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Gene Section
Review

IRS2 (insulin receptor substrate 2)

João Agostinho Machado-Neto, Paula de Melo Campos, Fabiola Traina

Department of Internal Medicine, University of São Paulo at Ribeirão Preto Medical School, Ribeirão Preto, São Paulo, (JAMN, FT), Hematology and Hemotherapy Center, University of Campinas - UNICAMP, Instituto Nacional de Ciência e Tecnologia do Sangue, Campinas, São Paulo, (PdMC) Brazil. jamachadoneto@gmail.com, pmcampos@gmail.com, ftraina@fmrp.usp.br

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Abstract

Insulin receptor substrate 2 (IRS2) belongs to the insulin receptor substrate protein family and was initially discovered as an alternative route for signaling mediated by the insulin receptor. Currently, IRS2 has been well-established to mediate mitogenic and antiapoptotic signaling from several important cellular receptors. In the last years, many studies have indicated that IRS2 participates in the regulation of important biological processes involved in cancer phenotype, including cell proliferation, clonogenicity, metabolism and survival. The present review contains data on IRS2 DNA/RNA, protein encoded and function.

Keywords: IRS2; mitogenic signaling; antiapoptotic signaling

Identity

Other names: IRS-2, 4PS

HGNC (Hugo): IRS2

Location : 13q34

DNA/RNA

Description

IRS2 was discovered as an alternative route from signaling mediated by the insulin receptor in Irs1 knockout mice (Patti, et al. 1995). The entire IRS2 gene is approximately 33.8 Kb (start: 109752698 and end: 109786568 bp; orientation: Minus strand) and contains 2 exons. The IRS2 cDNA contains 7 Kb.

Protein

Description

IRS2 belongs to the insulin receptor substrate (IRS) protein family, which is characterized by the presence of a pleckstrin homology (PH) domain and a phosphotyrosine binding (PTB) domain (Figure 1) in their protein structure. The PH domain contributes to protein-protein binding and facilitates the recruitment of IRS proteins by cell membrane receptors.

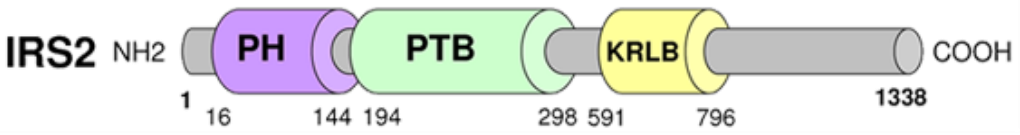

Figure 1. Schematic structure of IRS2. The pleckstrin homology (PH) domain (purple), phosphotyrosine binding (PTB) domain (green) and kinase regulatory loop binding domain (KRLB) are illustrated in the Figure. Amino acid (aa) positions are indicated.

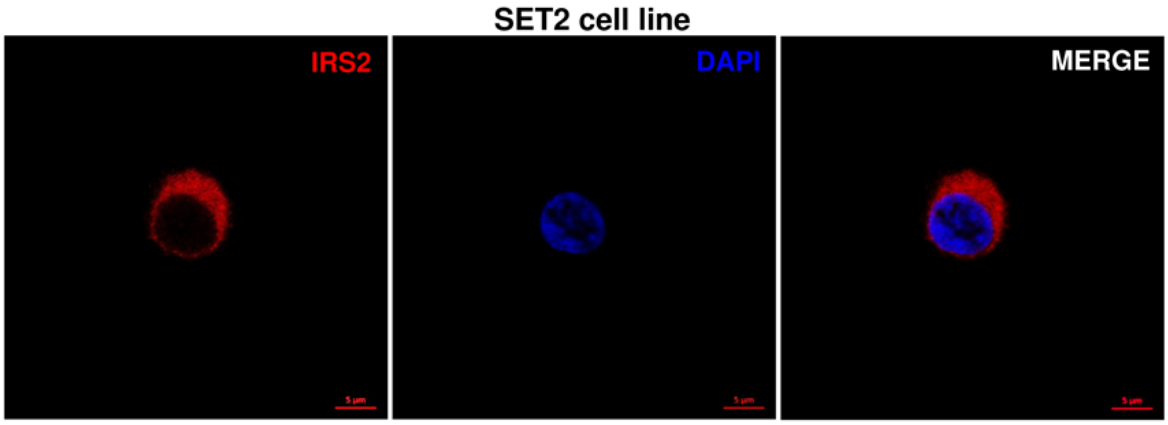

Figure 2. Intracellular localization of IRS2 protein in the SET2 cell line. Confocal analysis of SET2 (leukemia) cell line displaying IRS2 (red) and DAPI (blue) staining; MERGE shows the overlapped images. Scale bar: 5µm, as indicated. Note the predominant cytoplasm localization of IRS2. Anti-IRS2 (sc-1555) was from Santa Cruz Biotechnology and DAPI (P-36931) was from Life Technologies (Carlsbad, CA, USA). Personal data.

The PTB domain contains multiple tyrosine sites for phosphorylation and is activated by cell receptors. Differently to other IRS family members, IRS2 has a kinase regulatory loop binding domain (KRLB) that contributes to the recruitment to cellular receptor (Mardilovich, et al. 2009a).

Expression

Ubiquitous.

Localisation

IRS2 protein is predominantly found in the cytoplasm (Figure 2).

Function

IRS2 is a 180 kDa adapter protein described in 1995 as being equivalent to the 4PS protein previously identified as a substrate associated with the IL4 receptor in myeloid cells (Patti, et al. 1995). IRS2 mediates mitogenic and antiapoptotic signaling from insulin receptor (INSR), insulin-like growth factor 1 (IGF1R), erythropoietin receptor (EPOR), thrombopoietin receptor (MPL), vascular endothelial growth factor receptor VEGFR (KDR), leptin LEP, growth hormone (GH), interleukins and IFNα/ IFNB1/IFNG, playing an important role in the response to stimuli for cytokines and growth factors, influencing the proliferation and survival of normal and cancer cells (Argetsinger, et al. 1996; Dearth, et al. 2007; Gibson, et al. 2007; Johnston, et al. 1995; Platanias, et al. 1996; Sun, et al. 1995; Uddin, et al. 1995; Verdier, et al. 1997; White, et al. 1994; Yenush, et al. 1997). In addition, stimulation of the insulin receptor is known to result in IRS2 association with the p85 subunit of PI3K and GRB2, activating proteins involved in the PI3K/AKT/ MTOR and MAPK pathways, respectively (Patti, et al. 1995; Velloso, et al. 2006) (canonical pathway).

IRS2 also activates signaling pathways through other mechanisms (non-canonical pathways).

For instance, angiotensin II stimulates the rapid phosphorylation of JAK2 tyrosine residues, increasing its catalytic activity and JAK2 - IRS2 association (Folli, et al. 1997; Saad, et al. 1996; Saad, et al. 1995).

The IRS2 - JAK2 association has also been described in rat left ventricular cells after stimulation with angiotensin (Velloso, et al. 2006; Velloso, et al. 1996), and in rat liver after stimulation with leptin (Carvalheira, et al. 2003). Similarly, the mutant form of JAK2 ($JAK2^{V617F}$), which is constitutively activated, leads to enhanced interaction between JAK2 and IRS2 in myeloid cells (de Melo Campos, et al. 2016). The main signaling pathways stimulated by IRS2 are shown in Figure 3.

Homology

The N-terminus of IRS2 shares high homology with that of the other members of the IRS protein family. IRS2 also has a high homology among different species (Table 1).

Mutations

Recurrent mutations in the IRS2 gene are rare, and 88 substitution missense, 2 substitution nonsense, 38 substitution synonymous, 1 insertion inframe, 3 insertion frameshift, 4 deletions inframe and 3 deletion frameshift mutations are reported in COSMIC (Catalogue of somatic mutations in cancer; http://cancer.sanger.ac.uk/cancergenome/projects/cosmic).

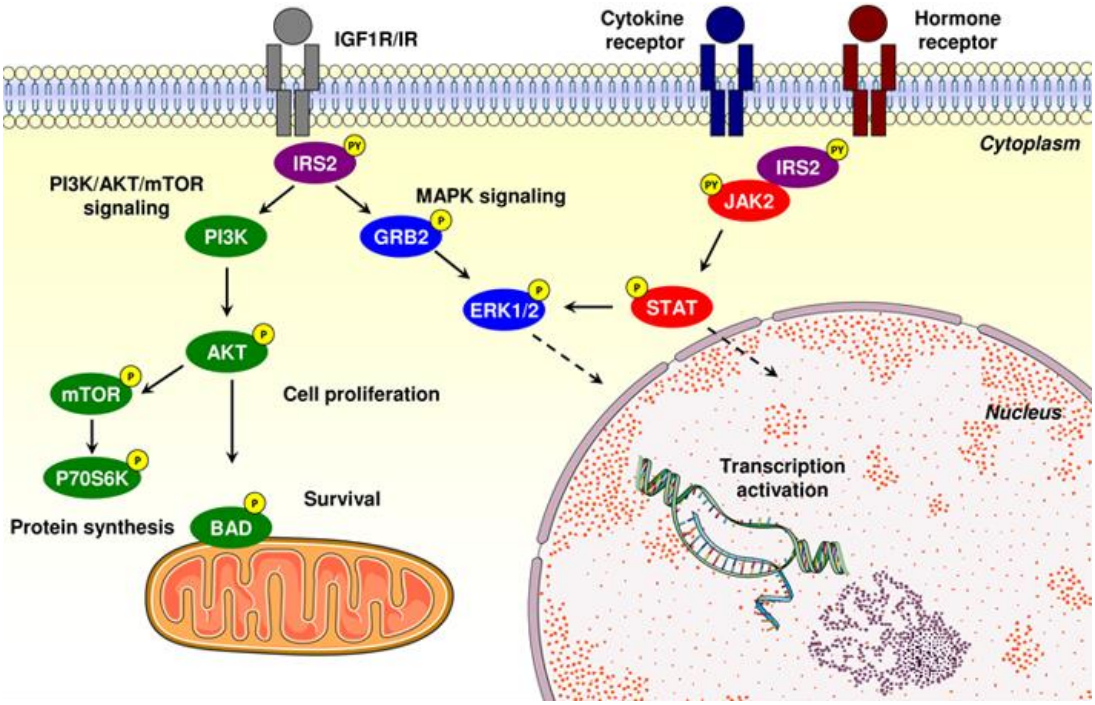

Figure 3. IRS2 signaling pathway. IRS2 is recruited by its PH/PTB domains and phosphorylated in tyrosine residues by upstream tyrosine kinase receptors (e.g. insulin receptor [IR], insulin-like growth factor receptor [IGF1R]). Tyrosine phosphorylation of IRS2 triggers PI3K/AKT/mTOR and MAPK signaling activation (canonical pathway), regulating many biological processes, including cell proliferation, protein synthesis, survival and gene expression in specific human tissues. IRS2 is also activated by cytokine and hormone receptors (e.g. IL4, leptin, angiotensin), which additionally induce JAK2 stimulation and IRS2/JAK2 interaction, leading to STAT, PI3K/AKT/mTOR and MAPK signaling activation in rat and mouse tissues. Abbreviations: P, phosphorylation; PY, tyrosine phosphorylation. Figure was produced using Servier Medical Art (http://www.servier.com/Powerpoint-image-bank).

% Identity for: *Homo sapiens* IRS2	Symbol	Protein	DNA
vs. P. troglodytes	IRS2	96.9	97.7
vs. M. mulatta	IRS2	97.4	95.9
vs. C. lupus	IRS2	88.8	87.4
vs. B. taurus	IRS2	85.0	84.8
vs. M. musculus	Irs2	84.7	80.8
vs. R. norvegicus	Irs2	85.7	81.5
vs. G. gallus	IRS2	73.7	74.4
vs. X. tropicalis	LOC100498409	59.4	57.1
vs. D. rerio	Irs2	60.7	61.7
vs. D. rerio	zgc:56306	58.9	56.5

Table 1. Comparative identity of human IRS2 with other species (Source: http://www.ncbi.nlm.nih.gov/homologene)

Implicated in

Breast cancer

Jackson and colleagues (Jackson, et al. 1998) observed that IRS2 is widely expressed in breast cancer cell lines and primary breast cancer cells. In breast cancer patients, membrane localization of IRS-2 was associated with reduced overall survival by multivariate analysis (Clark, et al. 2011). In breast cancer cell lines, high IRS2 expression was correlated with high breast tumor invasiveness (Porter, et al. 2013), and with increased survival and cell invasion under hypoxia conditions (Mardilovich, et al. 2009b). Breast cancer IRS2-depleted cells, using specific anti-sense constructs, presented reduced IGF1-mediated cell motility and lower anchorage independent growth (Jackson, et al. 2001). In agreement, others studies demonstrated that IRS2 activation was required for IGF1-induced cell motility of the human breast cell lines MCF-7 (Ibrahim, et al. 2008; Zhang, et al. 2004) and T47D-YA(Byron, et al. 2006). Nagle and colleagues (Nagle, et al. 2004), showed that mammary tumor cells from IRS2 knockout mice were less invasive and presented more prominent apoptotic response to growth factor deprivation compared to wild type mammary tumor cells. Using breast cancer cell lines, Morelli and colleagues (Morelli, et al. 2003) and Cui and colleagues (Cui, et al. 2003) also observed that IRS2 could be a target of estrogen and progesterone receptors, respectively. Cui and colleagues (Cui, et al. 2006) demonstrated that EGF signaling was also involved in IRS2 induction/activation at the mRNA and protein levels via c-JUN/AP-1 stimulation, establishing cross-talk between IGF1R and EGFR signaling. Furthermore, the authors demonstrated in

their study that IRS2 silencing reduced EGF-induced invasion and migration in the mammary adenocarcinoma cell line MDA-MB-468 (Cui, et al. 2006). Using the nontumorigenic mammary epithelial cell line MCF-10A and transgenic mice overexpressing human IRS2 by MMTV promoter, Death and colleagues (Dearth, et al. 2006) demonstrated the potential of malignant transformation of mammary cells by in vitro and in vivo IRS2 overexpression. Wu and colleagues (Wu, et al. 2010) observed that IRS2 silencing impaired breast cancer cell proliferation. In addition, they described that IGF1 induced nuclear translocation of IRS2 and NFKB, and promoted intranuclear association between IRS2 and NFKB in MCF-7 and BT-20 breast cancer cells, establishing a cross-talk between IGF1R and NFKB signaling. Slattery and colleagues (Slattery, et al. 2007), using a cohort of 1664 patients with breast cancer (1089 non-Hispanic white and 575 Hispanic) and 2054 controls (1328 non-Hispanic white and 726 Hispanic), found no association between IRS2 G1057D (rs1805097) polymorphism and breast cancer development. In contrast, Feigelson and colleagues (Feigelson, et al. 2008) observed an association between IRS2 polymorphisms rs4773082 (640 patients and 650 controls), rs2289046 (552 patients and 589 controls) and rs754204 (642 patients and 655 controls) and breast cancer development.

Colorectal cancer

Slattery and colleagues (Slattery, et al. 2004), using a cohort of 1001 patients with colon cancer and 1167 controls, and 766 patients with rectal cancer and 983 controls, reported that IRS2 G1057D (rs1805097) heterozygote GD genotype significantly reduced the risk of colon, though not rectal, cancer. In contrast, Yukseloglu and colleagues (Yukseloglu, et al. 2014), observed no association between IRS2 G1057D (rs1805097) polymorphism and risk for disease in a group of 161 patients with colorectal cancer and 197 controls. Gunter and colleagues (Gunter, et al. 2007) observed no association of IRS2 polymorphisms rs2241745 (754 patients and 765 controls) and rs2289046 (744 patients and 758 controls) with advanced colorectal adenoma. IRS2 (rs2289046) GG genotype compared with AA plus AG genotypes was found to have a protective factor for colorectal cancer risk in normal weight subjects (Karimi, et al. 2013). Day and colleagues (Day, et al. 2013) described that IRS2 mRNA and protein levels were positively correlated with progression from normal through adenoma to carcinoma in colorectal cancer, and that deregulated IRS2 expression activated the PI3K/AKT pathway and increased cell adhesion. Using FISH analysis, Huang and colleagues (Huang, et al. 2015) demonstrated that IRS2 amplification was a recurrent event and that IRS2 levels modulated the sensibility of colorectal cancer cell lines to the dual IGF-1R/IR inhibitor BMS-754807. In addition, the authors, using public available SNP array data on tumors, observed that the frequency of IRS2 copy number gain (648 samples evaluated from four datasets) is higher in colorectal cancer compared to other tumor types (Huang, et al. 2015).

Pancreatic cancer

In the rat pancreas RINm5F cell line, Irs2, but not Irs1, phosphorylation was associated with IGF1 stimulated DNA synthesis (Zhang, et al. 1998). Kornmann and colleagues (Kornmann, et al. 1998) reported that IRS2 mRNA and protein were expressed in human pancreatic cancer cell lines (ASPC-1 and COLO-357), and highly expressed in primary pancreatic cancer samples compared with normal pancreatic samples. IGF1 and IGF2 enhanced cell growth, stimulated IRS2 tyrosine phosphorylation and IRS2/PI3K association in ASPC-1 and COLO-357 cells (Kornmann, et al. 1998). In AsPC-1 cell line, IGF1R/IRS2 axis controlled the VEGF transcription, indicating that this axis is an important mediator for tumor angiogenesis (Neid, et al. 2004).

Neuroblastoma

In SH-SY5Y, a human neuroblastoma cell line lacking IRS1, IGF1 stimulation leads to IGF1R activation and IRS2 phosphorylation, and activates PI3K and MAPK signaling (Kim, et al. 1998; Kim, et al. 2004). IRS2 also protects SH-EP and SH-SY5Y neuroblastoma cell lines from glucose-induced apoptosis by activation of PI3K/AKT and MAPK signaling (Kim, et al. 2009; Stohr, et al. 2011).

Hepatocellular carcinoma

Boissan and colleagues (Boissan, et al. 2005) reported an overexpression of IRS2 in murine models of hepatocarcinogenesis. IRS2 mRNA and protein were found to be overexpressed in human hepatoma cell lines and primary human hepatocellular carcinoma specimens (Boissan, et al. 2005; Cantarini, et al. 2006). Of note, inhibition of IRS2 by siRNA resulted in increased apoptosis in the hepatocellular carcinoma Hep3B cells. In the human hepatoma SMMC-7721 cell line, IRS2 silencing suppressed aflatoxin B1-induced PI3K/AKT and MAPK activation and cell migration (Ma, et al. 2012). Rashad and colleagues (Rashad, et al. 2014) observed, in 334 patients and 426 controls, that the D allele and the DD genotype of IRS2 G1057D (rs1805097) polymorphism were significantly associated with hepatocellular carcinoma risk.

Hematological malignancies

IRS2 expression was found to be downregulated in myelodysplastic syndrome patients compared with healthy donors (Machado-Neto, et al. 2012).

Increased IRS2 expression and phosphorylation was observed during erythroid, granulocytic and megakaryocytic differentiation in establish leukemia cell line models (Machado-Neto, et al. 2012). IRS2 was found to be constitutively associated with JAK2 in the JAK2 ^{V617F}-mutated HEL cells, but not in the JAK2 wild type U937 cells (de Melo Campos, et al. 2016). In HEL cells, though not in U937 cells, IRS2 silencing reduced cell viability and increased apoptosis; these effects were enhanced when combined with ruxolitinib, a selective JAK1/2 inhibitor. In addition, $CD34^{+}$ cells from JAK2^{V617F}-mutated myeloproliferative neoplasm patients presented increased IRS2 mRNA levels (de Melo Campos, et al. 2016). Savage and colleagues (Savage, et al. 2015) described IRS2 mutations (S594W and H1328R) in three out of 22 chronic myeloid leukemia patients with tyrosine kinase inhibitors resistance. Expression of each of the two of the IRS2 mutations in Ba/F3 cells demonstrated transformation capacity in the absence of IL3 (Savage, et al. 2015). When co-expressed in Ba/F3 cells with BCR-ABL1, these IRS2 mutants conferred varying degrees of reduced sensitivity to imatinib in vitro (Savage, et al. 2015).

Glioblastoma

In a study focused on PI3K/AKT-related gene expression analysis in glioblastoma involving 103 patients, the IRS2 gene was amplified and overexpressed in 2 cases and IRS2 was also highly expressed in six cases with no demonstrated amplification (Knobbe, et al. 2003). Xu and colleagues (Xu, et al. 2011) identified IRS2 as a target of MicroRNA-153 and suggested that MicroRNA-153 suppressed PI3K/AKT signaling through IRS2 inhibition in the DBTRG-05MG human glioblastoma cell line.

Prostate cancer

Szabolcs and colleagues (Szabolcs, et al. 2009) reported a high expression of IRS2 in prostate cancer cell lines and in primary human prostate cancer samples, in which IRS2 was also correlated with MYC expression in prostate tumor samples. Ibuki et al. (Ibuki, et al. 2014) demonstrated an elevated IRS2 expression by immunohistochemistry in prostate cancer biopsies when compared to normal specimens. The in vitro treatment of LNCaP human prostate cancer cells with NT157, a IRS1/2 inhibitor, resulted in increased apoptosis and decreased cell proliferation (Ibuki, et al. 2014). Huang and colleagues (Huang, et al. 2012) observed that IRS2 rs7986346 polymorphism was associated with disease progression and impaired survival in prostate cancer patients treated with androgen-deprivation.

Thyroid cancer

In the FRTL-5 rat thyroid cell line, the "RET/PTC3 rearrangement" (inv(10)(q11q11) with NCOA4/RET rearrangement), a constitutively activated tyrosine kinase receptor that is frequent in papillary thyroid cancer, induces IRS2 upregulation, and enhances IRS2/PI3K interaction and AKT activation (Miyagi, et al. 2004).

Akker and colleagues (Akker, et al. 2014) observed no association between IRS2 G1057D (rs1805097) polymorphism and differentiated thyroid cancer development in a cohort of 93 differentiated thyroid cancer patients and 111 healthy controls.

Mesothelioma

IRS2 was found to be highly expressed in pleural mesothelioma samples and associated with cell motility in the H2461 cell line (Hoang, et al. 2004).

Clear cell renal cell carcinoma

Using semi-quantitative PCR, Al-Sarraf and colleagues (Al-Sarraf, et al. 2007) investigated IRS1, IRS2 and IRS5 mRNA expression in a cohort of 10 patients with clear cell renal carcinoma, comparing normal adjacent tissue with the respective tumor tissue for the analysis, and found an upregulation of IRS2 and IRS5 mRNA in tumor samples (Al-Sarraf, et al. 2007).

Endometrial cancer

Cayan and colleagues (Cayan, et al. 2010) reported that IRS2 G1057D (rs1805097) polymorphism was associated with the development of endometrial cancer in a cohort of 44 patients with colon cancer and 101 controls.

Malignant peripheral nerve sheath tumor

High expression of IRS2 was observed in malignant peripheral nerve sheath tumor compared to neurofibromas (Shaw, et al. 2012).

IRS2 expression was also associated with reduced survival in malignant peripheral nerve sheath tumors using univariate analysis (Shaw, et al. 2012).

Bladder cancer

Using cDNA microarray analysis, Zekri and colleagues (Zekri, et al. 2015) found IRS2 upregulation among the genes differently expressed identified in bladder cancer.

Lung cancer

Park and colleagues (Park, et al. 2015) identified IRS2 as a MIR146A (MicroRNA-146a) target and suggested that MicroRNA-146a might suppress lung cancer progression by IRS2 inhibition.

Melanoma

In the MDA-MB-435 melanoma cell line, IRS2 signaling was identified as a key mediator of

invasion promoted by α6β4 (Shaw 2001). In A375 human melanoma cells, the in vitro treatment with NT157, a IRS1/2 inhibitor, led to growth suppression of melanoma cells by degradation of IRS1 and IRS2 (Reuveni, et al. 2013). Moreover, NT157 strongly inhibited the development of lung metastases of melanoma cells in mouse models (Reuveni et al, 2013).

Esophageal squamous cell carcinoma

Liu and colleagues (Liu, et al. 2015) identified IRS2 as a target of MicroRNA-146a and suggested that MicroRNA-146a suppressed esophageal squamous cell carcinoma growth through inhibition of IRS2. Corroborating these findings, in the MicroRNA-146a-expressing EC109 esophageal squamous cell carcinoma cell line, IRS2 recovery experiments increased cell growth.

Gastric cancer

Yamashita et al. (Yamashita, et al. 2006) described that IRS2 was methylation-silenced in gastric cancer specimens. Zhao and colleagues (Zhao, et al. 2012), reported that IRS2 G1057D (rs1805097) polymorphism was associated with increased susceptibility for gastric cancer in a cohort of 197 patients with gastric cancer and 156 age- and sex-matched controls.

Oral squamous cell carcinoma

Gao and colleagues (Gao, et al. 2014) described that IRS2 expression was negatively associated with histological differentiation of oral squamous cell carcinoma. In addition, IRS2 inhibition reduces cell proliferation, clonogenicity, cell cycle progression and PI3K/AKT activation in the human oral squamous cell carcinoma Tca-8113 cell line (Gao, et al. 2014).

To be noted

Homozygous absence of the Irs2 gene results in **type II diabetes** and causes female infertility in mice (Burks, et al. 2000; Withers, et al. 1998). In view of the importance of IRS proteins for cancer development and progression, a great effort has been made in an attempt to develop or identify compounds capable of inhibiting signaling mediated by IRS proteins.

In this sense, a unique subfamily of IGF1R signaling inhibitors (NT compounds) has been developed (Reuveni, et al. 2013). NT157, the most characterized NT compound, binds to IGF1R and induces a conformational change, leading to the dissociation of IRS1/2 from the receptor and IRS1/2 degradation by the proteasome. NT157 was found to lead to long-lasting IGF1R inhibition, apoptosis, and present a potent antitumor effects in melanoma cells but not in normal melanocytes (Flashner-Abramson, et al. 2015; Reuveni, et al. 2013), osteosarcoma cells (Garofalo, et al. 2015), prostate adenocarcinoma cells (Ibuki, et al. 2014) and colorectal cancer cells (Sanchez-Lopez, et al. 2015).

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