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Review

Insulin-like growth factor-I receptor signal transduction: at the interface between physiology and cell biology

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Abstract

The insulin-like growth factor-I receptor (IGF-IR) mediates the biological actions of IGF-I and IGF-II. The IGFs play a critical role in promoting development, stimulating growth and organogenesis via mitogenic, antiapoptotic and chemotactic activity. Recent research has focused on the events that occur intracellularly upon receptor activation. Several pathways have been shown to be important. The insulin-receptor substrate (IRS), SHC, GRB2, CRKII and CRKL adaptor proteins have all been implicated in transmitting signals to the nucleus of the cell. This review outlines some of the signalling pathways believed to be important in converting IGF-IR activation into changes in cell behavior and metabolism.

Keywords: Insulin-like growth factor-I receptor; Signal transduction; Physiology; Cell biology

1. Introduction

The insulin-like growth factors (IGF-I, IGF-II) belong to a pleiotropic family of soluble peptide factors that circulate bound to one of six IGF binding proteins (IGFBP). Numerous developmental and physiological functions have been identified as being either influenced by or mediated by either of these factors [21,23,30]. At the cellular level, the IGFs can act as autocrine and paracrine growth factors to control mitosis, programmed cell death (apoptosis), differentiation, and chemotaxis. As a component of endocrine systems stemming from the hypothalamic–pituitary axis, the IGFs participate in the control of growth and possibly carbohydrate metabolism. These range from the well-known example of the control of growth, the somatomedin hypothesis, to the role(s) played by the IGFs and their binding proteins in ovarian function.

The actions of IGF-I and IGF-II in the adult are believed to result primarily from the activation of the type 1 insulin like growth factor receptor, commonly referred to as the IGF-I receptor [30]. It is interesting to note that the insulin receptor might mediate the mitogenic signals of IGF-II [33]. While the contribution of the insulin receptor to the fetal growth of mice is far less than that of the IGF-I receptor, the ramifications of this discovery to species such as humans in which IGF-II levels in plasma remain high postnatally [23] remains to be explored. Nevertheless, the IGF-I receptor plays a critical role in development, with mice lacking functional IGF-I receptors exhibiting severe dwarfism, muscle hypoplasia, abnormalities in CNS

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development, translucent skin, and an inability to survive postnatally [31]. The purpose of this review is to give an overview of what is currently known about how the IGFs, by binding to the IGF-I receptor, elicits change in cell behavior. The review is not intended to be comprehensive and, where appropriate, the reader has been directed to recent reviews.

2. The IGF-I receptor is a member of a gene family that includes the insulin receptor

The IGF-I receptor is a member of the insulin receptor family of receptor tyrosine kinases, a family that includes the insulin receptor and the insulin receptor related receptor [30]. Overall, the members of this receptor family share a heterotetrameric $\alpha_2\beta_2$ structure. A preproreceptor, a 1367-residue peptide containing the α and β domains and a 30 residue signal peptide, is transcribed from a single mRNA. The $\alpha\beta$ heterodimers, resulting from the proteolysis of the precursor peptide, are linked by disulfide bonds; secondary disulfide bonds link the $\alpha\beta$ heterodimers to form the mature $\alpha_2\beta_2$ receptor. The ligand binding domain is found in the entirely extracellular α subunit. The β subunit is largely intracellular, containing a short transmembrane domain, the tyrosine kinase domain and associated motifs that are responsible for the protein–protein interactions of the IGF-I receptor with downstream signaling proteins. For a more complete description of the IGF-I receptor, the reader is referred to a recent review [30].

3. The early events in the signal transduction cascade: receptor autophosphorylation and binding to adapter proteins

Effective signal transduction relies on the integration of two processes. First, the binding of ligand to receptor must transmit a signal through the plasma membrane to effector molecules situated on or adjacent to the interior (cytosolic) face of the membrane. Secondly, a signal is required to begin the appropriate colocalization and interaction of downstream effector proteins and molecules in the signal transduction cascade. The binding of IGF-I to the ligand binding domain results in activation of the tyrosine kinase domains within the β-subunit. Three tyrosine residues within the tyrosine kinase domain (tyr-1121, 1135 and 1136) are the first to be phosphorylated, with the phosphorylation of these residues markedly increasing the activity of the kinase domain towards downstream substrates. Deletion of any of these tyrosine diminishes receptor function, while deletion of all three results in the complete absence of several biological functions stimulated by IGF-I [30].

Several other tyrosine residues in the β-subunit are also phosphorylated and appear to have a role in IGF-I receptor signal transduction, while phosphorylation of serine residues might also be involved [30]. Three tyrosines within the juxtamembrane region (tyr-943, 950 and 957) are situated proximal to the tyrosine kinase domain. Tyr-950 is situated within an NPXY motif that has previously been shown to be important for the internalization of some receptors and for receptor–substrate interactions. Deletion of the NPXY motif in the IGF-I receptor affects receptor internalization, reduces autophosphorylation, and inhibits post receptor signaling. The adapter proteins SHC and IRS-1 both bind to this site. Site-directed mutagenesis indicates that three tyrosine residues within the C-terminal domain of the IGF-I receptor β-subunit (tyr-1250, 1251, and 1316) are also involved in the mitogenic signaling of the IGF-I receptor to varying degrees. In addition, several serine residues within the β-subunit also have a functional role in IGF-I receptor signal transduction, raising the possibly that a serine kinase is associated with the IGF-I receptor.

The phosphorylation of residues in the β-subunit creates high affinity binding sites for signaling proteins. Four domains involved in protein–protein interaction are relevant for this review: the Src-homology domains (SH2 and SH3), the Pleckstrin homology domain (PH), and the phosphotyrosine binding domain (PTB). The SH2 and PTB domains bind to motifs containing phosphorylated tyrosines, thus reversible tyrosine phosphorylation can act as a molecular 'switch' to induce the association of multiprotein complexes [18]. The SH3 domain binds to proline-containing motifs [18]. The PH domain differs from the other modules discussed in that it mediates protein–protein and protein–lipid interactions, and might also be important in mediating interactions with G-proteins [47]. Signaling proteins can contain one or more of the aforementioned modules, resulting in the selective formation of multiprotein complexes.

A relatively well characterized example of the roles that SH domains play in signal transduction is the complex containing the SH2–SH3 adapter protein GRB2 and the guanine nucleotide exchange factor Son of sevenless (mSos), which catalyzes the transition of the inactive Ras-GDP to active Ras-GTP form. mSos binds to the SH3 domains of GRB2, with the binding of mSos to GRB2 increasing the affinity of the GRB2 SH2 domain for its relevant binding sites [9]. The activation of membrane-localized receptor tyrosine kinases leads to the phosphorylation of tyrosines either on the receptor itself or on adapter proteins linked to the receptor itself (such as SHC or members of the IRS family), thereby creating high affinity binding sites for the GRB2 SH2 domain. In this model, the transloca-

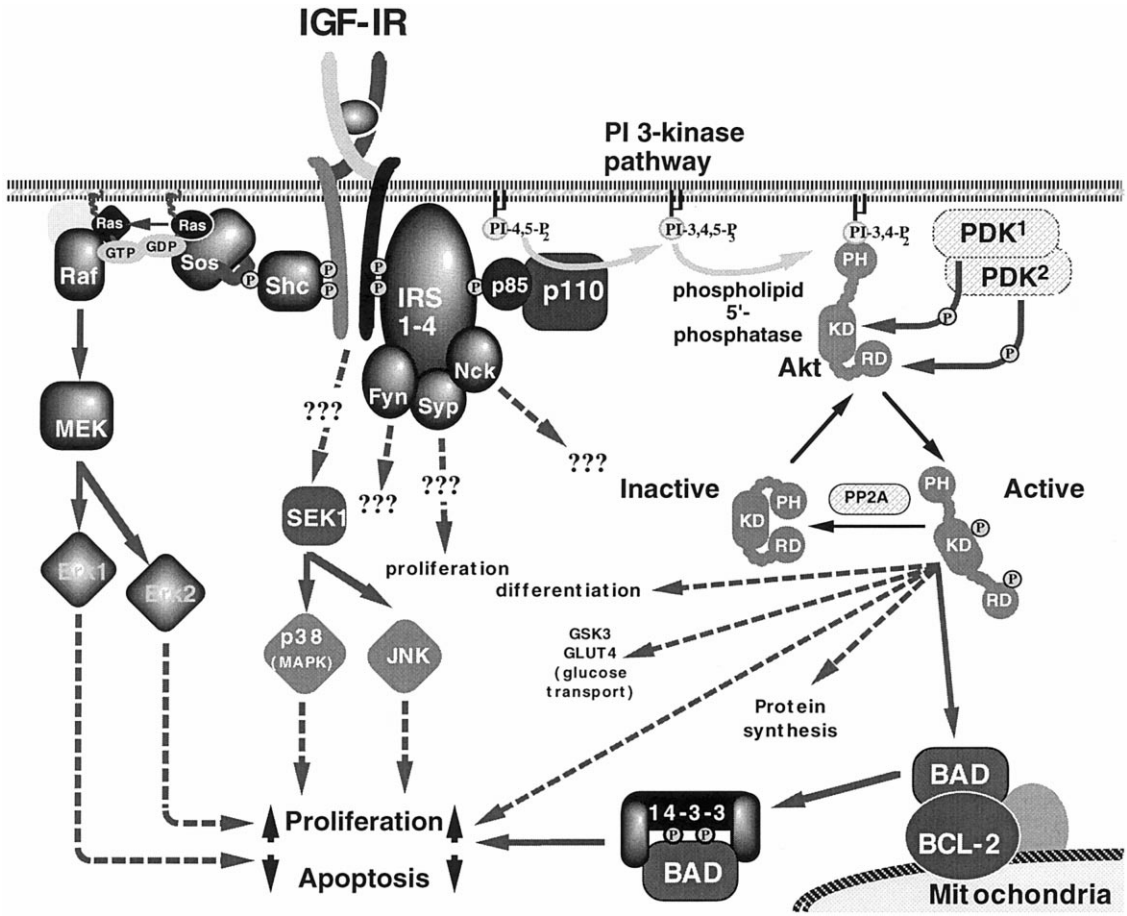

Fig. 1. Signal transduction cascades activated by the IGF-I receptor. Activation of the IGF-I receptor (IGF-IR) induces the binding and subsequent tyrosine phosphorylation of the SHC and IRS adapter proteins to the intracellular region of the IGF-I receptor b subunit. Tyrosine phosphorylation of SHC and the IRS proteins creates binding sites for other proteins in the signal transduction cascade such as GRB2 (SHC, IRS), p85, Nck, Syp, and Fyn. The binding of the p85 and p110 subunit of phosphoinositol 3′ kinase (PI 3-kinase) to members of the IRS family activates this pathway, ultimately resulting in the activation of the serine/threonine kinase Akt. A recently proposed model for the inhibition of apoptosis by Akt phosphorylation of BAD is shown.

tion of the GRB2-mSos complex to the membrane results in the colocalization of mSos with and activation of membrane-associated Ras. Activated Ras can then activate downstream components of the cascade, such as Raf-1 [5].

A schematic of the cascades activated immediately upon IGF-I receptor activation is shown in Fig. 1. At least five adapter proteins have been shown to bind to the cytoplasmic region of the IGF-I receptor. These include members of the insulin receptor substrate (IRS) family [11,22,58], SHC [11,58], 14-3-3ε [10], the p85 subunit of phosphoinositol 3- (PI3-)kinase [57], the tyrosine phosphatase PTP1D (Syp) [52], and mGRB10 [15,41]. As discussed below, the binding of each of these docking proteins to the IGF-I receptor has the potential to activate distinct signaling systems, although there may be some overlap. The ability of the IGF-I receptor to bind to and activate multiple species of docking proteins may also represent a mechanism to impart cell-type specificity, since the expression of these proteins can differ markedly between tissues and throughout development.

4. The IRS proteins connect the IGF-I receptor to multiple signal transduction pathways

The IRS proteins represent the largest (60–160 kDa) and most diverse, in terms of the number of downstream effector molecules bound, of the docking proteins that potentially bind to the IGF-I receptor. Four members of the IRS family have been cloned to date [26,27,45,54,55]. The highest degree of homology within the IRS family occurs within the N-terminal domains responsible for binding to the cytoplasmic domain of the IGF-I and insulin receptors. The rest of the protein coding sequence exhibits a high degree of variability, and contains motifs responsible for the binding of signaling proteins such as the adapter proteins GRB2 [40] and Nck [29], the p85 regulatory subunit of PI-3′ kinase [3], the tyrosine phosphatase

SH-PTP2 [8], the Src-like kinase Fyn [53] and the Ca^{2+}-ATPases SERCA1 and SERCA2 [1].

The variation in the carboxyterminal region of the IRS proteins might result in functional heterogeneity. Experimental observations support such a conclusion, with the overexpression of IRS-2 in 3T3 cells derived from IRS-1 knockout mice being insufficient to return mitogenic signaling from the IGF-I receptor to normal levels [6]. The ontogenic- and tissue-specific distribution of IRS-1, IRS-2 and IRS-3 mRNA also implies that a degree of signaling specificity might be imparted by the presence of cell- and developmental-specific IRS proteins. In the mouse embryo IRS-1 and IRS-3 mRNAs are expressed preferentially at different stages of development: maximum IRS-1 expression occurs late whereas maximum IRS-3 expression occurs early [51]. While IRS-1 and IRS-2 are coexpressed in many tissues, IRS-2 appears to predominate in hematopoietic cells where it might play a functional role in cytokine action [54].

The IRS family of proteins are responsible for connecting IGF-I receptor activation with several changes in cell behaviour. A portion of the mitogenic actions of the IGF-I receptor are mediated by IRS-1. In mice nullizygous for the IRS-1 gene, insulin resistance and fetal growth retardation are observed [2,56]. The important role that IRS-1 has in mediating the mitogenic functions of the IGF-I receptor is also evident from in vitro studies in which cell lines derived from IRS1 $-/-$ fetuses exhibit a 70–80% reduction in the mitogenic response to IGF-I [6]. Glucose transport is stimulated in response to the association and subsequent activation of the p85 and p110 subunits of the PI-3 kinases, with insulin-stimulated glucose transport markedly reduced in IRS1 $-/-$ cell lines relative to controls [6,24]. Finally, IRS-1 and IRS-2 have recently been shown bind with the adult fast twitch skeletal muscle Ca^{2+}-ATPases SERCA1 and SERCA2 [1], an interaction which might be related to the positive inotropic effects of insulin and IGF-I on cardiac muscle [20].

5. The phosphoinositol pathway and Akt

The binding of the p85 subunit to the IRS proteins and the subsequent activation of the p110 catalystic subunit of the phosphoinositol-3′ kinase links the IGF-I receptor to the phospholipid signal transduction pathways. The IGF-I receptor might also activate PI-3 kinase by binding the p85 subunit directly [57]. Many cellular processes are believed to be regulated by this pathway, including apoptosis, glucose transport and metabolism, protein synthesis, mitosis and differentiation [34].

An integral component of the phosphoinositide pathway is the serine/threonine kinase Akt, also refered to as protein kinase B (PKB) or 'related to A and C protein kinases' (RAC-PK). The activation of Akt following IGF-I receptor stimulation is a complex process that is poorly understood at present [34]. Two kinases have been implicated in the activation of Akt (PDK1, PDK2), while it is also possible that the binding of PI(3,4)P2 to the PH domain of Akt is also involved [34]. Akt phosphorylates serines or threonines contained within the consensus sequence RxRyz(S/T)(hy), where x is any amino acid, yz represent small residues other than glycine, and hy is a bulky hydrophobic group [34].

Several substrates of the Akt serine/threonine kinase have been identified. Akt phosphorylates enzymes involved in carbohydrate metabolism such as glucose synthase kinase 3 (GSK3) and 6-phosphofructo-2-kinase (PFK2) [34]. The α and β forms of GSK3 are both substrates of the Akt kinase, with their phosphorylation resulting in inactivation and subsequent stimulation of glycogen synthesis. GSK3 also controls several intracellular signaling pathways, including the tumor suppresser APC and the transcription factors CREB and AP1. Akt controls the activity of the ribosomal S6 kinase (p70S6K), which subsequently alters protein synthesis.

The use of pharmacological inhibitors of the PI-3 kinase pathway such as LY294002 and wortmannin and dominant negative PI-3′ kinase mutants has shown that this pathway is an important mediator of the antiapoptotic effects of IGF-I [12,17,25,32,37,43]. The activation of Akt is an important step in the inhibition of apoptosis, since the prevention of apoptosis by IGF-I is diminished in cells expressing dominant negative Akt mutants [17,25]. Two recent studies have led to better understanding of the role that Akt has in inhibiting apoptosis [13,14]. Current models of the regulation of apoptosis suggest that the balance between members of the Bcl-2 family plays a critical role in determining whether a cell survives or activates the cell death machinery. Several members of the Bcl-2 family (Bcl-2, Bcl-x_L, MCL-1, A1, and BAG-1) appear to promote survival, whereas others (Bcl-x_S, BAD, BAX, and BAK) promote apoptosis. The balance between hetero- and homodimerization of the various Bcl-2 family proteins is believed to be critical in determining cell fate [38,44]. The stimulation of Akt activity following IGF-I receptor activation culminates in the phosphorylation of BAD on ser-136. Serine phosphorylated BAD can then form a complex with 14-3-3ζ, thereby sequestering BAD and preventing its proapoptotic actions [13,14]. IGF-I can also promote cell survival by increasing the expression of Bcl-2 family members that inhibit apoptosis [38,44].

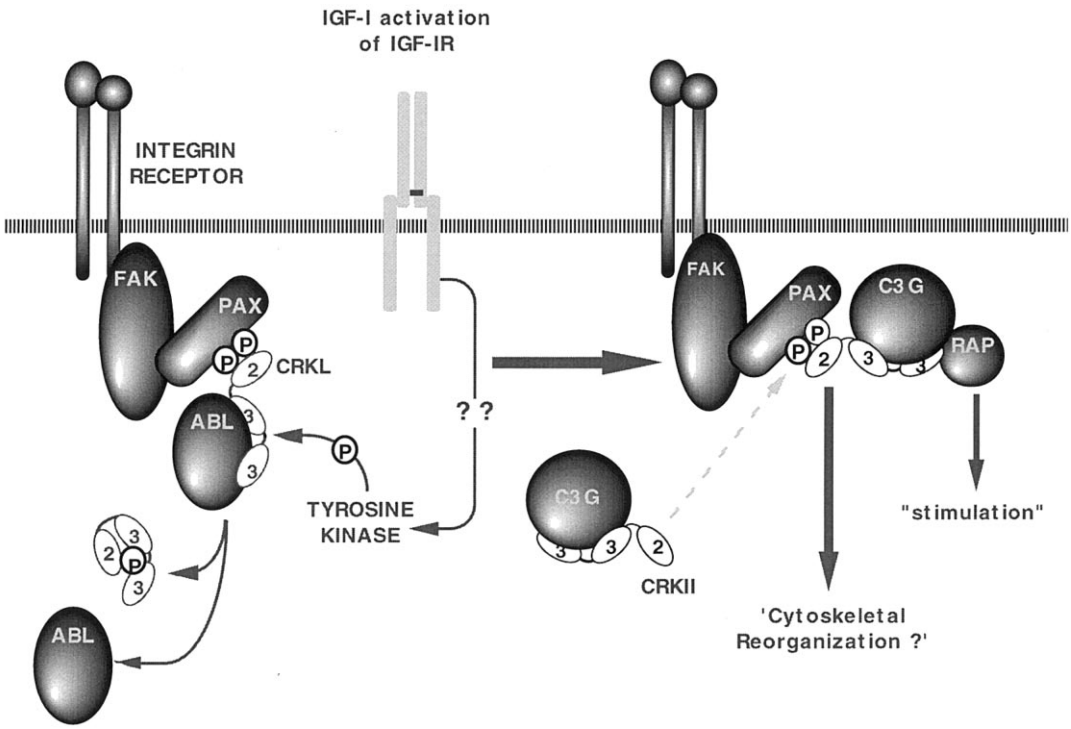

Fig. 2. A model of the role played by CrkII and CrkL in IGF-I receptor signal transduction based on in vivo data. In the uterus of starved female rats CrkL, which is markedly more abundant that CrkII is bound to paxillin, a component of focal adhesion. The stimulation of the IGF-I receptor (IGF-IR) results in the dissociation of CrkL from paxillin and the association of CrkII with paxillin. The steps that occur between IGF-I receptor activation and CrkL dissociation remain obscure, but tyrosine phosphorylation of CrkL might be involved. The phosphorylation of tyr-207 of CrkL creates a high affinity binding site for the N-terminal SH2 domain, thereby inhibiting the association of CrkL with other proteins.

6. The SHC-GRB2 complex and the p21Ras-MAPK pathway

Three isoforms of the SHC family are known to exist (p46, p52, and p66 kDa) [5]. IGF-I receptor activation results in the phosphorylation of SHC on tyrosine residues that then act as a docking site for the SH2 domain of GRB2. The guanine nucleotide exchange protein mSos, bound to the SH3 domains of GRB2, then catalyzes the exchange of GTP for GDP on the small GTP-binding protein Ras, resulting in the activation of Ras and subsequently the activation of the mitogenic Ras–Raf-mitogen activated protein kinase (MAPK) pathway [5]. Inhibition of the SHC pathway by the microinjection of antibodies inhibits the mitogenic response of Rat1 fibroblasts to IGF-I [49]. The SHC–GRB2 pathway has been shown to be the predominant activator of p21Ras for the IGF-I, insulin and epidermal growth factor (EGF) receptors [48,50]. Recent data suggests that the SHC isoforms may have distinct roles in signal transduction, with the p66 isoform having a negative effect on the activation of MAPK by the EGF receptor [36].

7. The mGRB10, CrkII, CrkL adapter proteins are involved in IGF-I receptor signal transduction

Several variants of mGRB10 (previously called GRB-IR) have been reported, although the nomenclature for these proteins has yet to be established [16,19,42]. Evidence for binding of several of these proteins to the IGF-I receptor has been established using yeast two-hybrid assays [15,39,41]. However, data from immunoprecipitation studies are contradictory. While coprecipitation of mGRB10 and the IGF-I receptor has been reported [39], another report suggests coprecipitation with the insulin but not IGF-I receptors [28]. Nevertheless, the mGRB10 proteins appear to have a negative effect on IGF-I receptor signaling, with IGF-I induced proliferation inhibited by overexpression of mGRB10α [39] and microinjection of a GST-mGRB10 SH2 domain fusion protein [41]. Further research is required to clarify where the mGRB10 proteins bind to the IGF-I receptor and which pathways are activated or inhibited by these proteins.

Our laboratory has focused on the roles of the CrkII and CrkL adapters proteins in IGF-I receptor signal

transduction. CrkII is the cellular homologue the viral oncoprotein, v-Crk, while CrkL was discovered more recently; both CrkII and CrkL share a similar structure with a single N-terminal SH2 and two C-terminal SH3 domains [35,59]. The SH3 domains of CrkII and CrkL bind to mSos and the related C3G [35,59], thus the CrkII- and CrkL-C3G/mSos might function in a manner analogous to the GRB2–mSos complex (Fig. 2).

IGF-I stimulation of cultured embryonic kidney (293) and NIH3T3 cells induces the tyrosine phosphorylation of CrkII [4]. In the rat uterus, IGF-I stimulation has markedly different effects on CrkII and CrkL tyrosine phosphorylation and association with paxillin [7]. The tyrosine phosphorylation of CrkL is increased following IGF-I stimulation, whereas CrkII is not affected. Whereas CrkL dissociates from paxillin, CrkII association with the component of the focal adhesion is stimulated. These data indicate that CrkII and CrkL might have distinct roles in IGF-I receptor signal transduction (Fig. 2). Our laboratory is also pursuing data indicating that IRS-4 binds CrkII and CrkL in a manner regulated by IGF-I.

8. Summary

Clearly, much remains to be done on characterizing the IGF-I receptor signal transduction process. This review has touched briefly on the major areas of research, however the size and scope of this field is such that much is beyond the scope of this review. The issue of cross talk between the signal transduction processes of the IGF-I receptor and others, such as the integrins and serpentine (G-protein-linked) receptors is important. Indeed, the IGF-I receptor can in some instances act as a component of pathways emanating from other ligand/receptor combinations, for example the tyrosine kinase Src phosphorylates and activates the IGF-I receptor [46]. Similarly, the role of hybrid IGF-I-insulin receptors and heterogeneity of the IGF-I receptor has not been discussed. The application of basic research into IGF-I receptor in the clinical arena is an important area, with the selective inhibition of signal transduction pathways as an inhibitor of tumorigenesis a distinct possibility. This review has attempted to convey the complexity that exists within the field of signal transduction research. The discovery of new pathways and new proteins will almost surely add to this picture.

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