Insulin Desensitization Caused by Obesity-Induced Inflammation of Adipose Tissue

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Introduction

Type 2 diabetes is the major metabolic disorder; it is caused by impaired insulin secretion and resistance to the effects of insulin, both taking place at the same time.

In obese individuals, adipose tissue inflammation is known to play a key role in the development of insulin resistance since it promotes the activation of different molecules (JNK, ERK, SOCS, MAPKs) due to the elevated concentrations of free fatty acids, to the production of numerous cytokines (mainly: TNF-α, IL-6 and IL-1β) and to the increased population of pro-inflammatory macrophages (M1). The activated molecules induce the expression of more inflammatory cytokines and produce the inactivation of insulin signalling.

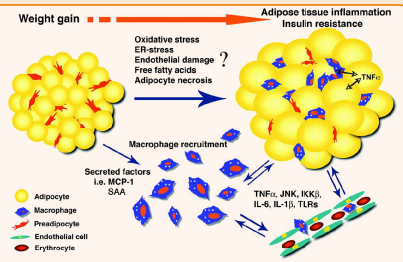

Figure 1: Obese adipose tissue expansion, resultant inflammation and metabolic dysregulation [1].

Insulin receptor and insulin receptor substrate

1. **Insulin-IR** interaction → IR autophosphorylation of Tyr960.
2. **IR-IRS** interaction → signalling cascade initiation.

Regulation of IRS-1 (most defects): it has multiple phosphorylation sites → phosphorylation pattern.

- Positive sites: tyrosine resides. Normally phosphorylated first.
- Negative sites: serine residues. If phosphorylated first → insulin signalling inhibition.
  - Near interaction site with IR.
  - Near interaction site for PI3K (IRS substrate).

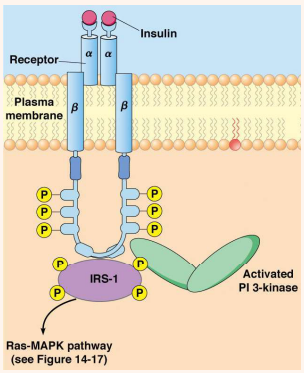

Figure 2: IR-IRS interaction [2].

Cytokines

- **TNF-α:** pro-inflammatory cytokine produced mainly by macrophages.
  - Overexpressed in obese adipose tissue → JNK activation → inhibition of IRS-1 expression
  - TNF-α neutralization → insulin sensitivity is partially improved.
- **IL-6:** produced by many cell types, including adipose tissue, which also is a target for the cytokine.
  - Expression increased with obesity → insulin signalling is altered.
  - Insulin signalling inhibition → beginning of the signal (IR-IRS interaction) → signal transduction (activation of Akt/PKB)
  - Altered SOCS expression.
  - IRS-1 serine phosphorylation is not induced.
- **IL-1β**: induces the activation of different kinases.
  - Increased expression during obesity → insulin resistance → decreased IRS-1 expression → impaired glucose uptake

Suppression of insulin signalling

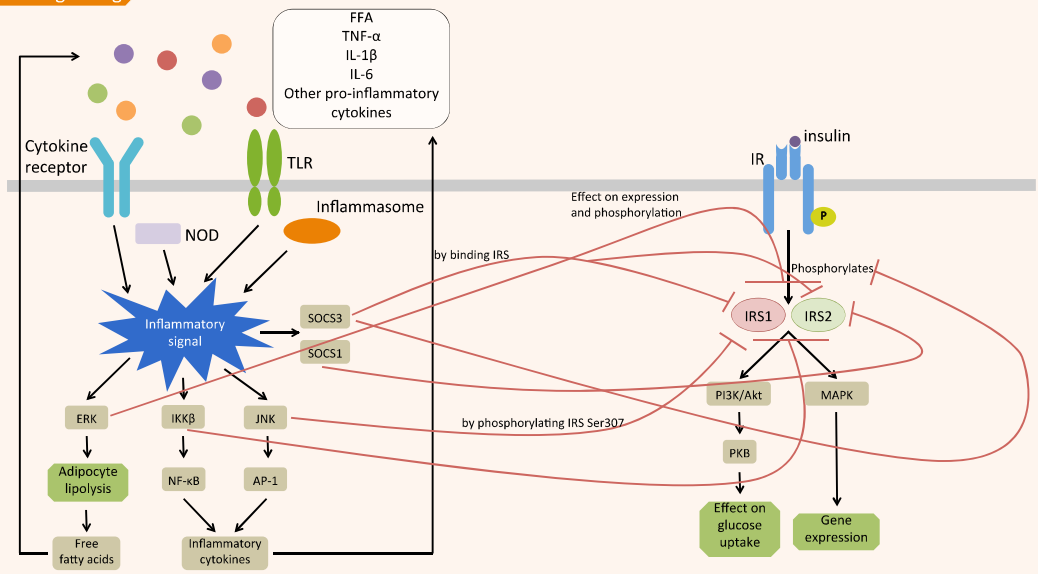

Figure 3: Representation of all the processes mentioned that inhibit insulin signalling

Suppressor of cytokine signalling (SOCS) family proteins are induced by inflammatory cytokines and stop their action by interacting with signal mediator tyrosine kinases (such as JAK). They are upregulated in obese insulin resistant mice and inhibit IR interaction with IRS since it interacts with an important region for IRS recognition; it can also inhibit IRS phosphorylation instead and bind to both IRS-1 and 2 targeting them for degradation.

C-Jun amino-terminal kinases (JNK) and **IκB kinase β** (IKKβ), activated during the inflammatory state, induce the production of the transcription factors NF-κB and AP-1 amplifying the inflammatory signal. They also participate in the phosphorylation of IRS-1 Ser307, close to the IR binding domain, which prevents it from binding to the IR. Although deletion of IKKβ or NF-κB doesn't completely solve insulin resistance, mice with this genotype show ameliorated insulin sensitivity, reduced adiposity and partial resistance against obesity.

Extracellular signal-regulated kinases (ERK) have increased activity in adipose tissue and muscle of obese patients with type 2 diabetes. It is mainly induced by IL-1β and leads to downregulation of IRS-1 expression, IRS-1 serine phosphorylation and stimulation of adipocyte lipolysis that results in the release of free fatty acids (FFA).

Conclusion

The implication of adipose tissue inflammation in the development of obesity-induced insulin resistance opens a wide field of investigation toward the determination of the sequence of events that take place.

Currently, the role of some inflammatory receptors and mediators is known, such as TLR, inflammasome, NOD, TNF-α, IL-6, IL-1β, among others. Their action affects the activation of some kinases that impair insulin signalling leading to insulin resistance.

For future progress, the aim is set in identifying and characterising all the elements involved in order to be able to develop possible therapies to prevent obesity and insulin resistance.

References

[1] Gustafson, B., Hammarstedt, A., Andersson, C. X., & Smith, U. (2007). Inflamed adipose tissue: a culprit underlying the metabolic syndrome and atherosclerosis. *Arteriosclerosis, Thrombosis, and Vascular Biology*, *27*(11), 2276–83.

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