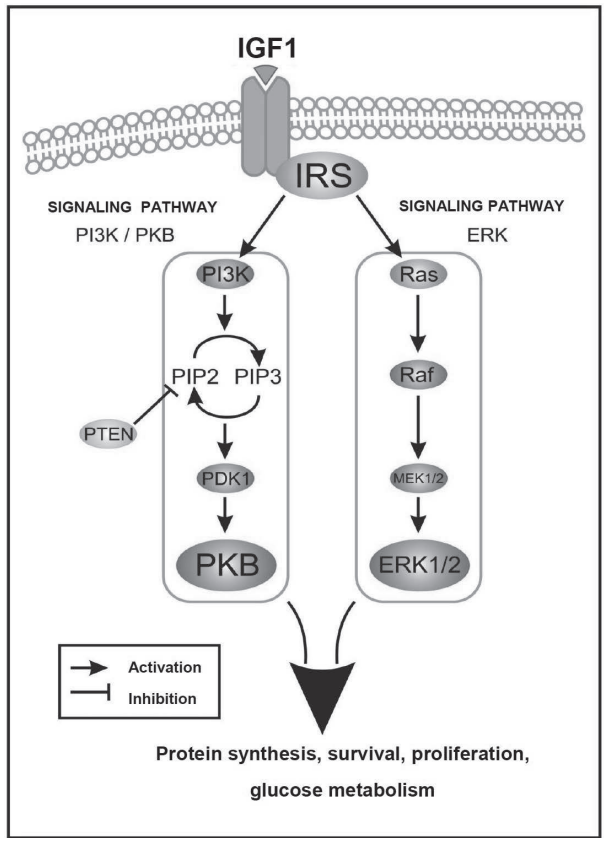

Fig. 1 Mechanism of IGFs effect

PIP3 further induces phosphorylation of PKB via PDK1 protein. Complex PI3K is under the normal condition negatively regulated by specific phosphatase PTEN. PTEN acts like a negative regulator of PI3K pathway, so that it hydrolyses PIP3 into PIP2 (6).

Mutation or epigenetic modification results in loss of PTEN function, but alteration resulting in hyperactivity of P13K may also occur. Loss of PTEN function stimulates PIP3 accumulation, which results in deregulation of signal transduction via PI3K/PKB cascade (7, 8).

PKB is involved in other signal cascades and it interferes with many cellular processes (proteosynthesis, survival, proliferation, glucose metabolism, etc.). Activation of deregulated signal pathway PI3K/PKB provides signals to the cells for unlimited growth and survival (9).

Second signal pathway is represented by the ERK cascade (extracellular signal regulated kinases). Signal is transmitted after IRS1 activation via Ras GTPase and Raf and MEK

kinase. This process finally results in MAP kinase activation, particularly ERK. ERK belongs among the first well explored MAP kinases of the mammalian cells. Group of enzymes called MAP kinases regulates gene expression and eventually cellular proliferation and differentiation (10).

Biological effect of IGFs is mediated by IGF1 receptor (IGF1R). IGF1 and IGF2 bind to extracellular domain IGF1R. Tyrosine kinase receptors autophospohorylate after their activation on the cytoplasmatic domain and via activation of adaptor protein insulin receptor substrate (IRS1/2) two main signal cascades activate. Signal pathway PI3K (phosphatidylinositol-3-kinase)/PKB (proteinkinase B) and signal pathway ERK (extracellular signal regulated kinases), which represents one of the several MAP kinase pathways (MAPK mitogen activated protein kinases) (11).

IGFS AND THEIR EFFECT ON MALIGNANT TRANSFORMATION OF THE CELLS

Based on knowledge of IGF1 and IGF2 effect on cells it is assumed that high IGFs serum levels increase the risk for cancer development. They also stimulate proliferation and risk of malignant transformation. But high serum levels of binding proteins IGFBPs, particularly dominant serum binding protein IGFBP3, should decrease the risk and inhibit the cellular growth.

It is assumed that malignant transformation of the cells can occur independently from serum levels of IGFs in case of presence of functional IGF1R. It is interesting that the potency of oncogenes to cause the malignant transformation is dependent on their ability of IGF1R phosphorylation. Intact tyrosine kinase domain is necessary for IGF1R functions – i.e. intensive anti-apoptotic and transformation effect (12).

Summarization above mentioned data provides three fundamental conditions for signal transduction of IGFs system into the cells.

- presence of functional receptors
- intact tyrosine kinase (TK) domain
- phosphorylation of TK domain

If the ability to receive signals remains, three extracellular risk factors start to play their role

- local extrahepatal IGFs production
- autocrine and paracrine IGFs function
- increased IGFs serum levels

Other two factors are intracellular and seem to be the most risky:

- signal pathway mutations
- gene mutations

With more sophisticated knowledge about IGFs system function, some hypotheses were evaluated in order to confirm the theory of the relationship between IGFs and some malignant diseases development. First pilot prospective epidemiology studies did not

confirm any relationship between elevated IGF1serum levels and cancers. But some recent extent clinical studies confirmed that high circulating IGF1 concentrations and low IGFBP3 serum levels are related to increase risk for cancer diseases. Negative correlation between IGFBP3 levels and risk of cancer diseases corresponds to protective role of IGFBP3 (i.e. high IGFBP3 concentration results in low free IGF1 levels).

Autocrine and paracrine role of IGFs seems to be also important. Increased local production of IGF1 or IGF2 or their combinations were found at different cancer diseases and there was usually the positive correlation with tumor progression (13, 14). Regarding to the IGF1R expression, some theories appear that increased expression suggest a worse prognosis of cancer disease. But the prognostic role of IGF1R must be interpreted very carefully, due to the inconsistent clinical studies results. Discrepancies may be caused by pre-analytical phases (tissues conservation, sample size), methods used and data interpretation (15, 16).

There has been an intensive discussion, why the results from individual studies are so different and why are the results from some study extremely contradictory. Based on the conclusions made by some authors, following are the potential causes of discrepant results:

- Circulating levels of IGFs and their binding proteins do not exactly reflect their tissue concentrations.
- There are other agents interfering with process of signal pathway activation of IGF receptor and with its effect on a cell, they may either facilitate or diminish its effect on cell (insulin, steroid hormones, adiponectin, etc.) and so the interpretation of IGF serum levels should reflect the serum levels of these agents.
- IGF receptor signal pathway is positively or negatively influenced by well known mechanisms (see the previous paragraph, but it is also affected by mechanisms, that are expected to exist but they have not been described in details so far.
- Some authors point out that there are inappropriate inclusion criteria for patients' groups and very insufficient medical data related to the period of elevated IGFs levels and presence of some kind of diseases.
- There are also other interaction which have to be taken into the account (e.g.: dietary habits, physical activity) and other diseases (diabetes mellitus, metabolic syndrome, liver diseases, etc.).

CONCLUSIONS

Functions of IGFs signal pathway have been described recently. Many interactions with other signal pathways have been also described. Intact IGF1R represents a key factor for signal pathway function. Gene locations for IGFs, binding proteins and receptors have been also described. Based on this knowledge it was possible to develop IGF1R inhibitors that are very promising for oncology treatment. IGFs are absolutely important to the investigation of processes in the human body at the cellular level.

SUMMARY

The interaction between growth factors and cancer incidence and development has been discussed recently. Insulin-like growth factors (IGF, insulin-like growth factors, formerly named somatomedines) are peptides, that participate on growth regulation, metabolism regulation, cell survival and differentiation. They are regulated by growth hormone (GH). IGFs are synthesized in liver and they occur in other body fluids. IGFBPs occur in different body fluids like serum, amniotic fluid and cerebrospinal fluid. IGFBPs are synthesized in liver. These binding proteins serve as storage of IGFs in intercellular space. Effect of IGF1 and IGF2 on cell is mediated by receptors. Signal transduction follows the successful binding to the receptor via signal intracellular pathway – i.e. cascade of enzymes and its substrates.

Based on knowledge of IGF1 and IGF2 effect on cells it is assumed that high IGFs serum levels increase the risk for cancer development. They also stimulate proliferation and risk of malignant transformation. High serum levels of binding proteins IGFBPs, particularly dominant serum binding protein IGFBP3, should decrease the risk and inhibit the cellular growth. It is assumed that malignant transformation of the cells can occur independently from serum levels of IGFs in case of presence of functional IGF1R. Recent clinical studies confirmed that high circulating IGF1 concentrations and low IGFBP3 serum levels are related to increase risk for cancer diseases. Negative correlation between IGFBP3 levels and risk of cancer diseases corresponds to protective role of IGFBP3.

Inzulinu podobné růstové faktory (IGFs) a nádory

SOUHRN

Interakce mezi růstovými faktory a vznikem a rozvojem nádorového onemocnění je v poslední době předmětem řady odborných diskuzí. Inzulinu podobné růstové faktory (IGF, dříve označované somatomediny) jsou peptidy, které se podílejí na regulaci růstu, metabolizmu, přežívání a diferenciaci buněk. Jsou regulovány růstovým hormonem (GH). IGF jsou syntetizovány v játrech a vyskytují se v tělních tekutinách. IGF vazebné proteiny (IGFBP) jsou syntetizovány v játrech. Tyto vazebné proteiny slouží jako zásoba IGF v mezibuněčném prostoru. Vliv IGF1 a IGF2 na buňku je zprostředkován receptory. Po vazbě na receptor následuje přenos signálu přes signální intracelulární dráhy – tj. kaskádu enzymů a jejich substrátů.

Na základě znalosti účinku IGF1 a IGF2 v buňkách se předpokládá, že vysoké hladiny IGF v séru mohou zvyšovat riziko vzniku a rozvoje nádorů. IGF mohou také stimulovat proliferaci buněk a riziko maligní transformace. Vysoké hladiny IGFBP v séru, zejména IGFBP3 – dominantního vazebného proteinu v séru, by měly snižovat riziko a inhibovat buněčný růst. Předpokládá se, že k maligní transformaci buněk může dojít i nezávisle na sérových hladinách IGF v případě přítomnosti funkčních receptorů pro IGF. Nedávné klinické studie potvrdily, že vysoké cirkulující koncentrace IGF1 a nízká úroveň IGFBP3

v séru souvisí se zvýšeným rizikem nádorových onemocnění. Negativní korelace mezi hladinami IGFBP3 a rizikem nádorových onemocnění potvrzuje určitou ochrannou roli IGFBP3.

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