ReviewArticle

Insulin-like Growth Factor 1 Signalling and Its Role in Cell Survival and Radiation Sensitivity

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ABSTRACT

Insulin like growth factor 1 signalling is a potent biological regulator for the growth and development in mammals. It controls tissue homeostasis throughout life via regulation of cell proliferation and apoptosis. Increased insulin like growth factor 1 signalling stimulates proliferation, promotes metastasis, and causes radio-resistance of cancer cells whereas decreased IGF-1 signalling is associated with increased incidence of cancer and enhanced cellular radio-sensitivity. The important role of insulin like growth factor 1 signalling as a pro-survival factor and its potential as a modifier of cellular radiosensitivity motivated research in the area of radiation oncology. Therefore this paper will review recent literatures on the insulin like growth factor 1 system and its role in cell survival and cellular response to radiation. The connection of IGF-1 signalling to classical pro-survival and anti-apoptotic signaling cascades will be reviewed.

Keywords: Insulin-like growth factor 1, survival, apoptosis, radiosensitivity

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The insulin-like growth factor system is a cell signalling system including two ligands, the insulin-like growth factor 1 and the insulin-like growth factor 2 (IGF-1 and IGF-2), two cell surface insulin-like growth factor receptors (IGF1R and IGF2R), at least six different insulin-like growth factor binding proteins (IGFBP1-6), and multiple IGFBP proteases.[1,2]

The insulin-like growth factors (IGFs) are polypeptides with high sequence similarities to insulin. There are two main IGFs: IGF-1 and IGF-2, that have been isolated and characterized.[3] Both IGFs have the characteristics of a circulating hormone and a tissue growth factor. IGF-1 is a single chain polypeptide of 70 amino acids, with a molecular weight of 7,649 Daltons.[3] It is a growth factor that circulates at high levels in the blood stream. The majority of circulating IGF-1 is produced in the liver. However, many other tissues including bone, adipose tissue, kidney, and muscle also produce IGF-1 and are sensitive to its action.[4] The regulation of IGF-1 production in hepatic tissue is mainly mediated by growth hormones and insulin. In turn, IGF-1 feeds back to suppress growth hormones and insulin release. In addition to growth hormones, developmental factors as well as the nutrition status can modify IGF-1 production.[4,5] IGF-1 is one of the most potent natural stimulators of cell growth, cell proliferation and a potent inhibitor of programmed cell death. IGF-2 is a single polypeptide, with a molecular weight of about 74 kD.[6] IGF-2 plays a fundamental role in embryonic and fetal development, whereas its role in the post-natal period is less important.[7] Most circulating IGF-1 and IGF-2 form a complex with IGF binding proteins (IGFBPs). IGFBPs coordinate and regulate the biological activities of IGFs by acting as transport proteins in plasma, controlling the efflux of IGFs from the vascular space, and regulating IGFs metabolic clearance. Furthermore, IGFBPs can directly modulate the interaction of IGFs with their receptors and thereby indirectly control their biological actions.[1]

The biological effects of IGF-1 and IGF-2 are mediated by their cell surface receptors. The type-1 IGF receptor (IGF1R) binds both IGF-1 and IGF-2 with high affinity. Virtually all of the biological activities of the IGFs result from binding to IGF1R. The type 2 IGF receptor binds IGF-2 with a high affinity and IGF-1 with low affinity. This receptor does not transduce a signal because it lacks a tyrosine kinase domain, but acts as a negative regulator of IGF activity by sequestration, endocytosis and degradation of IGF-2.[8]

IGF1R is a receptor tyrosine kinase which carries out most of the biological activities of IGFs.[9] IGF1R is synthesized as a single chain pre-proreceptor which is

subsequently terminally glycosylated and proteolytically cleaved to yield the α- (130-135 kDa) and β- (90-97 kDa) subunits of the mature receptor.[10] These assemble into a disulphide-linked hetero-tetramer comprised of two extracellular α-subunits necessary for ligand recognition and binding, and two transmembrane β-subunits transmitting the ligand-induced signal.[10,11] The IGF1R gene is constitutively expressed in most tissues and cell types, consistent with the role of IGF-1 as a progression factor throughout the cell cycle. Activation of IGF1R also protects cells from death induced by a variety of agents, including osmotic stress, hypoxia, radiation, and anti-cancer drugs.[12,13]

The biological actions of IGFs

In general, the effects of IGFs in vitro are either acute anabolic effects on protein and carbohydrate metabolism, or long term effects on cell proliferation and differentiation[1]. The critical function of IGF-1 for the stimulation of cell proliferation is demonstrated intensively in a variety of cell types. IGF-1 has been shown to be a potent mitogenic factor stimulating cell proliferation in fibroblasts, chondrocytes, smooth muscle cells, and epithelial cells.[1] In humans, deletions in the IGF-1 gene result in severe pre- and post- natal growth and developmental defects and in mental retardation.[14] Moreover, several studies have provided evidence that proliferation and metastasis of cancer cells are increased by IGFs receptor activation, either in relation to higher levels of circulating IGFs or overexpression of the IGF receptors.[15,16] IGFs also control tissue homeostasis throughout life by providing essential signals for the regulation of cell growth, cell proliferation, cell cycle progression, cell differentiation, and cell survival.[1]

The IGFs/IGF1R signal transduction pathways

Binding of IGFs to the extracellular part of IGF1R initiates the cytoplasmic signaling cascades that include conformational change of the receptor which enables IGF1R to bind to ATP and become autophosphorylated at tyrosine residues within the β-subunits. This results in activation of the intrinsic tyrosine kinase activity of IGF1R and subsequent tyrosine phosphorylation of several substrates which leads to the activation of intracellular signalling pathways, allowing the induction of growth, proliferation, transformation, differentiation, and survival (Fig 1).

The proximal substrates for IGF1R include insulin, the receptor substrate 1-4 (IRS1-4) and the Src-homology collagen protein (Shc).[17-21] Once activated, Shc and IRSs bind to a complex of the growth factor receptor bound-2 (Grb2) and Son of sevenless (Sos). This complex function allows the activation of Ras and its downstream cascade, the Ras/Raf/mitogen activated protein kinase and extra-cellular-signal-regulated kinase kinase (MEK)/extra-cellular-signal-regulated kinase (ERK) pathway. The Ras/Raf/MEK/ERK cascade is involved in cell proliferation, differentiation, and protection against apoptosis. Activated IRS proteins also bind to the p85 regulatory subunit of the phosphatidyl inositol 3-kinase (PI3K). The activation of PI3K leads to an increase in the phosphatidyl inositol 3,4,5 triphosphate (PIP3) level which induces the recruitment of Akt (protein kinase B). This allows the constitutively activated 3'-phosphoinositide-dependent kinase (PDK)-1,-2 to phosphorylate and activate Akt. Many downstream targets of Akt

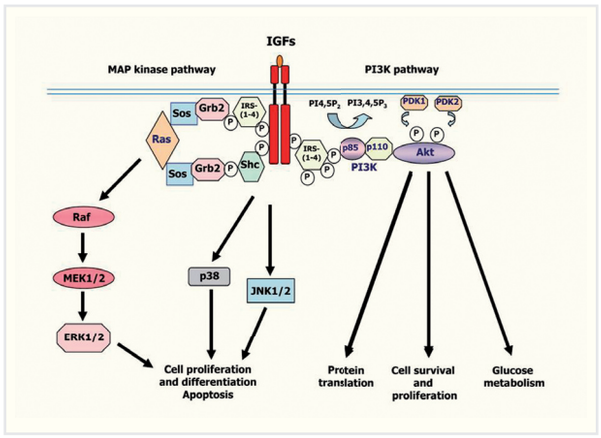

Fig 1. Scheme of the IGF1R activation and downstream signalling. Activated IGF1R by its ligand (IGFs) stimulates signaling through intracellular networks that regulate cell proliferation and cell survival. Key downstream networks include the Ras/Raf/MEK/ERK and the PI3K/Akt pathways. Two other mitogen- activated protein (MAP) kinases, p38 and JNK, are also activated in response to IGF-1. The MAP kinases are involved in cell survival, differentiation, proliferation, and apoptosis. The PI3K/Akt pathway is involved in protein translation, cell survival, proliferation, and glucose metabolism (see more details in the text).[17-24]

have been shown to prevent apoptosis and to stimulate cellular proliferation or glucose transportation.[1,22-26]

IGF-1 and cell survival

In addition to being important for stimulation of cell proliferation, the IGFs system has been characterized as a cell survival factor in certain cells.[27] IGF-1 is a highly efficient anti-apoptotic agent, not only because it has strong anti-apoptotic activities, but also because it protects cells from a variety of apoptotic stimuli, including osmotic stress, hypoxia, ionizing radiation and anti-cancer drugs.[12,13,28,29] The overexpression of the IGF-1 receptor increases the survival chance of cells exposed to hypoxia, low pH and low glucose in the solid tumor.[13] IGF-1 was found to alter anti-cancer drug sensitivity by inhibition of apoptosis in several cancer cell types.[12,30,31] Furthermore, an impaired anti-apoptotic effect of IGF-1 contributes to UV susceptibility in HaCaT keratinocytes.[32] Recently, it was reported that the potential of radiation-induced apoptosis in the crypt cells and intestinal stem cells was decreased in the presence of IGF-1.[33]

The IGFs system acts at different levels of the apoptotic machinery through different signaling pathways. However, the PI3K/Akt cascade is considered as the canonical pathway involved in the inhibition of apoptosis by IGF-1.[34] Following IGF1R activation, PI3K is phosphorylated and activated, then it in turn activates Akt. The activated Akt induces phosphorylation and then inactivation of pro-apoptotic factors, including the Bcl-2 family member Bad, members of the fork head transcription factor (FOXO) family, and caspases.[27,35] In addition, activation of Akt by IGF-1 has also been shown to increase expression of anti-apoptotic factors, including Bcl-x, and NF-κB.[36,37] The effects of IGFs on survival are also mediated by the activation of the Ras/Raf/MEK/ERK pathway.[35] However, studies in most cell

types indicated that the PI3K/Akt pathway was also functioning when the Ras/Raf/MEK/ERK pathway was operating. It should be noted that both pathways may have either cooperative actions by objecting identical anti-apoptotic targets or synergistic actions by activating different target molecules.[38-42]

Furthermore, several studies reported that the anti-apoptotic effect of IGFs is independent of the PI3K/Akt or Ras/Raf/MEK/ERK cascades. The additional pathways are meditated through 14-3-3-dependent mitochondrial translocation of Raf and Nedd4. The presence of Raf and Nedd in the mitochondria maintains the mitochondrial integrity, and thus rescues cells from apoptosis.[43] Moreover, activation of IGF1R has been reported to rescue cells from apoptotic signal-regulated kinase 1 (ASK1)-induced cell death independently of PI3K.[44] ASK1 is a MAPK kinase involved in the activation of JNK and subsequent triggering of apoptosis by death-inducing receptors. Activation of IGF-1 signaling induces a complex formation between activated IGF1R and ASK1 thereby antagonizing ASK1-induced apoptosis. Several studies also reported that additional pathways such as the p38 MAPK and JAK/STAT-3 may participate in the inhibition of apoptosis by IGF-1.[45,46]

IGF-1 and cellular response to radiation

Ionizing radiation is a potent inducer of cell death by provoking damage in DNA and other cellular components in eukaryotic cells. Evidence accumulated from several studies has revealed a strong link between the IGFs system and cell death after exposure to ionizing radiation.[47-49] However, the precise molecular mechanism of the IGFs system influencing radio-resistance of the cells is poorly understood. Following radiation damage, several intracellular events are trigged. The plasma membrane receptors such as IGF1R and Fas are activated.[50-52] The expression of the genes that influence cell survival and cell death pathways such as Fas ligand, tumor necrosis factors, and p53 are changed.[53-55] The DNA repair systems and cell cycle checkpoints that are crucial for maintaining the genomic integrity of cells damaged by radiation are activated.[56,57] Several studies indicate that IGF-1 signaling can modify cellular radiosensitivity. IGF1R overexpression mediates radio-resistance in breast cancer following radiotherapy.[48] Blocking of IGF1R activity by tyrosine kinase inhibitors or by anti-IGF1R neutralizing antibodies was shown to increase radio-sensitivity in several types of human tumor cell lines.[58,59] Dual targeting of IGF-1R and PDGFR inhibits proliferation in high-grade gliomas cells and induces radiosensitivity in JNK-1 expressing cells.[60] Moreover, RNAi silencing targeting IGF-1R could induce a radiosensitizing activity in human osteosarcomas.[33]

The level of IGF1R is often elevated in breast cancer cells and this characteristic has been assumed to be the cause for increased radioresistance and cancer recurrence in estrogen receptor (ER)-positive breast tumors.[48,61] In addition, the IGFs system may also prevent radiation-induced cell death by interfering with proteins involved in the repair or signaling of DNA lesions. The link between the IGFs system and the cellular response to radiation has arisen from an association of IGF-1 and Nbs1 protein. The Nbs1 protein is a component of the trimeric MRN (Mre11-Rad50-Nbs1) complex, which is implicated in multiple cellular responses related to DNA damage, such as apoptosis, cell cycle control, DNA double strand break repair, maintenance of telomeres and genomic stability.[62-66] Recently, it was demonstrated that Nbs1 is involved in the promotion of cell proliferation and cell cycle progression by influencing the IGF-1 signalling cascade.[63] Moreover, the disturblances of IGF-1 signalling were found to be responsible for the increased radio-sensitivity of NBS1 siRNA transfected cells.[67] It was also found that the ataxia telangiectasia mutated (ATM) gene which plays an important role in the DNA damage response pathway is involved in the regulation of IGF1R activation and expression. Indeed, disturbed expression and activation of IGF1R has a major influence on the increased radiosensitivity in ataxia telangiectasia (AT) patient cells.[29,68,69]

CONCLUSION

The potential of the IGFs system as a modifier of cellular responses to radiation has been of increasing interest to investigators. Ongoing studies attempt to target IGFs system to improve the clinical outcome of treatment of cancer patients, particularly in the case of radioresistant cancers. However, there are controversies about the proficiency of IGFs system on the regulation of radiation induced-cell death in several studies. Therefore, it is a valuable goal to get a better understanding of the precise molecular mechanisms of the IGFs system on radiation responses of the cell. This will provide important information for improved molecular targeting of cancer treatments.

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