Diabetes

Guide to molecular pathways in the pathogenesis of Type 2 Diabetes

INTRODUCTION

Welcome to the Type 2 Diabetes Booklet, a document that helps scientists and researchers appreciate and navigate the diversity of the molecular pathways associated with the development Type 2 Diabetes. As the disease continues to impact the lives of an ever-growing number of people worldwide, Revvity shares your commitment to eradicating the global diabetes epidemic.

Diabetes mellitus is a complex disease, increasingly recognized as a heterogeneous condition. The collection of molecular pathways presented in the document was prepared based on authentic and highly regarded articles and journals. All pathways have been curated for scientific knowledge and accuracy by Revvity's scientific team. Due to the expertise of its creators, you will find this document to be more than just a compiled and curated list of molecular pathways. This document is organized around the organs affected or contributing to Type 2 Diabetes. Hence you will find sections dedicated to the pathophysiological role of Muscle cell, adipocytes, hepatocyte, pancreatic α and β cell as well as intestinal L-cell.

Our goal is to speed up and simplify your investigations by providing a complete portfolio of assays, so you can research multiple targets and pathways using the same simple detection protocol.

Easy to use GPCRs, kinases and cytokines, or hormones are available for anything from target identification to screening to preclinical sample testing. At the end of the document you will find a series of application notes and scientific documents, illustrating the use of the Revvity HTRF products in diabetes research.

TABLE OF CONTENTS

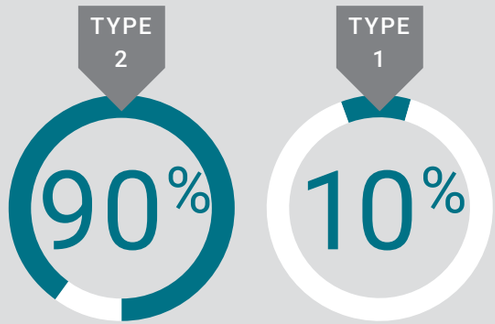
Diabetes in numbers

FIVE DIABETES-RELATED TARGET ORGANS

1

ONE TECHNOLOGY PLATFORM FOR FASTER, SIMPLER RESEARCH

PERCENTAGE OF TYPE 2 VERSUS TYPE 1 DIABETES CASES WORLDWIDE



80% OF PEOPLE WITH DIABETES LIVE IN LOW- AND MIDDLE-INCOME COUNTRIES

NUMBER OF PEOPLE WORLDWIDE CURRENTLY LIVING WITH DIABETES

425,000,000

2X

EXPECTED INCREASE IN ANNUAL DEATHS FROM DIABETES BETWEEN 2005 AND 2030

TABLE OF CONTENTS

revvity

Diabetes in numbers

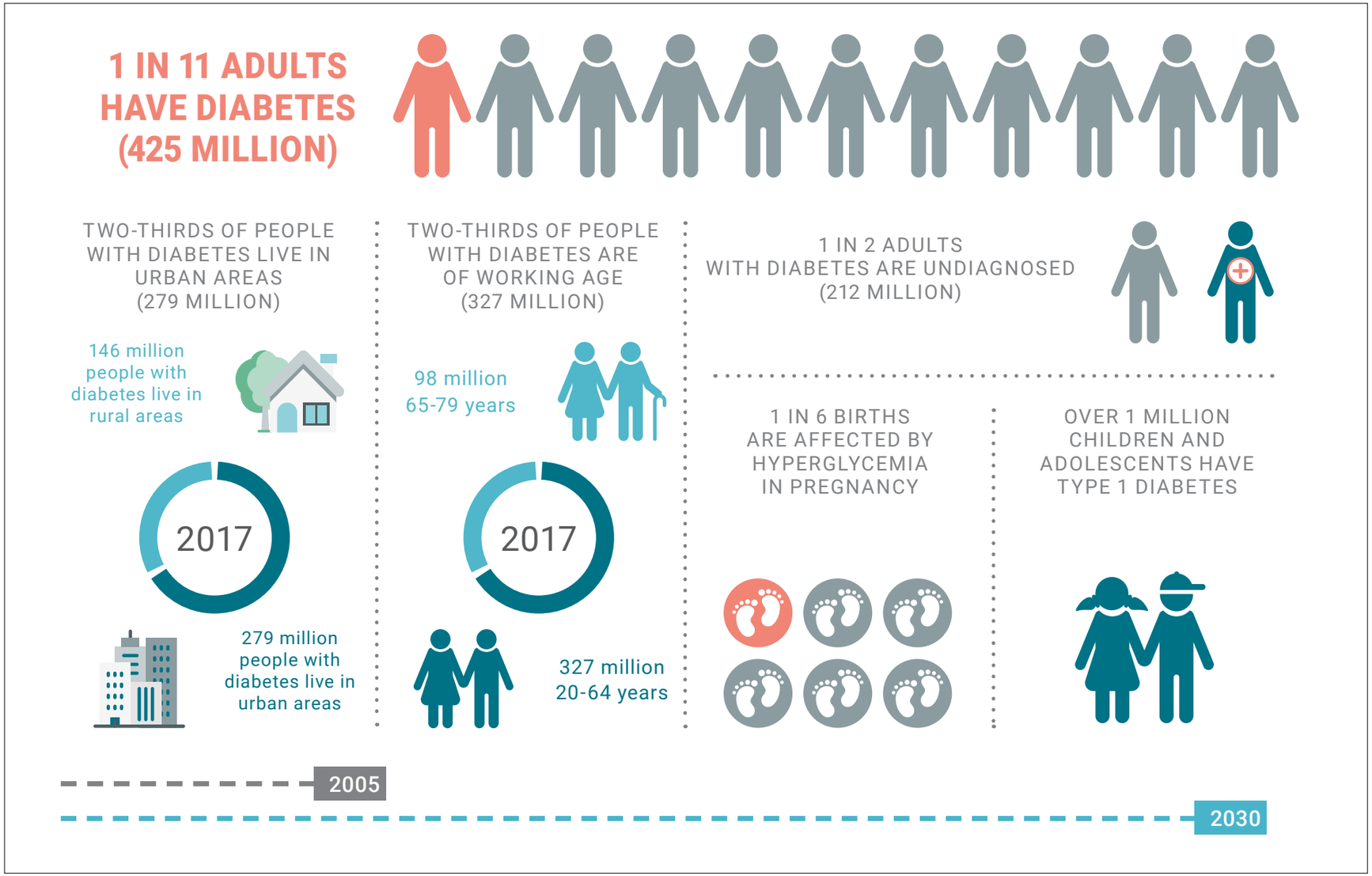


TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS

The 5 diabetes-related organs

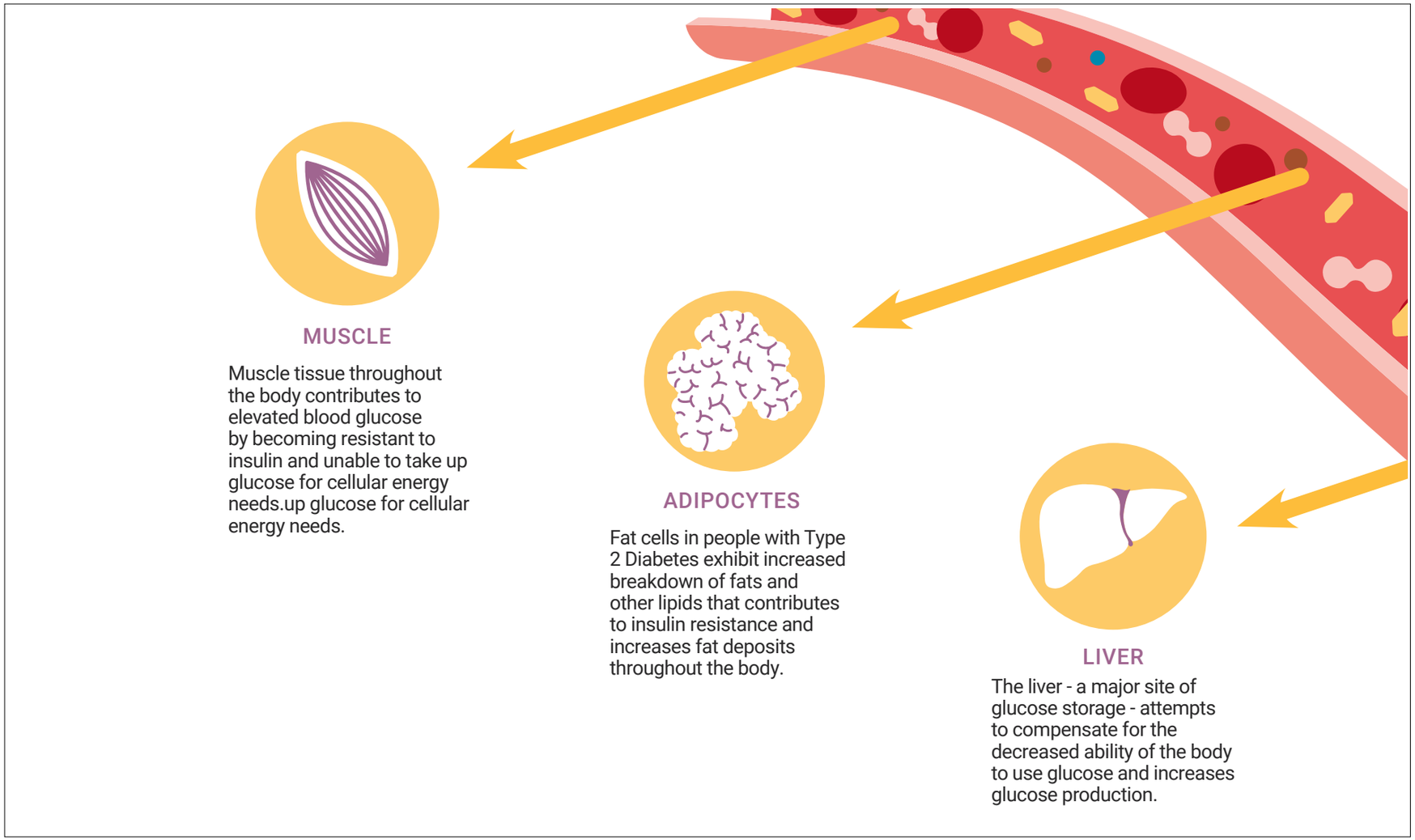


TABLE OF CONTENTS

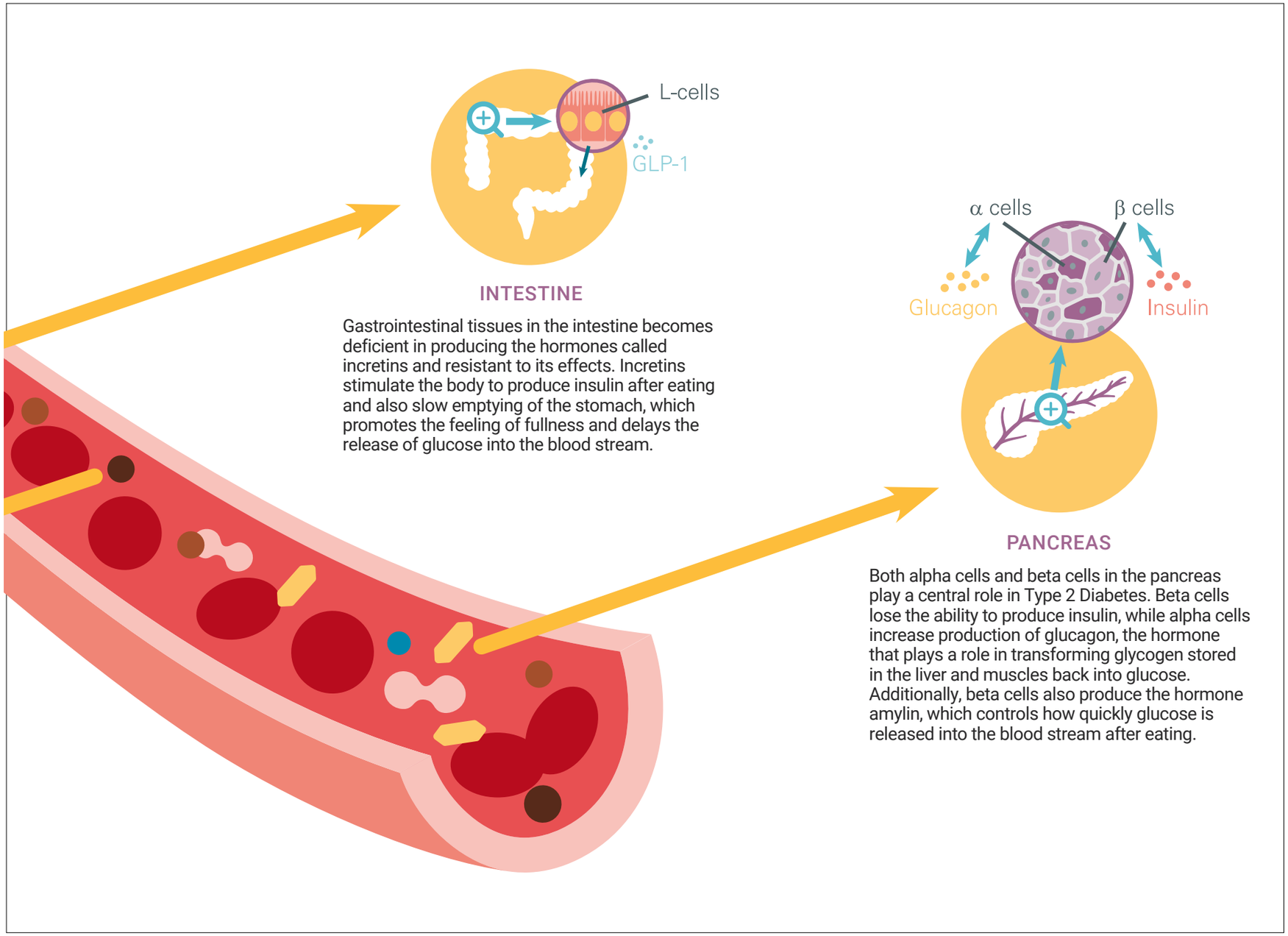


TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS

Muscles

Muscle Cell Pathway

Insulin stimulation leads to its receptor auto-phosphorylation followed by phosphorylation of IRS1/2 and signaling via the PI3K pathway. Subsequent phosphorylation of AKT results in GLUT4 translocation to the cellular membrane and greater glucose uptake, glycogen synthesis by phosphorylation of GSK-3 and protein synthesis by phosphorylation of S6RP and EIF4e. In addition to signaling via PI3K, insulin can activate the mitogen-activated protein (MAP) kinase, ERK, leading to gene expression and modulation of both proliferation and differentiation processes.

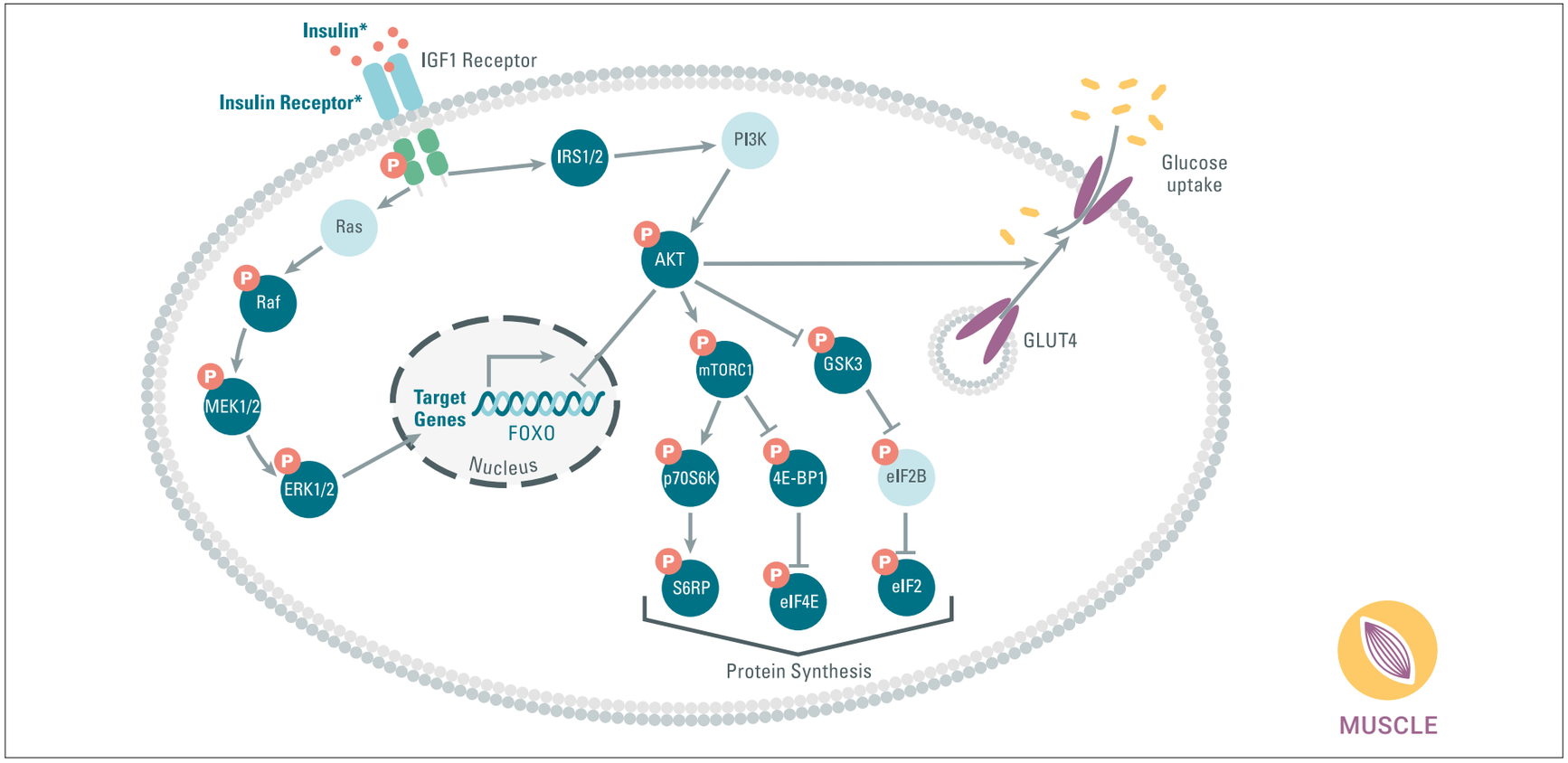


TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS

Adipocytes

Adipocytes: healthy pathway

Insulin drives:

- Glucose uptake by the activation of PI3K/AKT pathway
- Cell proliferation through MAPK pathway
- Protein synthesis through the activation of the transduction machinery.

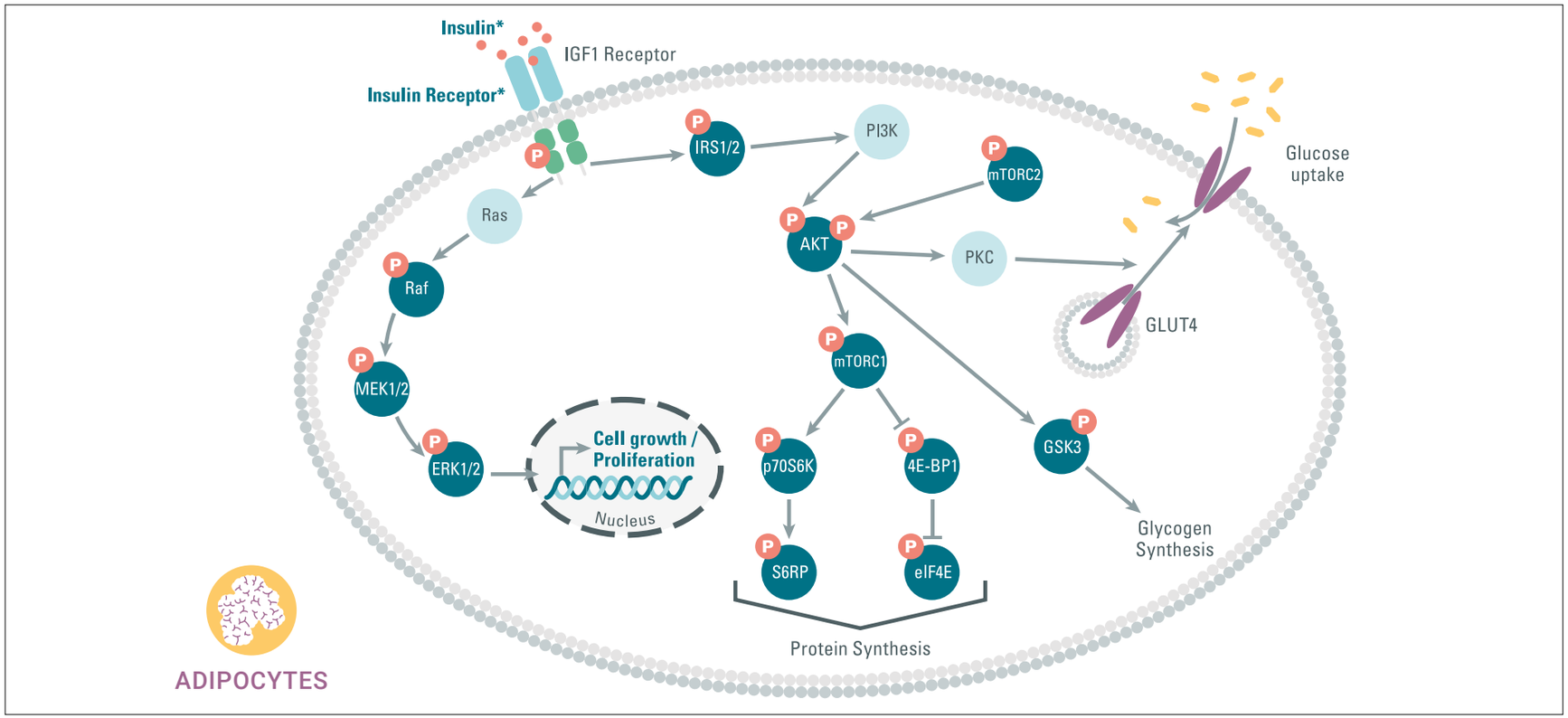


TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS

Adipocytes

Adipocytes: Inflammation pathway

In Type 2 Diabetes (T2D), inflammation induced by activated macrophages may lead to insulin resistance by:

- Inactivation of IRS1 by NFkB/JNK pathways
- Decrease of PI3K/AKT signaling
- Decrease of glucose uptake.

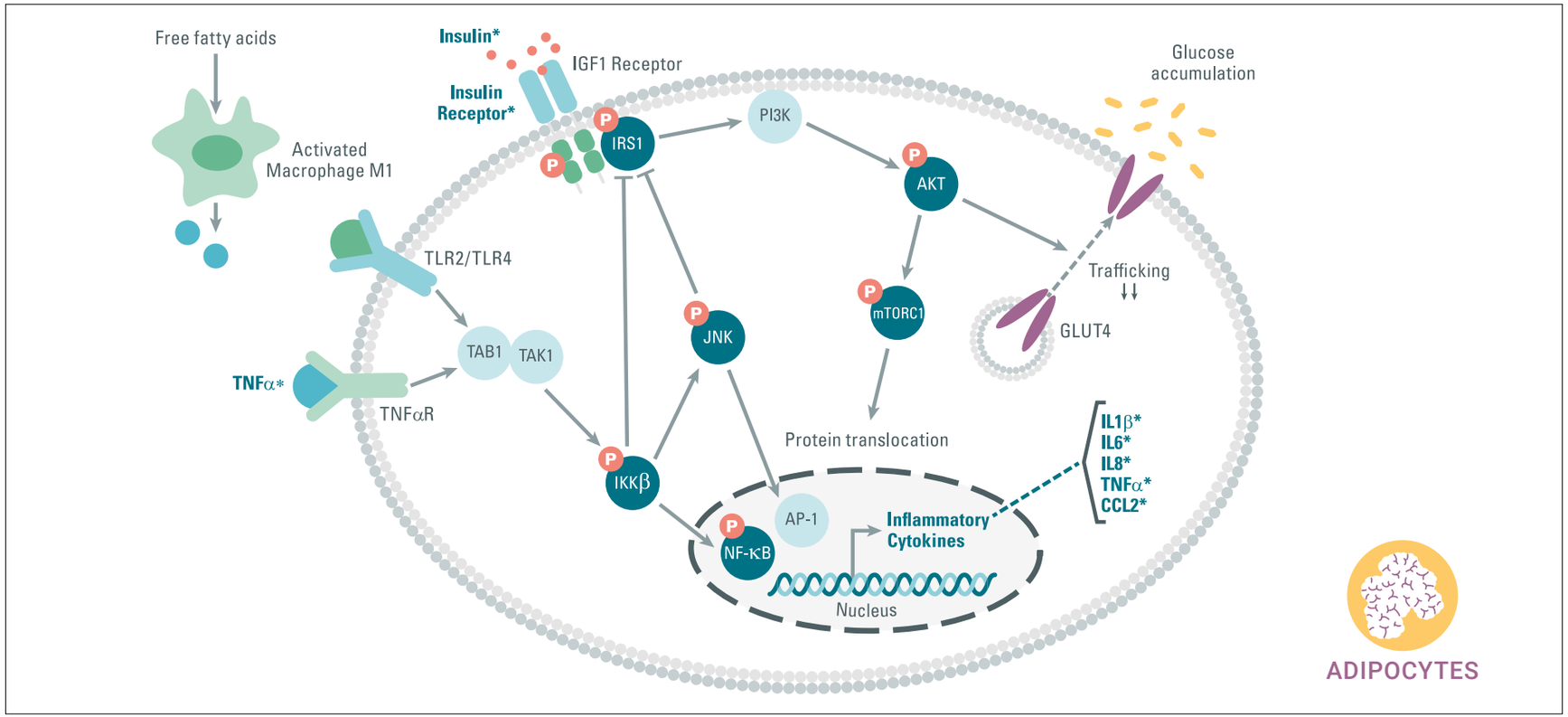


TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS

Liver

Liver - Hepatocyte pathway

Glucagon stimulation leads to Gq recruitment to the receptor followed by production of IP-3, IP-1 and activation of the endoplasmic reticulum calcium release channel. Glucagon stimulation also results in cAMP production and ultimately CREB phosphorylation by recruitment of Gαs to the receptor.

Activation of the Gαs pathway is responsible for increased glycolysis and gluconeogenesis and decreased glycogenolysis and glucogenesis. Insulin stimulation leads to its receptor auto-phosphorylation followed by phosphorylation of IRS1/2 and signaling via the PI3K pathway. Subsequent phosphorylation of AKT leads to decreased glycogenolysis, gluconeogenesis and increased glycolysis and glucogenesis.

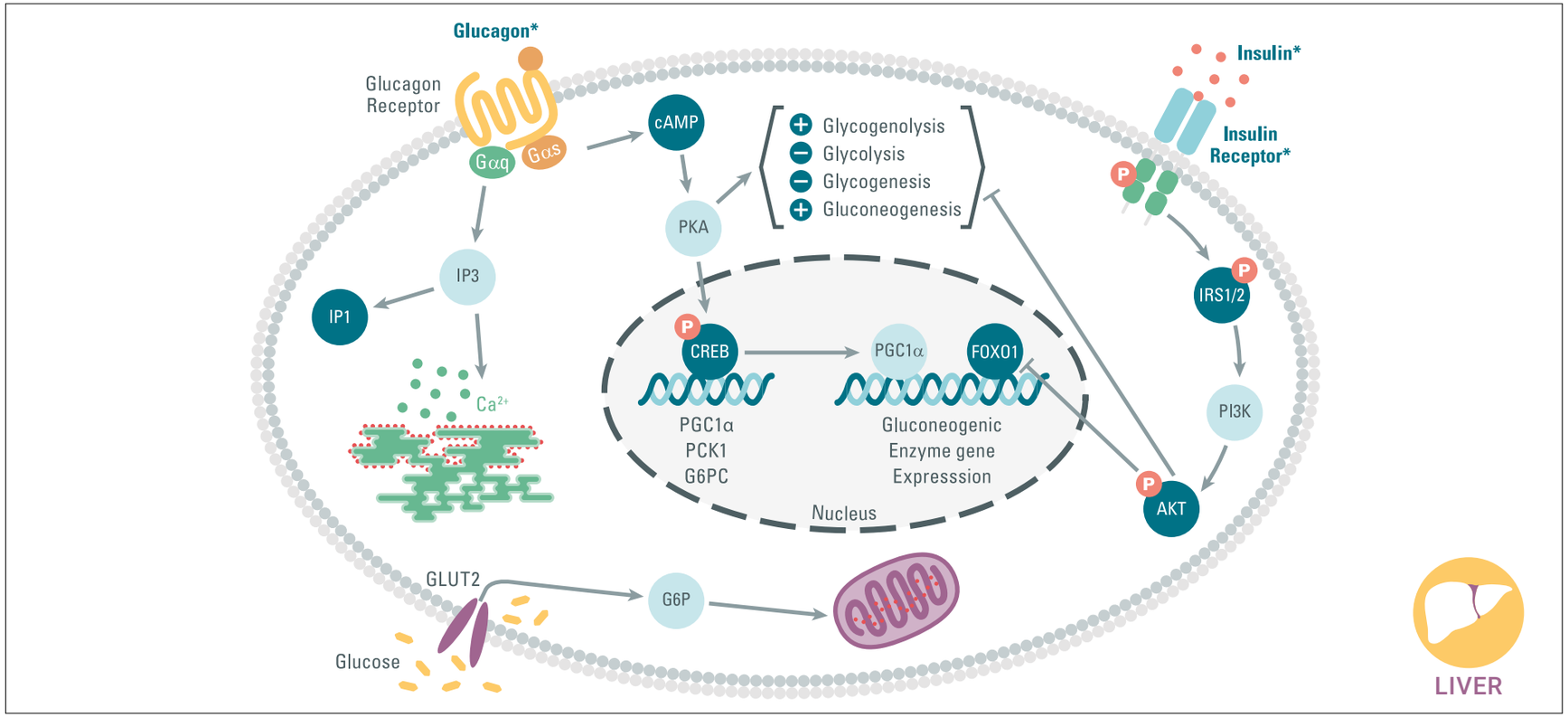


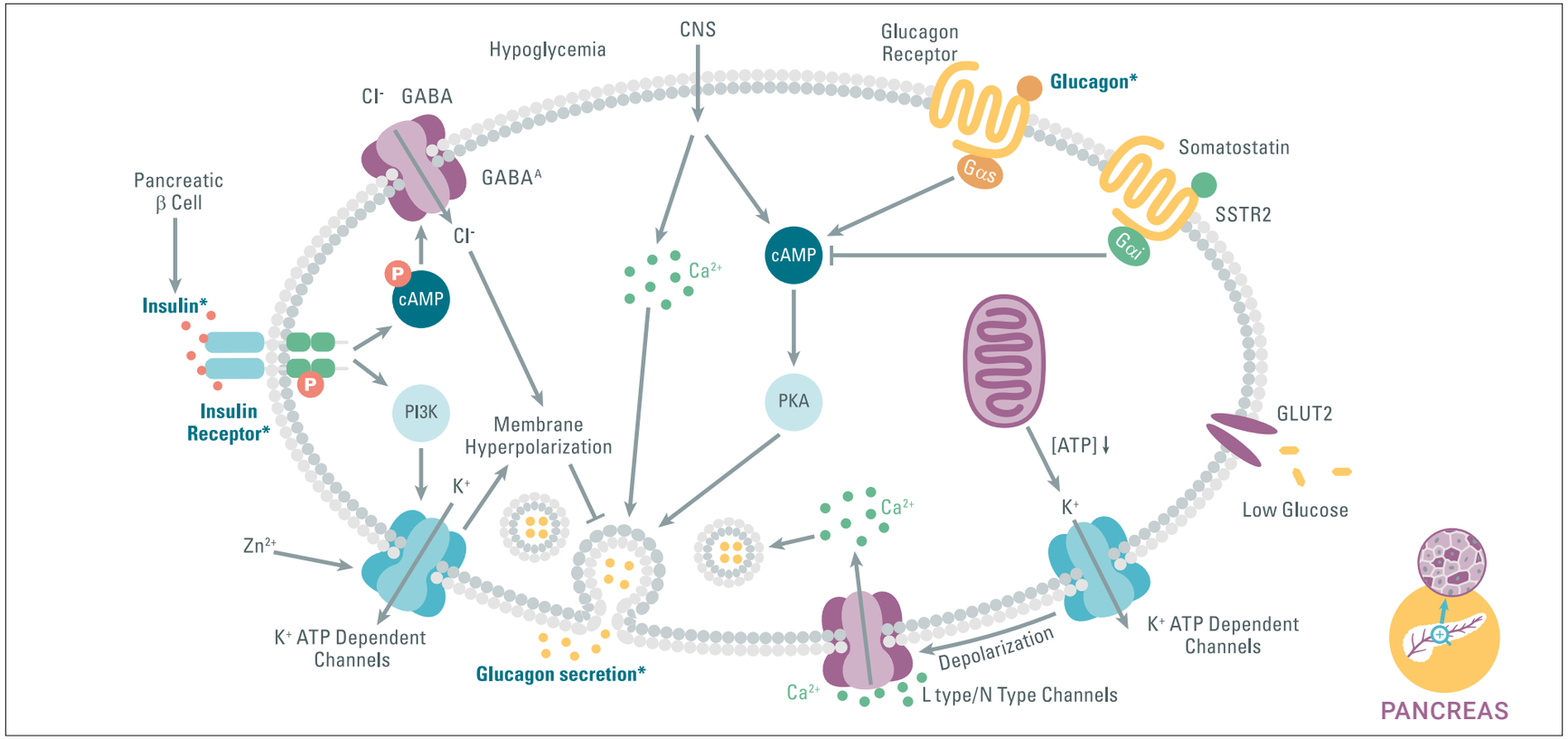
TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS
Pancreas

Pancreatic α cell pathway

Low blood glucose levels (hypoglycemia) trigger Ca^{2+} entry in alpha-cells and increase of intracellular cAMP level, leading to exocytosis of glucagon containing granules. Glucagon binds its own receptor and positively regulates its secretion through cAMP production.

- High blood glucose levels inhibit glucagon secretion through the inactivation of Ca^{2+} channels. Insulin negatively regulates glucagon secretion by activating the PI3K/AKT pathway leading to membrane hyperpolarization. Somatostatin also acts negatively through its receptor by inhibiting cAMP production.



DIABETES MOLECULAR PATHWAYS

Pancreas

Pancreatic β cell pathway: Insulin secretion

High blood glucose levels trigger Ca^{2+} entry in beta-cells. Ca^{2+} drives cAMP production and phosphorylation of ERK1/2 and CREB, leading to insulin gene transcription and secretion. The incretin hormones GLP-1 & GIP increase glucose-mediated insulin secretion through binding to their specific Gs protein-coupled receptor and induction of cAMP production.

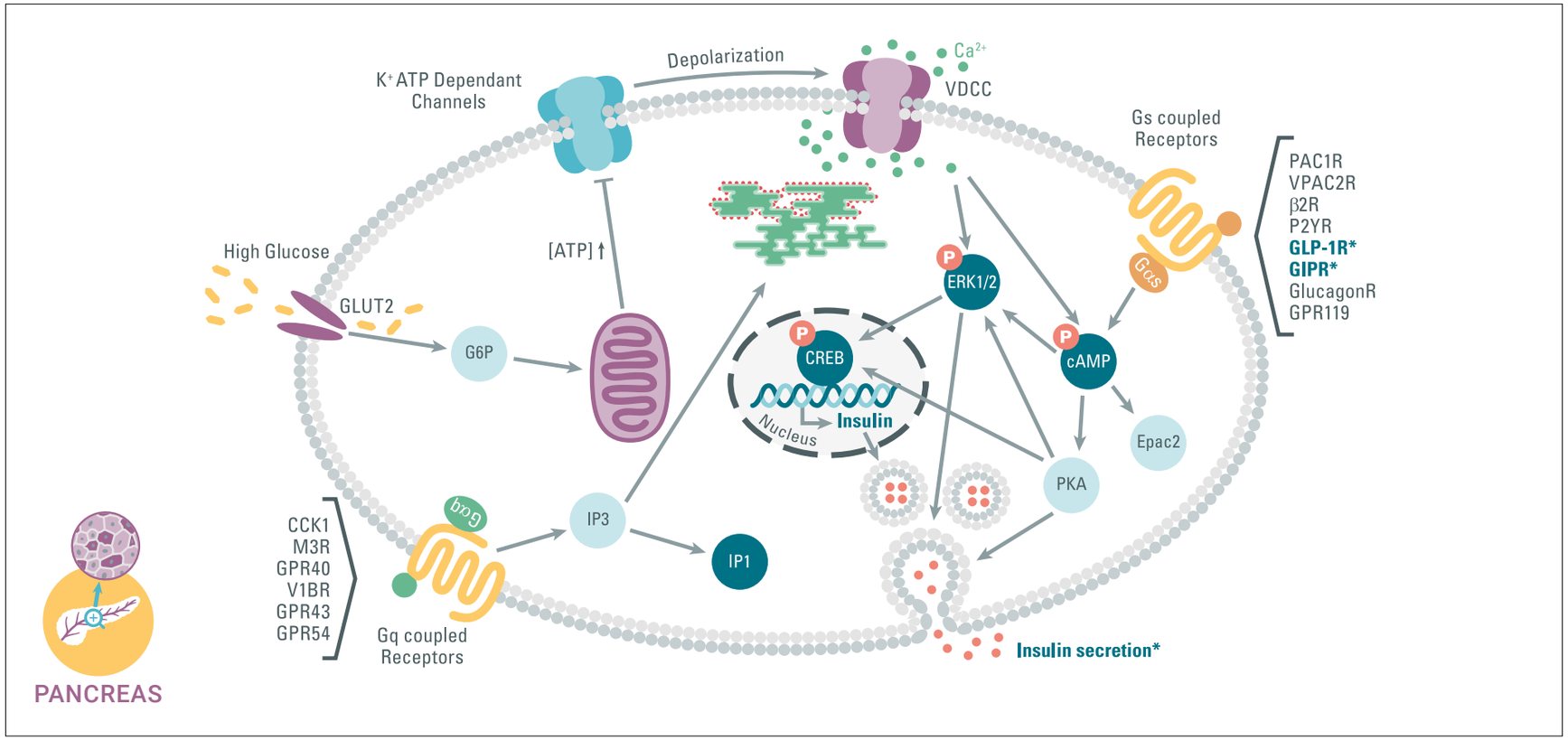


TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS

Pancreas

Pancreatic β cell pathway: survival / proliferation

Beta-cell growth and survival is regulated by multiple stimuli including nutrients, hormones and growth factors:

- Glucose acts through the ERK/CREB and cAMP pathways to induce IRS gene transcription and activation
- Insulin secreted by beta-cells and IGF-1 bind their own receptors that phosphorylate IRS1/2 which in turn activates the PI3K/AKT/mTOR pathway, leading to cell proliferation and protein synthesis
- Activated GLP-1 and GIP receptors also have anti-apoptotic and proliferative effects through cAMP production and ERK/CREB activation pathway
- GLP-1 also activates EGFR which amplifies the PI3K/AKT/mTOR pathway.

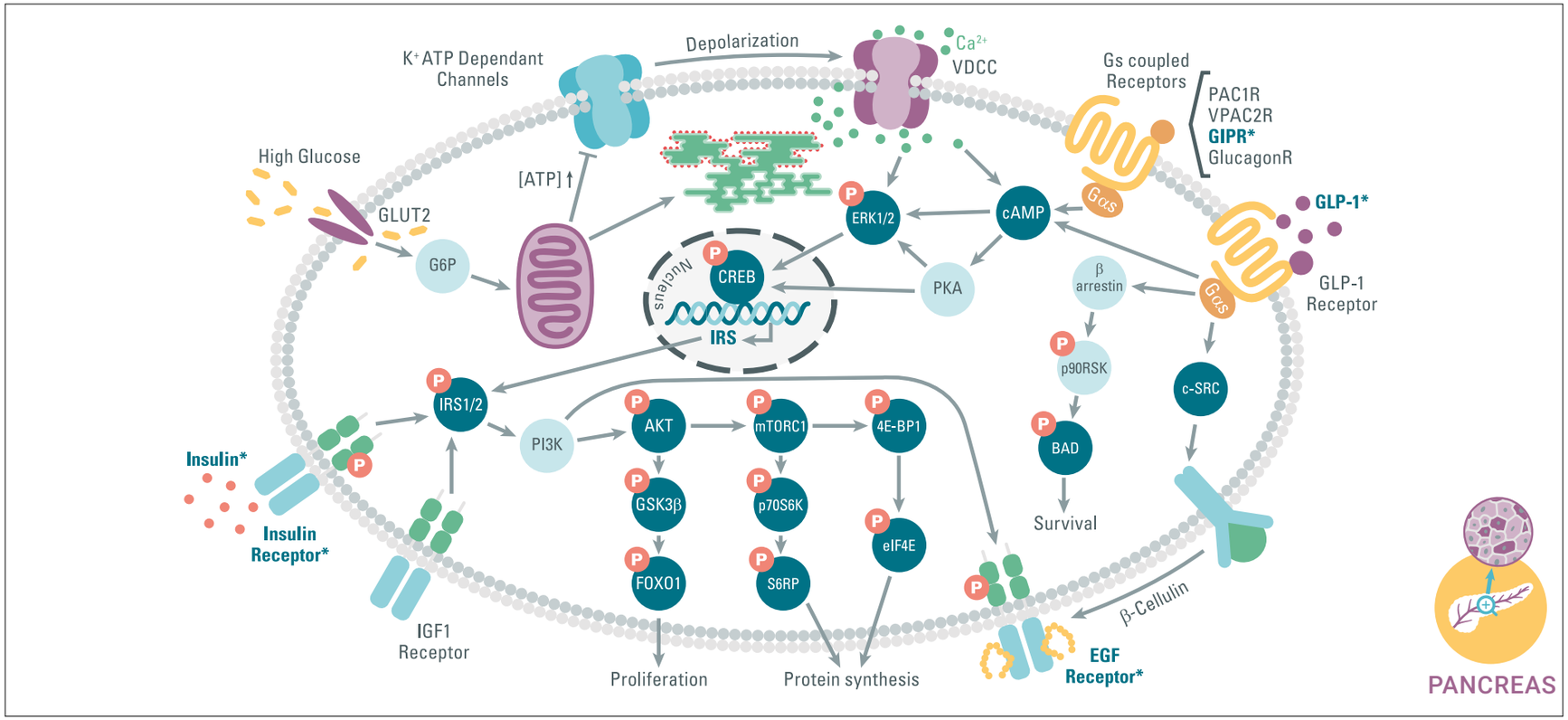


TABLE OF CONTENTS

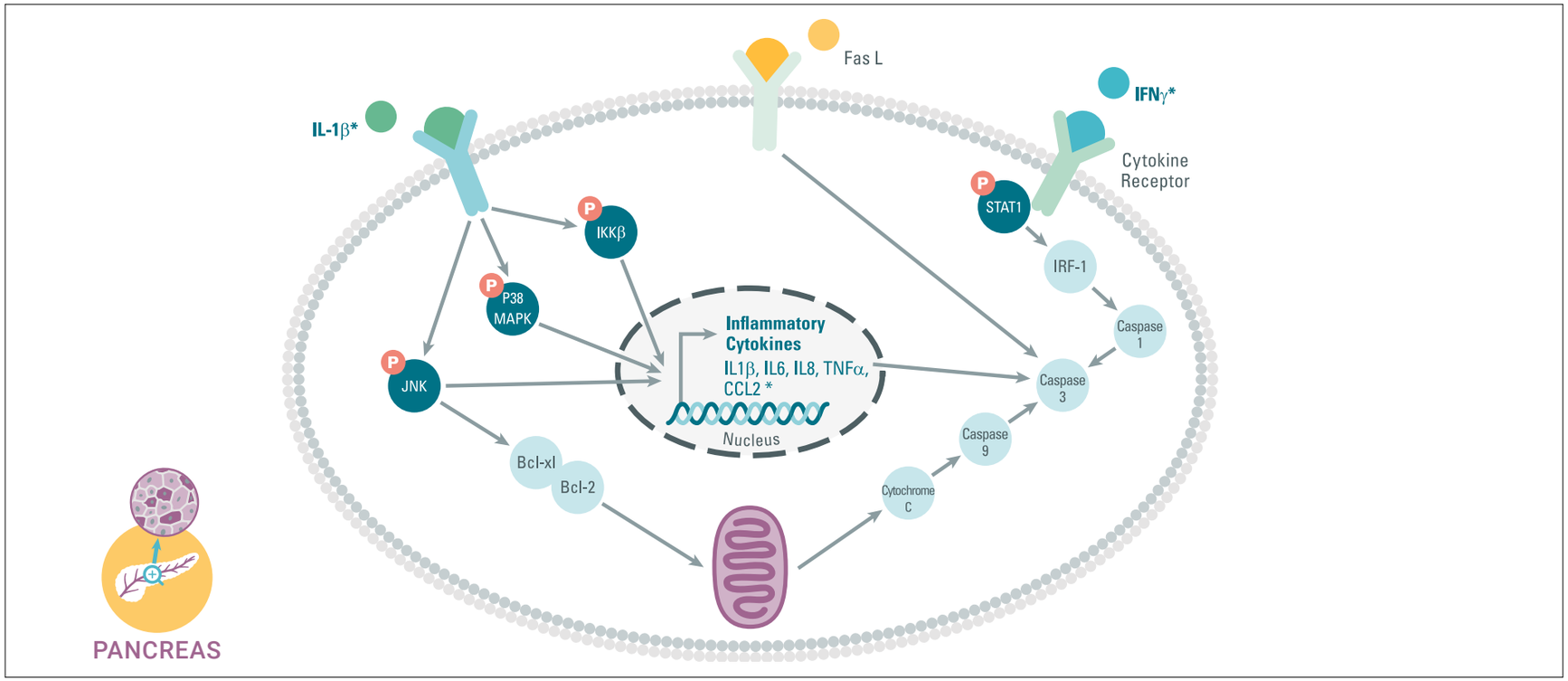
DIABETES MOLECULAR PATHWAYS

Pancreas

Pancreatic β cell pathway, inflammation in Type 1 Diabetes (T1D)

In T1D infiltrating immune cells (macrophages and T-cells) secrete pro-inflammatory cytokines (IL-1beta and IFN-gamma) and activate Fas receptors, leading to beta-cell dysfunction (loss of insulin production) and apoptosis.

- IL-1beta activates the stress and inflammatory signaling pathways JNK, p38 MAPK and NFKb that control numerous genes involved in beta-cell function, inflammation, stress responses and apoptosis.
- IFN-gamma specifically activates STAT1 that is an important regulator of genes mediating stress and apoptotic pathways.
- Apoptosis is orchestrated by the caspase family of proteases.



DIABETES MOLECULAR PATHWAYS

Pancreas

Pancreatic β cell pathway, inflammation in Type 2 Diabetes (T2D)

In T2D, glucolipotoxicity or hyperglycemia induces beta-cells dysfunction by activation of inflammatory signaling pathways.

- Pro-inflammatory IL-1beta cytokine release
- Toll-like receptors activation mediating chemokine release
- M1 macrophage recruitment.

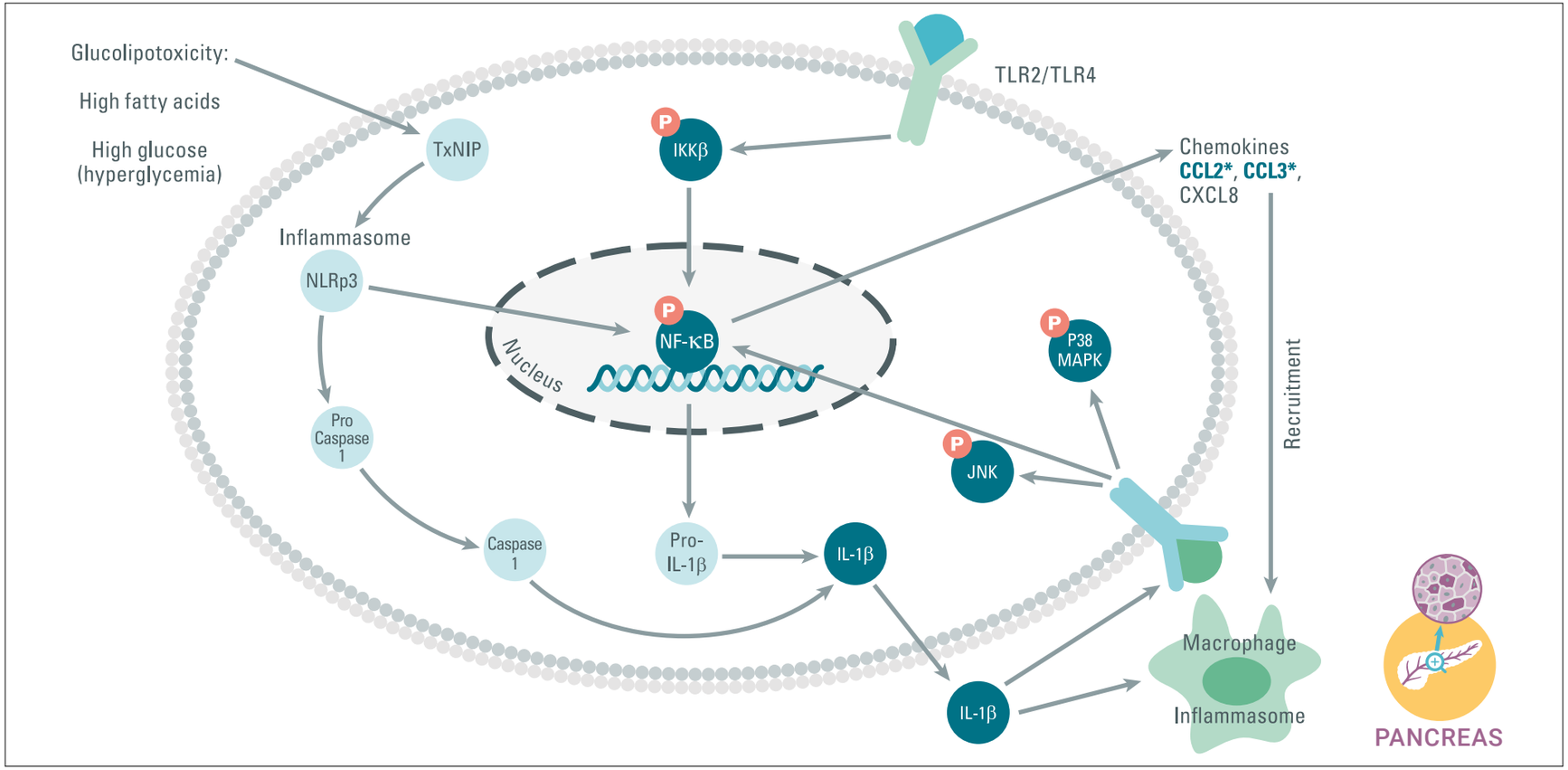


TABLE OF CONTENTS

DIABETES MOLECULAR PATHWAYS
Intestine

Intestinal L-cell pathway

In L cells, rising blood glucose levels trigger Ca^{2+} entry in L-cells leading to GLP-1 secretion. GRP, GPR120, GPR49 are potent stimulators of GLP-1 secretion in L-cells. Stimulation of these receptors leads to recruitment and binding of Gq protein followed by production of IP-3, IP-1 and activation of the endoplasmic reticulum calcium release channel. GIPR, GPR110 and TGR5 stimulate the activation of adenylyl cyclase through Gαs recruitment, resulting in increases in cAMP and ultimately GLP-1 release. SST5R opposes the effect of these receptors by recruitment of a Gi and inhibition of adenylyl cyclase.

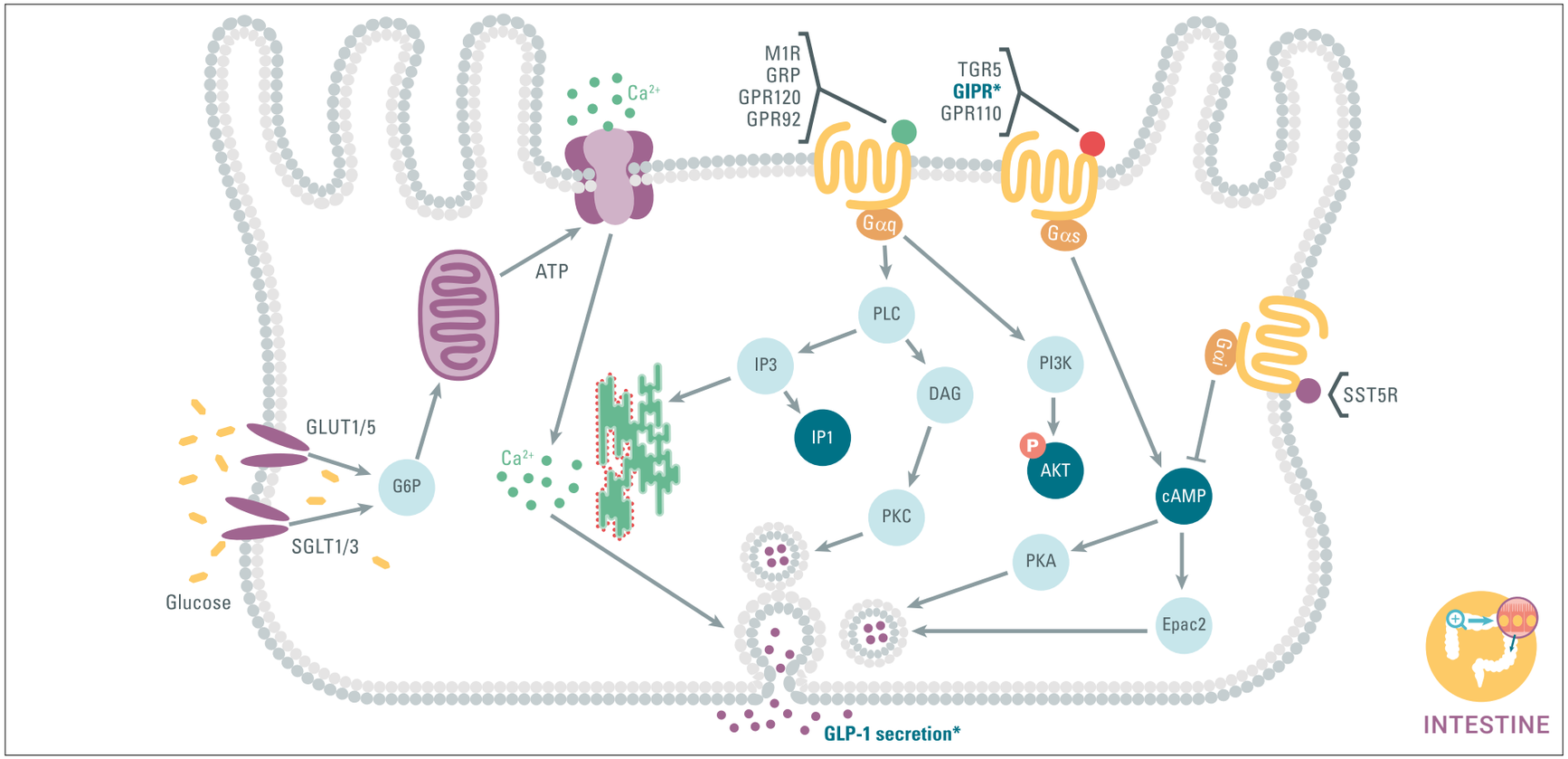


TABLE OF CONTENTS

APPLICATIONS

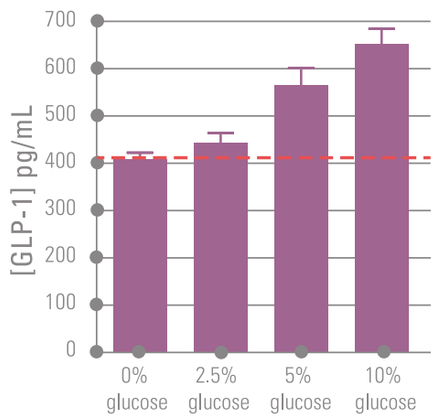
Kits, reagents, and services

Every day, Revvity invests in Diabetes research in order to offer you many solutions to investigate each step of the disease development.

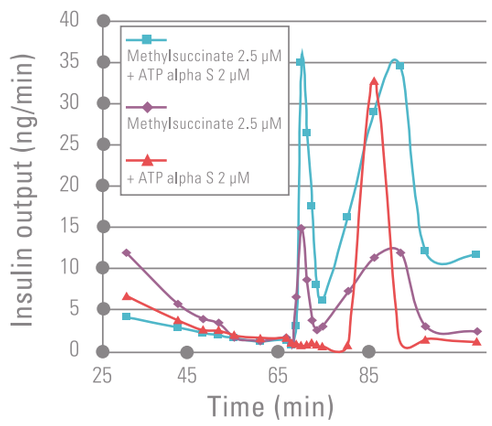
No matter what your area of investigation, Revvity assays can accelerate and simplify your day-to-day work. They have a long history of performance and validation on your cell line for added confidence in your results.

Highly validated on relevant diabetes models.

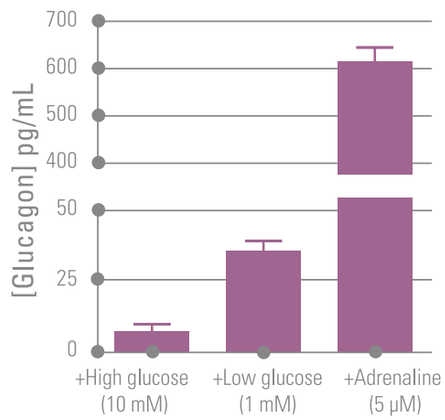
PRODUCT LIST: Active GLP-1 Kit, Glucagon kit, Insulin kit



A GLP-1 secretion assay on human intestinal L-cells



B Insulin assay on isolated perfused rat pancreas



C Glucagon secretion assay on isolated mouse pancreatic islets

TABLE OF CONTENTS

APPLICATIONS

Discover our most advanced solutions for insulin quantification

Accurate quantification of insulin in various sample matrices is essential to preclinical studies of insulin secretion. Current assay strategies heavily rely on ELISA methods, involving multiple washing steps as well as a high price per point.

Revvity offers a comprehensive line of insulin quantification assays designed to significantly reduce the time to achieve results, sample consumption, and cost of quantifying insulin. All Revvity assays have been extensively validated on relevant cellular models for insulin release and they show high correlation with established methods.

PRODUCT LIST: Insulin High range kit, Insulin Mouse serum kit, Insulin ultra sensitive kit

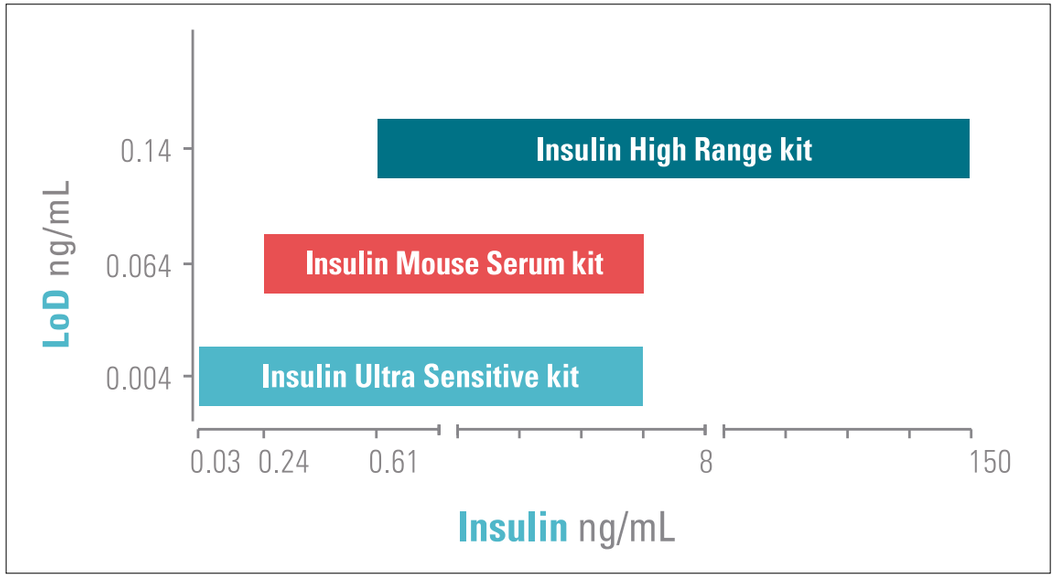


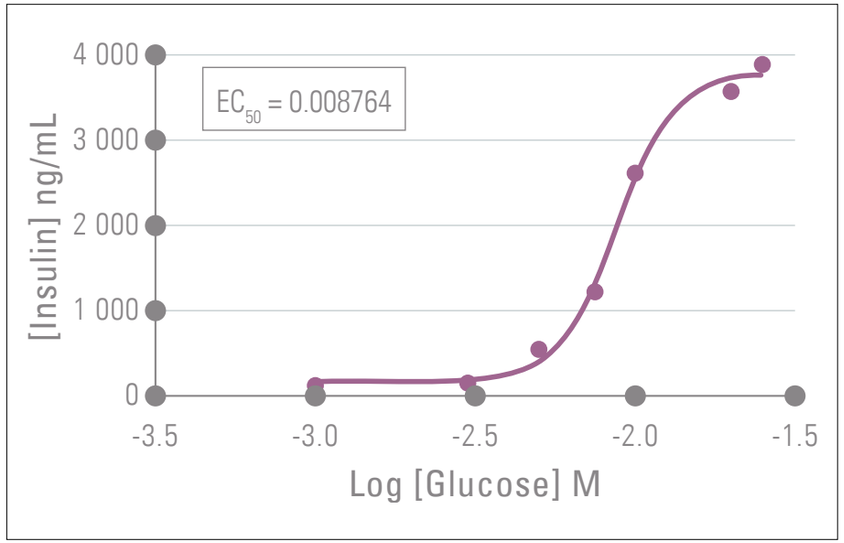
TABLE OF CONTENTS

APPLICATIONS

Cytokines and hormones

Chronic inflammation and activation of the immune system have a proven connection to diabetes. The release of pro-inflammatory cytokines from adipocytes, including TNFα, IL-6 and IL-1β correlates with the risk of insulin resistance in patients. Revvity's biomarker portfolio includes a number of markers directly associated with diabetes to further advance research in this area.

PRODUCT LIST: IL-1β, IL-6, TNFα, GLP-1, Glucagon, Insulin



Glucose-stimulated insulin secretion of pancreatic β-cell MIN6

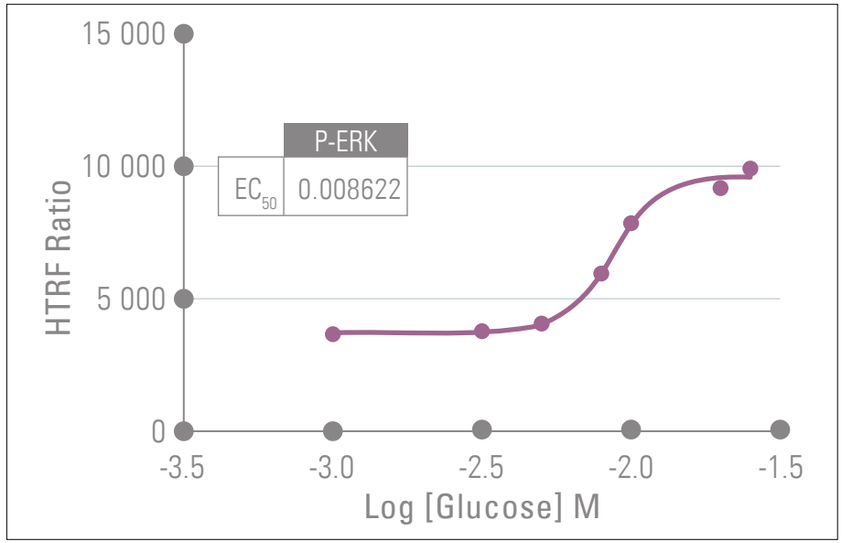
TABLE OF CONTENTS

APPLICATIONS

Kinases and pathway readout

The ability to activate, inhibit or simply modulate major diabetes signaling nodes may lead to important drug discoveries. Pharmacological agents that selectively modulate kinase activities have the potential to reverse the metabolic abnormalities observed with Type 2 Diabetes. Revvity's ever-expanding portfolio of cell-based phospho-protein assays covers many of the pathways linked to diabetes.

PRODUCT LIST: phospho- & total AKT kits, phospho- & total ERK1/2 kits, phospho-CREB kit, phospho-mTOR kit, phopsho-S6RP kit, phospho-EIF4e kit, phospho-BAD kit, phospho-4EBP-1 kit, phospho-P70S6K kit, phospho- & total STAT3 kits, phospho-JNK kit, phospho-p38 kit, phospho- & total IKKβ kits, phospho- & total MEK1/2 kits.



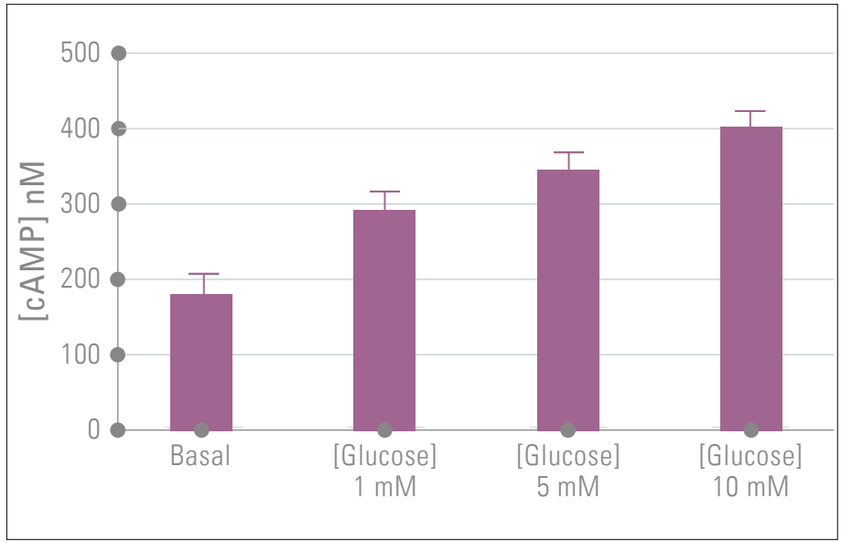
Glucose-stimulated ERK phosphorylation of pancreatic β-cell MIN6

TABLE OF CONTENTS

APPLICATIONS
GPCRs

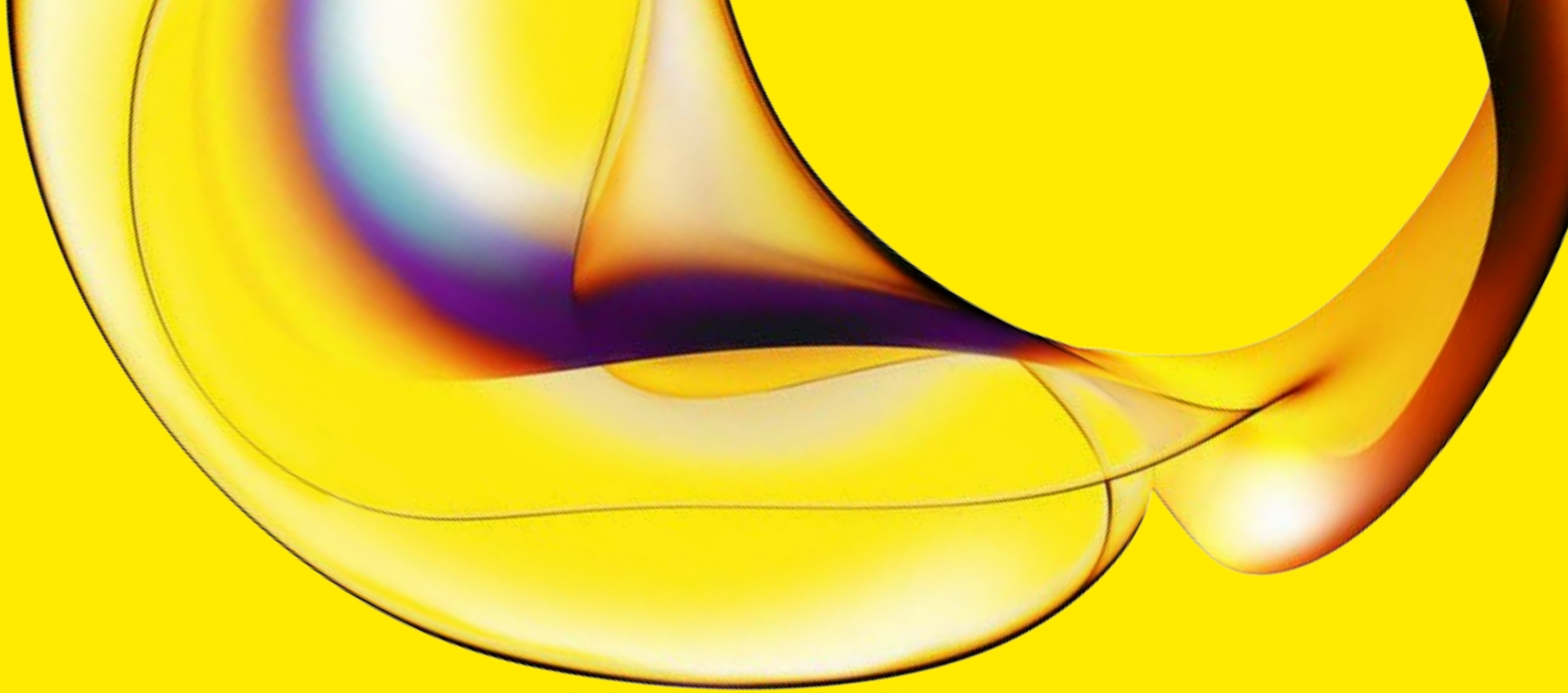
The importance of GPCRs in diabetes signal transduction and the resulting impact on glucose levels is widely recognized. Revvity helps uncover the role of GPCRs in diabetes signaling with a range of tools stretching from the most established second messenger assays in the industry (IP-1 and cAMP) to our award-winning Tag-lite® technology for studying receptor ligand binding.

PRODUCT LIST: Second Messengers: cAMP, IP-One - Ligand Binding: Tag-lite GLP-1 and GIP



Glucose-stimulated cAMP accumulation of pancreatic β-cell MIN6

TABLE OF CONTENTS



www.revvity.com

Revvity, Inc.
940 Winter Street, Waltham, MA 02451 USA
(800) 762-4000 | www.revvity.com

For a complete listing of our global offices, visit www.revvity.com

288339