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ORIGINAL RESEARCH

Distinct signaling properties of IRS-1 and IRS-2 in mediating insulin/IGF-1 action - A review of the evidence

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1. ABSTRACT

The analyzed study examined whether IRS-1 and IRS-2, two proteins that transmit signals from insulin and insulin-like growth factor 1 (IGF-1), produce different intracellular responses. In brown adipose tissue precursor cells obtained from mice, the authors compared normal cells with cells lacking IRS-1 or IRS-2, measuring thousands of chemical protein modifications after stimulation with IGF-1. Approximately 10% of the 6,262 phosphorylation sites detected were found to be regulated by IGF-1, with preferential profiles associated with the presence of each isoform.In section 4.2 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the narrative that IRS-1 and IRS-2 are not fully interchangeable and that their proper balance supports the efficiency of insulin signaling. Independent studies in mice confirm a particularly relevant role for IRS-1 in skeletal muscle and for IRS-2 in the liver and central nervous system. However, the functions of the two proteins partially overlap, and direct evidence in humans remains limited.

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2. ANALYZED STUDY

The research question was whether IRS-1 and IRS-2, adapter proteins that link the insulin and IGF-1 receptors to other intracellular signals, transmit identical or partially different biological instructions. The hypothesis was that the strong structural similarity between the two isoforms did not imply complete functional equivalence.The relevance to paragraph 4.2 of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi lies precisely in this point: the efficiency of the insulin signal depends not only on the generic presence of IRS proteins, but also on the specific isoform available and its ability to activate certain intracellular pathways.The study can demonstrate that, in a murine cell model stimulated with IGF-1, the loss of IRS-1 or IRS-2 is associated with different phosphorylation profiles. However, it cannot directly demonstrate that IRS-1 is predominant in human muscle, that IRS-2 is predominant in the human liver or central nervous system, nor establish clinical consequences such as individual diabetes risk.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The study used murine brown preadipocyte cell lines, which are precursor cells of brown adipose tissue, obtained from normal mice and from mice genetically lacking IRS-1 or IRS-2. The cells were evaluated under basal conditions and after stimulation with IGF-1, a molecule that partially uses the same intracellular mediators as insulin.The authors applied SILAC, a technique that labels proteins with amino acids distinguishable by mass spectrometry, to precisely quantify phosphorylation changes. Phosphorylation is the addition of a phosphate group to a protein; it can modify the protein's activity and therefore the direction of the cellular signal.A phosphoproteomic profiling based on mass spectrometry was performed, which is an extensive analysis of the phosphorylated proteins present in the cells. The authors also used computational predictions to identify the kinases potentially responsible for the observed modifications. The number of biological cultures, exclusion criteria, IGF-1 concentrations, detailed exposure times, and complete statistical methods are not reported in the available material, which consists only of the abstract.

4. RESULTS

The overall result is that IGF-1 did not trigger an indiscriminate response. It selectively modified many proteins involved in signal transduction, and some modifications were more dependent on IRS-1 while others were more dependent on IRS-2.The authors identified 6,262 unique phosphorylation sites. Of these, approximately 10% were found to be regulated by IGF-1 stimulation. Both previously known targets of insulin/IGF-1 signaling and targets not previously described in the context of the study were observed, including Nuclear Factor I X and Semaphorin-4B.Computational analyses indicated protein kinase B, also known as AKT, protein kinase C, and cyclin-dependent kinases as likely mediators of a portion of the phosphorylation events. Notably, the presence of IRS-1 was preferentially associated with signals involving PDHK1, MAPK3, and PKD1; the presence of IRS-2 was preferentially associated with signals involving PIN1 and protein kinase C beta.In simple terms, the two IRS proteins functioned as similar but not identical platforms: following the same stimulus, they favored partially different sets of intracellular messages. The abstract does not report P-values, confidence intervals, percentage variations for each individual site, nor independent functional validations for all identified targets.

5. INTERPRETATION

The biological significance is that the cell does not necessarily use IRS-1 and IRS-2 as two equivalent copies of the same component. The relative availability of the two isoforms can alter which signals are prioritized following the activation of the insulin or IGF-1 receptor.This supports the narrative segment of "The Choice to Live in Health or Illness" by Dr. A. Colonnese and R. Panzironi, which states that the correct balance, tissue-specific expression, and functional integrity of IRS isoforms contribute to the efficiency of insulin signaling. The publication subject to the Review of evidence directly documents, above all, the non-equivalence of the downstream signals of the two proteins, not their distribution in various organs.The observed difference concerns murine brown adipose cells and stimulation with IGF-1. It is therefore mechanistic evidence, useful for understanding how different functions can emerge,

but not a clinical demonstration in humans. Furthermore, the predictions regarding kinases are computer-generated indications and require targeted experimental confirmation.

6. INDEPENDENT SUPPORTING EVIDENCE

Initial independent confirmation concerns skeletal muscle. In mice lacking IRS-1, insulin stimulation resulted in reduced PI3-kinase activation, glucose transport, and protein synthesis in the muscle. In the liver of the same animals, however, the activation of PI3-kinase and the MAPK pathway was not significantly reduced. The authors also observed that IRS-2 phosphorylation in the liver was approximately equal to that of IRS-1 in normal mice, whereas in the muscle, the IRS-2 signal was only 20-30% of that of IRS-1. This animal study directly supports the claim that IRS-1 plays a primary role in muscle insulin signaling and shows that compensation by IRS-2 is tissue-dependent [1].A second study in mice evaluated the absence of IRS-2. Animals lacking IRS-2 progressively developed type 2 diabetes and showed insulin resistance with a defect in insulin-induced signaling in the liver, but not in skeletal muscle. At six weeks, pancreatic beta-cell mass was reduced to 83% compared to normal mice. This evidence confirms that IRS-2 has physiological functions that are not overlapping with those of IRS-1 and links its hepatic activity to the maintenance of glucose homeostasis [2].The reference to the central nervous system is supported by a mouse model with selective reduction of IRS-2 in pancreatic beta cells and in brain regions including the hypothalamus. Irs2 expression was reduced by approximately 90% in pancreatic islets and markedly reduced in the hypothalamic arcuate nucleus, with no differences detected in the liver, muscle, or adipose tissue. The animals developed obesity, peripheral insulin resistance, and diabetes. The study does not prove that IRS-2 is the only important protein in the central nervous system, but it confirms that its alteration in this area can have systemic metabolic consequences [3].Taken together, these studies are independent of the analyzed publication and build a coherent chain: distinct signaling profiles in cells, a major role for IRS-1 in muscle, a significant role for IRS-2 in the liver, and specific functions of IRS-2 in the brain-pancreas axis. The main common limitation is that these are primarily experiments in rodents or cells, with the possibility of biological compensations that do not fully replicate human physiology.

7. CONFLICTING EVIDENCE

The distinction between muscular IRS-1 and hepatic IRS-2 should not be interpreted as an absolute separation. In a hyperinsulinemic-euglycemic clamp experiment—a procedure that maintains stable glycemia while measuring the response to insulin—mice lacking IRS-1 and mice lacking IRS-2 both showed a reduction in insulin-stimulated whole-body glucose utilization. In mice lacking IRS-2, peripheral glucose utilization, the suppression of endogenous glucose production, and glycogen synthesis in the liver were also reduced [4].These results do not negate the existence of differentiated roles. However, they indicate that IRS-2 also influences muscle and adipose tissue and that its function depends on the physiological context being studied. Consequently, the statement in the book is sustainable if read as a relative predominance of functions, rather than an absolute exclusivity of IRS-1 in muscle or IRS-2 in the liver and central nervous system.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the original study, which documents differentiated intracellular signals, from independent research that contextualizes their significance across different tissues.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Cellular and phosphoproteomic	Normal mouse brown preadipocytes, IRS-1-deficient or IRS-2-deficient	IGF-1 regulated approximately 10% of 6,262 phosphorylation sites, with preferential profiles dependent on IRS-1 or IRS-2.	direct confirmation	moderate
[1]	Animal with genetic knockout	IRS-1-deficient mice; muscle and liver analysis	The absence of IRS-1 reduced glucose transport and other insulin signals in muscle, with greater compensation by IRS-2 in the liver.	direct confirmation	moderate
[2]	Animal with genetic knockout	IRS-2-deficient mice	The absence of IRS-2 caused hepatic insulin signaling defects, reduced beta-cell mass, and progressive diabetes.	direct confirmation	moderate
[3]	Animal with tissue-specific alteration	Mice with reduced IRS-2 in beta cells and hypothalamus	Reduced IRS-2 in the brain-pancreas axis was associated with obesity, insulin resistance, and diabetes.	indirect confirmation	moderate
[4]	Animal with genetic knockout and metabolic clamp	IRS-1 or IRS-2-deficient mice	The absence of IRS-2 also reduced peripheral glucose utilization, in addition to impairing hepatic functions.	discordant evidence	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The study analyzed clearly supports, at the cellular level, that IRS-1 and IRS-2 can direct different signals following stimulation with IGF-1. This is consistent with their role as platforms that help the cell select its response to insulin.Independent evidence in rodents confirms that IRS-1 plays a particularly important role in skeletal muscle and that IRS-2 has relevant functions in the liver, pancreatic beta cells, and the central nervous system. This distinction is not absolute, as both isoforms contribute in part to multiple tissues and metabolic processes.The book's narrative is therefore well-supported at the mechanistic and animal level, but requires further direct validation in humans to define the extent to which the differences between IRS-1 and IRS-2 contribute to individual metabolic health and metabolic diseases.

Aggiornato al 17/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.

To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

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