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FOREWORD

Welcome again to the ninth edition of ESTEEM Academic Journal (Social Science and Technology issue). It also marks the second successive issue that Unit Penerbit, Universiti Teknologi MARA (Pulau Pinang) has published online journal in tandem with the marked growth of popularity among readers in electronic journals. Apart from that, it has made accessible the online journal in both PDF and EPUB files. It is hoped that these two formats will facilitate readers to view the content using different gadgets and options available to them. This will definitely advance the sharing of research materials and discussions between the authors and the wider fraternal scholars.

ESTEEM Academic Journal 9(2) has also received overwhelming support from many authors from within UiTM main campus as well as from branch campuses and also likewise from other local public institutions. The Editorial Board has its hands full trying its level best to process as many articles as possible for the intended publication. It is therefore befitting that thanks should be accorded to all the relevant parties for making this publication of academic journal yet another reality.

First and foremost, I would like to thank Associate Professor Mohd Zaki Abdullah, outgoing Rector of UiTM (Pulau Pinang), Associate Professor Ir. Hj. Bahardin Baharom, former Deputy Rector of Academic & International Affairs and Dr. Mohd Subri Tahir, Deputy Rector of Research, Industry, Community & Alumni Network for their selfless guidance and enduring support. Next, I would like to register my sincere thanks to the panel of reviewers, managing, language and formatting editors for toiling tirelessly through trying times in order to make this online journal more available to a wider academic community. Lastly, I would like to thank all the authors who have contributed their articles for consideration in ESTEEM Academic Journal and congratulate those who have had their articles published. I look forward to the continued firm support from all the concerned parties. To the readers and researchers alike, I once again hope that you will gain some insights and knowledge from reading these articles.

Liaw Shun Chone
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CONTENTS OF JOURNAL

p-ISSN 1675-7939; e-ISSN 2289-4934

p-ISSN 1675-7939; e-ISSN 2289-4934

ESTEEM Academic Journal
Vol. 9, No. 2, December 2013, 87-95

INSULIN AND INSULIN-LIKE GROWTH FACTOR SIGNALLING (IGF) PATHWAYS AND CANCER

Wan Iryani Wan Ismail[1], Mohd Nazri Abu[2], Muhammad Ashraf Mohd Salleh[3], Izmil Haikal Zainol[4] and Rosmadi Mohd Yusoff[5]

[1, 3, 4, 5]*Department of Pharmaceutical Life Science, Faculty of Pharmacy, Universiti Teknologi MARA, 43200 Puncak Alam, Selangor, Malaysia.*
[2]*Department of Medical Laboratory Technology, Faculty of Health Sciences, Universiti Teknologi MARA, 43200 Puncak Alam, Selangor, Malaysia.*
[1]*w_iryani@salam.uitm.edu.my;* [2]*nazri669@salam.uitm.edu.mu;*
[3]*muhd.ashraf93211@gmail.com;* [4]*milhaikal89@gmail.com;*
[5]*rosmadi0365@puncakalam.uitm.edu.my*

ABSTRACT

Cell signalling is part of a strategy in drug discovery. Among the focus is by studying the insulin and insulin-like growth factor (IGF1R) signalling pathways. The molecular mechanism of insulin and IGF1R signalling pathways have been studied extensively. Both pathways are vital in many of the mechanisms in human body particularly in regulating the metabolism and cell growth. Besides, both pathways have been found to be involved in numerous diseases such as in various types of cancer. This review briefly revealed the information on the pathways, their correlations and current findings in cancer study.

Keywords: cancers; cell signalling; insulin; insulin-like growth factor signalling pathways.

1. INTRODUCTION

Cell signalling is a cell-to-cell interaction or communication between the inter- and intra-cells. It is essential to monitor the cell environment and to respond to external stimuli. The cell signalling can trigger numerous effects including differentiation, proliferation, survival and other cellular functions for cell endurance. Thus, cell signalling has been applied as part of a strategy in drug discovery (Aggarwal, Sethi, Baladandayuthapani, Krishnan, & Shishodia, 2007). One of such fascinating cell signalling is insulin and insulin-like growth factor (IGF) pathways. Alterations of the pathways have been associated with insulin resistance and other related diseases such as hyperinsulinaemia, hyperglycaemia, diabetes, and cardiovascular diseases (Frasca et al., 2008). Moreover, recent studies have revealed significant functions of insulin and IGF signalling pathways in several types of cancers including breast, colon, ovary and liver cancers (Clayton, Banerjee, Murray, & Renehan, 2011; Frasca et al., 2008; Giovannucci, 1995; Koohestani et al., 1998; Tran, Medline, & Bruce, 1996).

Interestingly, the cancer is associated with type 2 diabetes or in other words, there are correlations between insulin and IGF signalling pathways with the disease (Hu et al., 1999; Michels et al., 2003; Yang, Hennessy, & Lewis, 2004). Perhaps, understanding the cell

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signalling, i.e., insulin and IGF signalling pathways is a key in developing a more appropriate treatment for cancer (Chappell et al., 2001; Lindsay & Evans, 2008).

1.1 Insulin Signalling Pathway

Insulin signalling pathway is one of the examples of cell signalling in human body. It is classified according to distance signalling as an endocrine signalling and according to receptor signalling as tyrosine kinase, i.e., receptors with intrinsic enzymatic activity. It is considered as an endocrine receptor signalling as it involves the insulin hormone secreted by *β*-cells in islets of Langerhans in the pancreas. Meanwhile, it is also known as receptor tyrosine kinase signalling or as a phosphorylation of tyrosine amino acid on *β*-subunit of insulin receptor (IR) to regulate the signal transduction in cells. However, the latter classification is the most commonly applied (Kido, Nakae, & Accili, 2001; Leney & Tavare, 2009).

One of the major components in insulin signalling is IR. Discovery of the IR by Roth and colleagues in 1971 has created a new paradigm in understanding the molecular basis of insulin action which is involved with other molecular signalling such as insulin receptor substrate 1(IRS-1), Src homology 2 (SH2) domains, phosphoinositide 3-kinase (PI3-K), PIP3-dependent protein kinases (PDK), Protein Kinase B (PKB) or also known as AKT and glucose transporter 4 (GLUT4) (Ismail, King, & Pillay, 2009; Leney & Tavare, 2009).

IR is located on the chromosome 19. The expression is detected during embryonic and in adulthood stages (Kido et al., 2001). Basically, the IR is a heterotetrameric structure that contains two α- and two β-subunits receptor that plays a key role in providing insulin binding site. The intracellular receptor consists of ligand-activated tyrosine kinase that facilitates the docking site for downstream molecules. IR is classified into two isoforms, i.e., IR fetal isoform A (IR-A) and B (IR-B) (Frasca et al., 2008). Moreover, it also exists in a hybrid form with IGF receptor 1 (IGF1R). The major ligand is insulin but in certain cases, it also has an affinity to insulin-like growth factor II (IGF-II) ligand (Frasca et al., 2008; Menting et al., 2013).

The primary function of the insulin signalling pathway is to regulate the glucose metabolism homeostasis (glucose intake and storage) in human body (Leney & Tavare, 2009). Thus, IR is mostly expressed in insulin-sensitive tissues such as skeletal muscle, liver and adipose tissues. Other than that, numerous studies have revealed that the pathway is also involved in the cell growth promotion *in-vitro* and *in-vivo*, and in cancer development (Aleem, Nehrbass, Klimek, Mayer, & Bannasch, 2011; Frasca et al., 2008; Clayton et al., 2011; Friedrichs et al., 2008; Heuson, Legros, & Heimann, 1972; Novosyadlyy et al., 2010; Nunez et al., 2006; Shafie & Hilf, 1981). In the latter function, IR-A is involved as it has the peculiar characteristic to bind not only to insulin but also to IGF-II (Frasca et al., 2008).

1.2 Insulin-Like Growth Factor (IGF)

The insulin-like growth factor (IGF) was first discovered by Salmon and Daughaday in 1957 (Bruchim, Attias, & Werner, 2009; Werner, Weinstein, & Bentov, 2008). It is another endocrine signalling which mediates the growth hormone (GH) to induce metabolic and anabolic processes in human body. It is a polypeptide that acts in a paracrine and autocrine manner which is involved in the growth, apoptosis, differentiation and transformation of cells

p-ISSN 1675-7939; e-ISSN 2289-4934

(Lindsay & Evans, 2008; Moschos & Mantozoros, 2002). Other than that, it is also classified under the receptor tyrosine kinase signalling pathway which is similar to insulin signalling pathway i.e. require tyrosine phosphorylation on receptors prior to the downstream signal transduction IGF system contains two growth factors (IGF-1 and IGF-II), two cell surface receptors (IGF-1R and IGF-IIR) and six specific binding proteins (IGFBP-1 to IGFBP-6) (Le Roith, 2003).

IGF-I is located on the chromosome 12q22. IGF-I expression is low during the embryonic stage and plays an important role in growth and development. IGFs is a system involving hormones, cell surface receptors and binding proteins that control normal growth and differentiation of most organs and this system is active at most stages of the life cycle which includes the fetal period, infancy and adulthood (Bruchim et al., 2009). Thus, IGF1R is expressed in almost all body tissues (Le Roith., 2003). IGF displays biological activities at both cell and organism levels, function as cell progression factors and pushing cell through various phases of the cell cycle at cellular level, while at the organism level; it participates in the control of multiple systems, such as neuronal activity, kidney function and reproduction (Bruchim et al., 2009).

Moreover, the IGF system is evident in the cancer development and progression since IGF shows common events in several malignancies including IGF-IR over-expression and over-activation and production of IGF-IR ligands (IGF-I and II) (Frasca et al., 2008; Khandwala, McCutcheon, Flyvbjerg, & Friend, 2000). IGF-1 can act as a potential growth factor in cancer cells and it can also promote tumorgenesis (Hadsell et al., 2000; Gunter et al., 2009). Down-regulation of IGF-1 inhibits the progression of tumorgenesis (Hadsell et al., 2000; Wu et al., 2003). Epidemiological studies also show a high level of IGF-1 in colorectal, prostate and breast cancer.

1.3 Synergetic Effects Of Insulin And Insulin-Like Growth Factor (IGF) System

Insulin and insulin-like growth factor system (IGFs) are growth factors that were thought only to be involved in glucose metabolism and in the activation of cellular signalling cascades mediating cell proliferation, differentiation, and survival (Cannata, Fierz, Vijayakumar, & LeRoith, 2010; Nakae, Kido, & Accili, 2001). However, several studies suggest that insulin also exhibited a number of IGF-I like activities such as growth stimulation (Cannata et al., 2010; Werner et al., 2008). It is because even though insulin and IGF have different functions, both share the same downstream cascade which involves various networks and pathways (Figure 1).

p-ISSN 1675-7939; e-ISSN 2289-4934

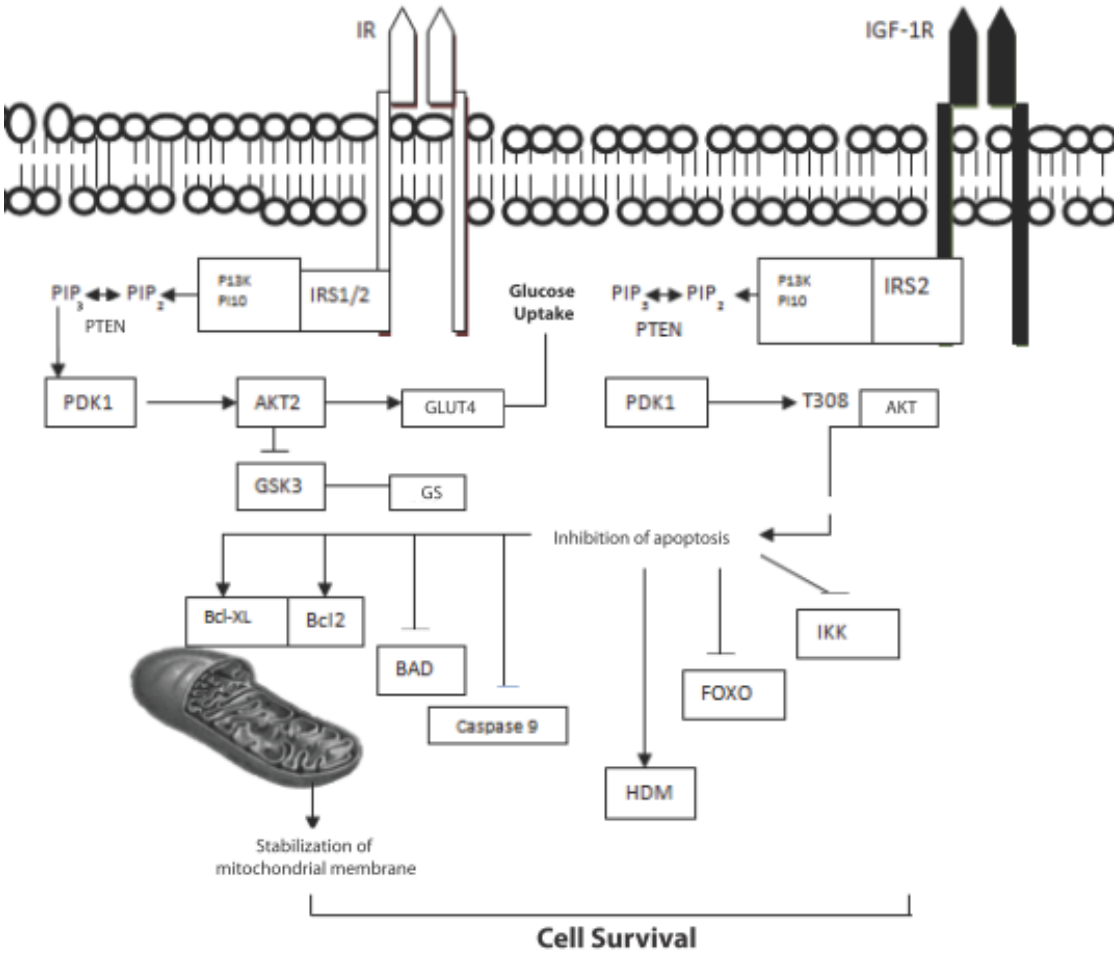

Figure 1: Downstream Cascades Regulation By IR And IGF-1R.

Moreover, insulin and IGF receptors share remarkable similarities in term of structures, genetic and downstream cascades activities (Cannata et al., 2010; Werner et al., 2008). Both IGF-1R and IR are known as members of the ligand-activated receptor kinase super family, once they are activated by the ligands, they will undergo conformational changes which lead to ATP binding and autophosphorylation of the tyrosine kinase domain (Werner et al., 2008) (Figure 1). This will enhance the kinase activity of the receptors and confers upon them the ability to phosphorylate a series of cytoplasmic substrates, collectively known as downstream signal transduction mediators (Werner et al., 2008).

Other than that, both insulin receptor and IGF-1 receptor can be activated by insulin binding. The insulin could enhance IGF signalling by directly stimulating the IGF-1R receptor. However the signalling by insulin activation of IGF-1 receptor will lead to growth promotion and cell proliferation (Khandwala et al., 2000).

Similarities between both IR and IGF-1R might be due to the fact that both are synthesized as single polypeptide chains that are processed to produce glycopeptides of M_r 180 kDa (Werner et al., 2008). After the translational process, a mature heterotetrameric with β-α-α-β conformation is produced with the α-subunit residing entirely in the extracellular with the cysteine-rich region and several N-linked glycosylation sites (Werner et al., 2008).

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The remarkable similarity between IGF-1R and IR in terms of structure and genomic information is consistent with the theory that both receptor genes share a common evolutionary origin (Werner et al., 2008). Originally, both IR and IGF-1R are thought to bind only towards their specific ligands at high affinities, however, the existence of 2 isoforms of IR portray a new understanding on both insulin and IGF system (Mosthaf et al., 1990; Werner et al., 2008).

The two isoforms of IR (IR-A and IR-B) are formed from the alternative splicing of the IR transcript. IR-A mediates the anti-apoptotic and mitogenic effects, whereas IR-B exerts metabolic effects (Sciacca et al., 2003). IR-A binds to IGF-II and insulin, meanwhile IR-B is poorly responsive towards IGF-II (Cannata et al., 2010). Since IGF-II is a powerful stimulator of cell proliferation, the ability of IR-A to bind to IGF-II may explain the difference in cell signalling of the two isoforms (Cannata et al., 2010). Insulin and IGF-I bind to their own cognate receptor with the highest affinity (Cannata et al., 2010).

Because there is a high degree of homology, IGF-1R and IR can form hybrid receptors consisting of 1 α-subunit and 1 β-subunit of IR, and 1 α-subunit and 1 β-subunit of IGF-1R (Cannata et al., 2010) (Figure 2). This hybrid receptors behave more like IGF-1R compared to IR due to their high affinity towards IGF-I rather than insulin. Therefore, the hybrid receptors provide additional binding sites for IGF-I and leads to increased cell sensitivity to IGF-I (Cannata et al., 2010).

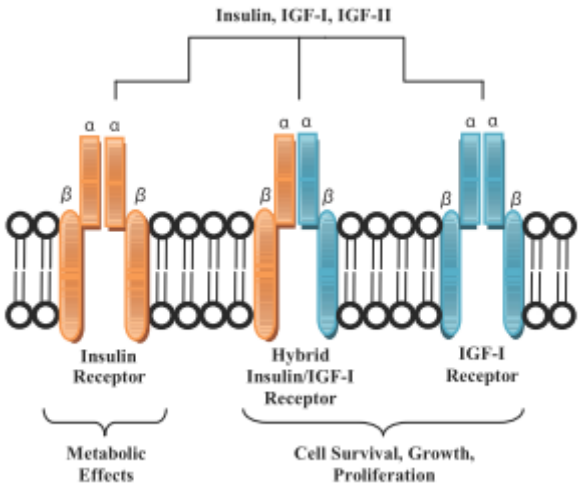

Figure 2: Insulin Receptor, Insulin-Like Growth Factor 1 Receptor (IGF-1R) And Hybrid Insulin-Like Growth Factor 1 Receptor.

Both insulin and insulin-like growth factor 1 (IGF-1) trigger complex downstream cascade such as the PI3K pathway, and the mitogen-activated protein kinase (MAPK) pathway (Samani, Yakar, LeRoith, & Brodt, 2007). The PI3K activation promotes PKB pathway (Taha & Klip, 1999) and PI3K/PKB pathway whereas MAPK pathway promotes cell growth and has an anti-apoptotic effect (Frasca et al., 2008; Saltiel & Kahn, 2001).

A huge component of these pathways are shared by both IR and IGF-1R and a number of potential mechanisms were proposed to explain how these two receptors succeed in engaging different biological activities (Werner et al., 2008). These mechanisms include different

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tissues distributions of IR and IGF-1R, different internalization kinetics and sub cellular distributions of the hormone receptor complex, and different hormones receptor affinities (Werner et al., 2008).

2. CONCLUSION

Current studies on insulin and IGF signalling pathways have discovered the importance of both pathways in regulating metabolic and mitogenic effects in the body. Better understanding particularly on the molecular mechanism of cancer and type 2 diabetes via the insulin and IGF signalling pathways may provide a constructive key in developing an effective drug in the future.

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