Understanding obesity:

Exploring cellular pathways and mechanisms.

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Introduction

Obesity is a condition characterized by excessive fat accumulation that has become a global epidemic with significant health and socioeconomic implications. Understanding the cellular pathways and mechanisms underlying obesity is crucial for developing effective interventions to combat this complex disorder. In this guide, we will delve into the intricate cellular processes contributing to obesity that are under investigation for therapeutic avenues.

Several cellular pathways can become deregulated and contribute to the development and progression of obesity. These often interact and intersect, forming a complex network that influences energy balance, metabolism, and fatty tissue function. The main cellular mechanisms involved in obesity and covered in this document include:

- The formation of new fat-storing cells and fatty tissues via **adipogenesis**
- The regulation, or lack thereof, of **lipid metabolism**
- The role of **insulin signaling** and the deleterious effects of insulin resistance
- The **neuroendocrine regulation of appetite** that coordinates behaviours and food intake

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Adipogenesis

Adipogenesis is the process by which stem cells differentiate into adipocytes, a specialized cell type capable of storing lipids as triglyceride droplets. It is a key mechanism of metabolic regulation and one that is central to the disorders related to obesity, since ongoing adipogenesis results in the fat buildup around organs and weight gains that characterize obesity. As such, the regulation of adipogenesis, and in particular its inhibition, is a potential therapeutic avenue to improve obesity development and outcomes.

Adipogenesis is a multiregulated process under the control af a short set of transcription factors, which are themselves under regulation from multiple pathways, all interacting with other aspects of the metabolism. As such, adipogenesis is closely connected to other mechanisms described in this review and share many pathways with them.

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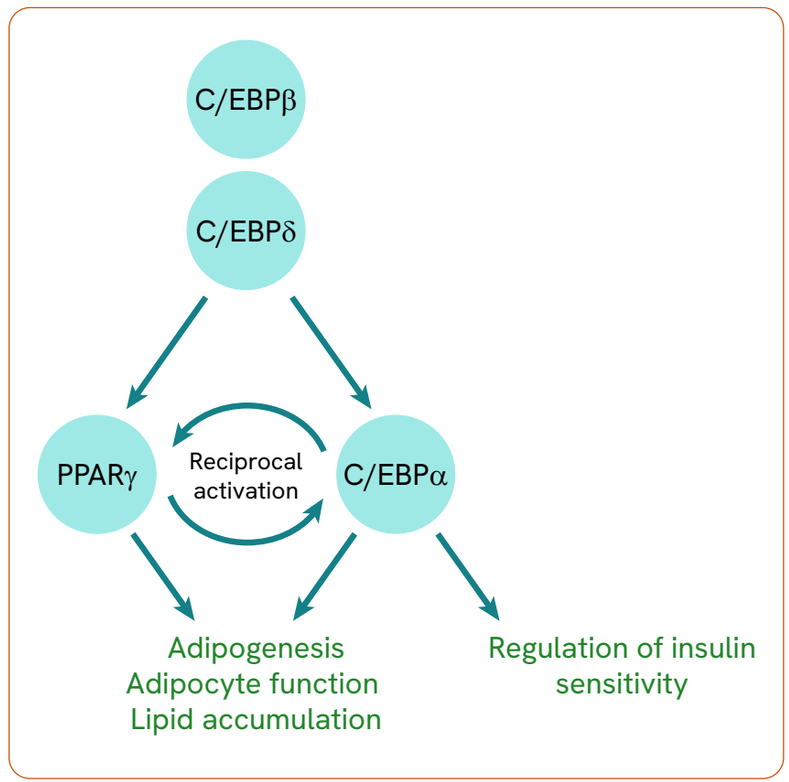
ADIPOGENESIS

Key transcription factors

The main master regulator of adipogenesis is **PPARγ (Peroxisome Proliferator-Activated Receptor Gamma) transcription factor**, whose activation is required and sufficient to induce the differentiation of commited pre-adipocytes into mature adipocytes. PPARγ is promoted and regulated by several environmental cues and signaling pathways and allows the expression of an array of genes orchestrating the differentiation directly. Being so necessary to adipogenesis, the expression or repression of PPARγ is usually the outcome of all pathways that stir pre-adipocytes toward or away from differentiation.

The **C/EBP family of transcription factors** is another lever for the regulation of adipogenesis. In particular, the **C/EBPα** is induced by transiently expressed C/EBPβ and C/EBPδ in early differentiating adipocytes, and is the other master regulator of adipogenesis. It is required for normal adipogenesis and adipocyte function, regulating and being regulated by PPARγ.



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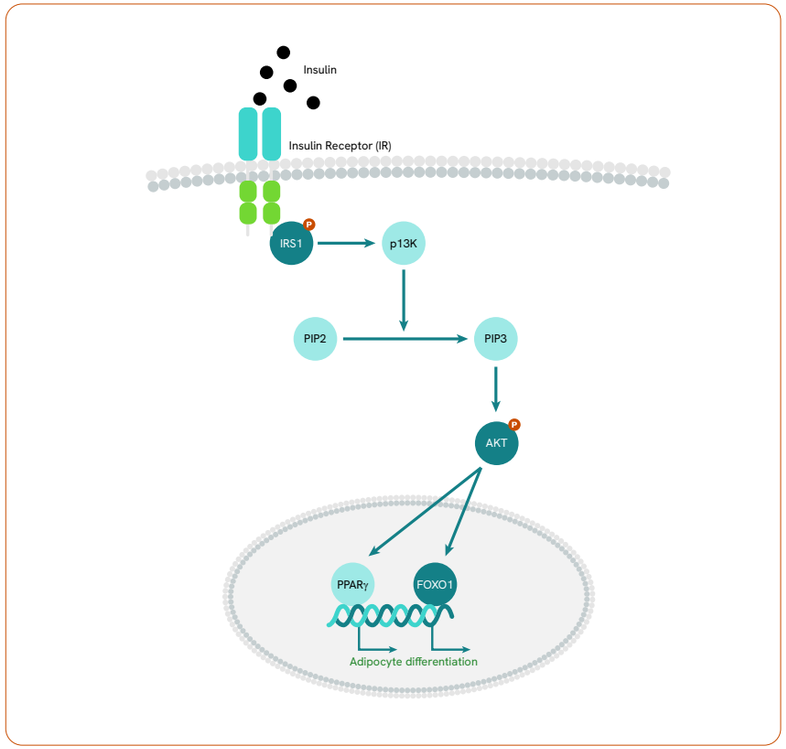
ADIPOGENESIS

Intra-cellular signaling pathways

Functionally ahead of those main transcription factors are a set of signaling pathways that pick on environmental cues to promote or inhibit adipogenesis. These pathways cover a range of functions including the management of inflammation, metabolism, and homeostasis and survival of tissues.

Among the adipogenic pathways, the most obvious and significant one is the **insulin-dependant p13K/AKT pathway**, which is driven by insulin through its canonical receptor (IR) and signaling through IRS1, p13K and AKT phosphorylation to promote genes with differentiation, survival and expansion roles, including FOXO1β and the master regulator adipogenic factor PPARγ. These take committed pre-adipocytes over to the terminal differentiation phase and promote lipogenesis in these cells.



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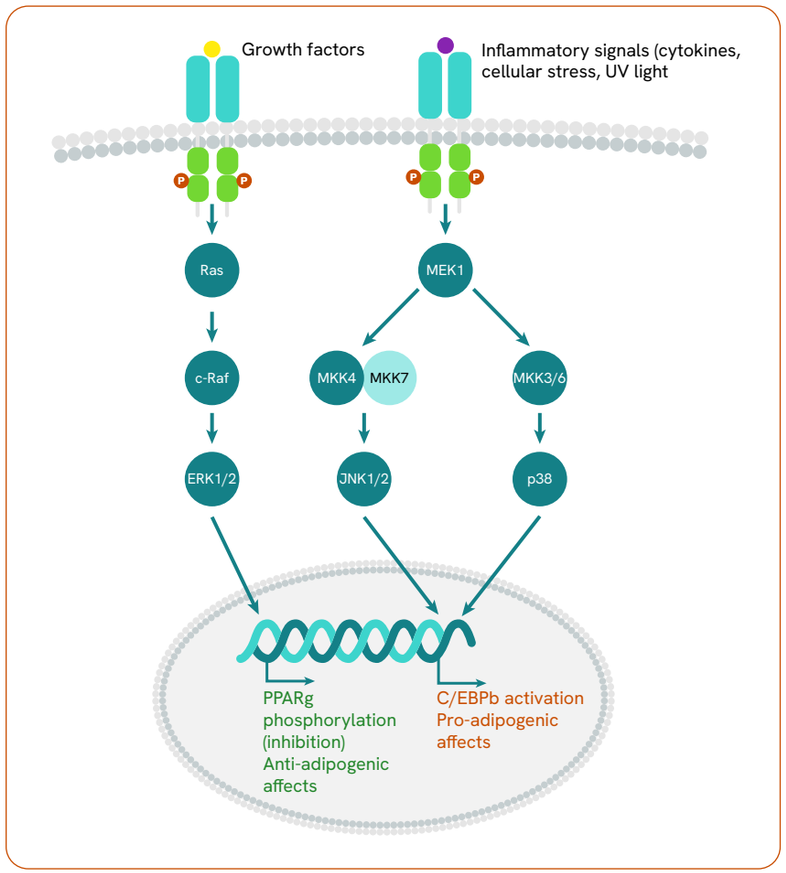
ADIPOGENESIS

Intra-cellular signaling pathways

The **MAPK (Mitogen-Activated Protein Kinase) pathway** plays a more nuanced role, being either pro- or anti-adipogenic depending on which branches of the pathway are activated. The effectors at the end of either branch have opposite effects on the state of adipogenesis, with ERK1/2 being usually anti-adipogenic by phosphorylating PPARγ and thus preventing its activation, while p38 and JNKs tend to be on the pro-adipogenic side by promoting C/EBPβ activation, which then goes on to induce PPARγ and C/EBPα



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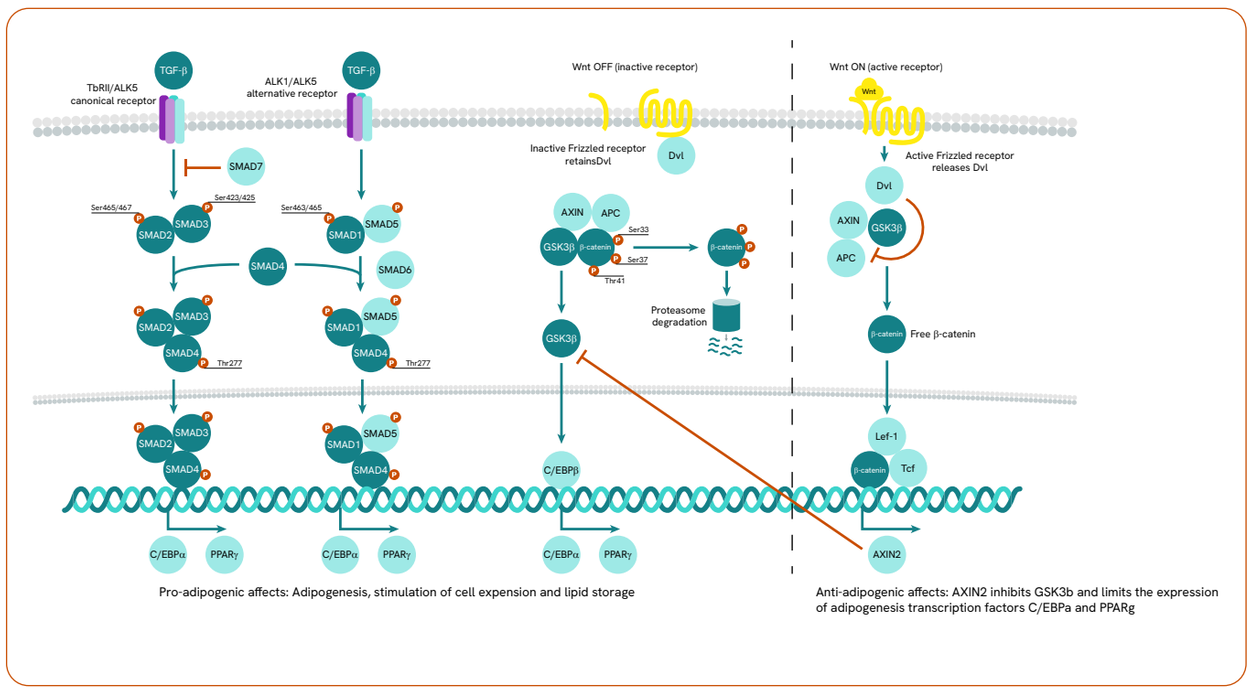
ADIPOGENESIS

Intra-cellular signaling pathways

On the side of adipogenesis inhibition, several pathways have been identified. A potent one is the TGF-β-induced SMAD signaling, which is a ubiquitous anti-inflammatory pro-homeostasis and wound healing pathway. Here, the cytokine TGF-β targets its corresponding receptor and promotes SMADs phosphorylation and association into complexes (SMAD1, 2, 3, and 4 mainly). These complexes then translocate to the nucleus and repress the expression of PPARγ and C/EBPα.

The Wnt/β-catenin axis also has an anti-adipogenic role. When active, Wnt signaling allows β-catenin to migrate to the nucleus where it binds the LEF/TCF transcription factor and promotes the expression of Axin2. This protein targets GSK3b in the cytosol and prevents it from accessing the nucleus where it would act as an activator of C/EBPα , C/EBPβ, promoting adipogenesis.



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ADIPOGENESIS

Inter-cellular cross-talks

Beyond the main signaling pathways that drive it, adipogenesis is also influenced by the cellular environment where it happens. In particular, there are several cross-talks between different cell types that promote or inhibit it. These cross-talks offer additional opportunities for regulation and therapeutic intervention to control and/or mitigate adipogenesis.

- **Endothelial cells** that make up the walls of blood vessels are first in line for the generation of new tissues everywhere in the body. They are the key effectors of the angiogenesis process which elongates blood vessels in new areas and is absolutely indispensable to bring nutrients to new tissues and sustain the growth of new adipocytes in a given area. Communication between these new adipocytes and neighbouring endothelial cells is operated via the Vascular Endothelial Growth Factor (VEGF) and is critical for the expansion of fatty tissues we observe in obesity.
- Adipocytes that are overloaded with fatty acid become inflammed and express inflammatory mediators in the form of cytokines and chemiokines. These in turn attract local **macrophages** of the innate immune system, adding more pro-inflammatory elements to the environment. This inhibits adipogenesis at the cost of a sustained chronic inflammation, which is often observed in chronically obese patients.
- Finally, the micro-environment of adipocytes also participates in a cross-talk with these cells. In this case, the **fibroblasts** that compose the extracellular matrix and hold adipocytes together can become triggered and inflamed from the local mediators secreted by adipocytes and macrophages. When this inflammation is chronic, the resulting disfunction of fibroblasts can stir the local matrix toward a stiffening process. This leads to the hardening of pockets of fat in the tissues and can eventually escalate to a state fibrosis, which are all agravating factors for the local inflammation of the affected tissues.

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Lipid metabolism

The lipid metabolism is a complex set of processes encompassing all cellular activities involved in the digestion, absorption, transportation, storing, and degradation of fatty molecules in the organism. It comprises four main events that are under the regulation of environmental cues and internal signals, and it is piloted by a set of hormones, mediators, and their respective signaling pathways.

- **Lipid transportation** is performed in the blood using lipoproteins that encapsulate their hydrophobic portions to make them soluble (VLDL, LDL, HDL and chylomicrons).
- **Lipogenesis** is the process by which free fatty acids are esterified into triglycerides for storage as droplets inside adipocytes. It is mostly being performed in the liver and fatty tissues, where the triglycerides are then stored.
- **Lipolysis** is the opposite process where stored triglycerides are degraded into free fatty acids and glycerol, which can then be transported in the blood again and used as an energy source.
- Finally the **β-oxidation of fatty acids** is the mitochondrial process that oxidate fatty acid into acetyl-CoA, which then runs the Krebs cycle to make ATP.

As a central mechanism in metabolism, all of its parts interact with one another and are susceptible to modulation from other metabolic systems. As such, the metabolism of lipids is for instance co-regulated by the metabolism of sugar, but also inflammatory signals, on top of its own cues.

In obese patients, these key mechanisms of lipid metabolism become impaired and dysfunctional for several reasons. Firstly, as the organism increases and sustains lipolysis over time to compensate for the accumulation of fatty acids in tissues, it creates a state of **hyperlipidemia,** where both the FFAs (Free Fatty Acids) from the lipolysis and VLDLs (Very Low-Density Lipoproteins) from the liver become excessive in the blood of patients. This promotes the deposits of LDLs in vessels and arteries with increased cardiovascular risks. Secondly, due to fatty tissues becoming saturated, patients present an **ectopic accumulation of lipids,** where fats begin to collect around organs that are not supposed to store them. This is especially true for the liver (risks of hepatic steatosi or “human fatty liver”, which can lead to liver fibrosis), the heart (weakening of the cardiovascular function), and other muscles (local inflammation and loss of muscle mass). Thirdly, this accumulation of lipids in non-fatty tissues like the liver is a driver of **insulin resistance,** which has ramifications and consequences in the entire metabolism and management of sugars and lipids. And finally, the hypertrophy of lipid-saturated adipocytes is a source of **lipotoxicity and chronic inflammation** in the affected tissues, which overall damages the tissues and aggravates the condition of the patients while meddling with their metabolism and furthering insulin resistance.

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LIPID METABOLISM

Intracellular signaling pathways

The metabolism of lipids is a complex system with multiple moving parts and regulations pathways, which become altered in the context of obesity. Some of these signaling pathways are intertwined with other mechanisms involved in obesity such as insulin resistance or adipogenesis.

Pathway and roles	Alterations in obesity setting
Insulin-dependent pI3K/AKT signaling Promotes translocation of the GLUT4 receptor from its cytosolic storage pool to the membrane, where it absorbs glucose from the blood. Insulin also promotes the elaboration of new fatty acids via an increase in lipogenesis and a decrease in lipolysis.	Insulin resistance hinders the translocation process and diminishes glucose absorption while letting lipolysis run free. This leads to more FFAs in the blood (**hyperlipidemia**) and increased accumulation in non-fatty tissues (**ectopic accumulation**).
AMPK (AMP-Activated Protein Kinase) Acts as a sensor of available cellular energy. When acitve, AMPK promotes the b-oxidation of fatty acids and inhibits lipogenesis to use lipids as an energy source.	The excess in available energy typically associated with the obesity-related diet leads to a low activation of AMPK, which in turns decreases b-oxidation and increases lipogenesis. This exacerbates the **accumulation of lipids** and **insulin resistance** over time.
SREBP-1c (Sterol Regulatory Element-Binding Protein 1c) Transcription factor regulated by insulin signaling, which increases the expression genes that drive lipogenesis such as ACC (Acetyl-CoA) and FAS (Fatty Acid Synthase).	Hyperinsulinemia forces high levels of SREBP-1c activation, which promotes lipogenesis in the liver and fatty tissues with long term risks of **hyperlipidemia** and **ectopic accumulation of lipids** with risks hepatic steatosis and chronic lipotoxicity.
PPARγ (Peroxisome Proliferator-Activated Receptor Gamma) As a master regulator of adipogenesis, PPARγ regulates lipid accumulation in adipocytes via a stimulation of lipogenesis.	Excessive and chronic activation of PPARγ in obese patients' fatty tissues may lead to uncontrolled **expansion of fatty tissues** and increased **insulin resistance**.
HSL (Hormone-Sensitive Lipase) signaling Key enzyme in lipolysis which allows the destocking of fatty acids from triglycerides to be made available for lipolysis. HSL is under the regulation of the AMPC/PKA axis.	Insulin resistance promotes a chronic activation of HSL, which results in high levels of free fatty acids in the blood (**hyperlipidemia**), and therefore, chronic and body-wide **lipotoxicity and inflammation**.
NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) signaling Important regulator of inflammation. Gets activated by cellular stress and promotes the expression of pro-inflammatory cytokines that attract and stimulate immune cells (monocytes from the blood and resident macrophages) and fibroblasts.	Lipotoxicity in fatty-tissues and satured adipocytes trigger a chronic activation of NF-κB. This persistant activity increases insulin resistance and promotes the infiltration of pro-inflammatory macrophages into fatty tissues.

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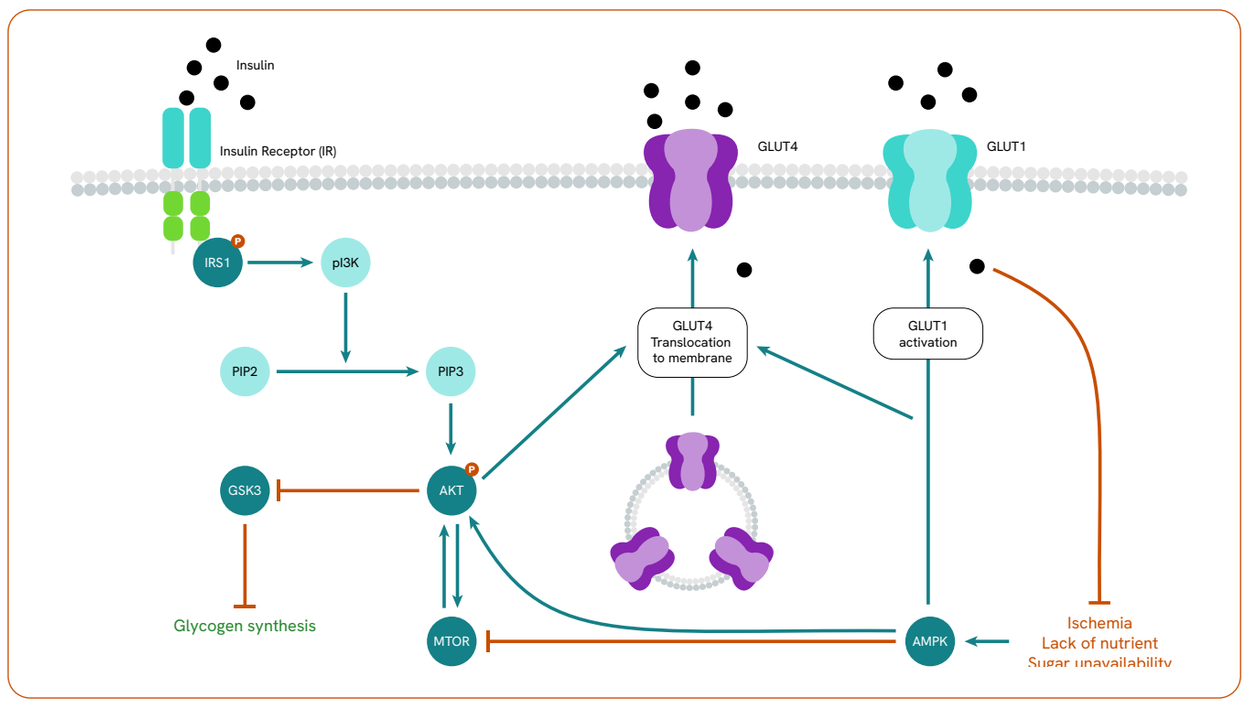
Insulin signaling

Insulin is a hormone secreted by pancreatic β-cells, which is increased by the levels of glucose in the blood and plays a critical role in the regulation of the lipid and glucid metabolisms. Under normal circumstances, insulin binds its receptor (IR) and initiates a signaling cascade that translocates GLUT4 receptor from cytosolic vesicles to the membrane to bind glucose, thus increasing the absorption of glucose into the affected cells. On top of promoting this absorption, insulin promote its degradation through glycolysis and inhibits the neoglucogenesis in the liver, while instead stimulating the assimilation of excess sugars into lipids by lipogenesis and inhibiting lipolysis in fatty tissues. Overall, insulin stirs the metabolism toward the use of available sugars as energy sources instead of fats.

When insulin resistance sets in, these regulatory functions get impaired as cells become less sensitive and require higher levels of the hormone to produce the same results. In an attempt to improve that, the organism resorts to increased levels of insulin which cause hyperinsulinemia. This course of action is, however, not a robust solution as it not only carries consequences on the many processes where insulin is involved, but fails to correct insufficient glucose absorption, causing chronic hyperglycemia.



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INSULIN SIGNALING

Intracellular signaling pathways

Pathway and roles	Alterations in obesity setting
Insulin-dependant pI3K/AKT signaling Insulin binds its receptor IR, which phosphorylates intracellular IRS1 on tyrosine residues to activate it at the receptor. The phosphorylation site of IRS1 is critical to its function and acts a switch on/off regulation sytem where serine/threonine phosphorylation makes it capable of interacting with the next part of the cascade, but phosphorylation on tyrosine residues inhibits this interaction and shut down insulin signaling at the receptor. When active IRS1 recruits and activates pI3K, which in turn activates the kinase AKT. Active AKT then promotes translocation of the GLUT4 receptor from its cytosolic storage pool to the membrane, where it absorbs glucose from the blood. Insulin also promotes the elaboration of new fatty acids from the available glucose via an increase in lipogenesis and a decrease in lipolysis.	The phosphorylation of active IRS1 happens on serine/threonine residues instead of tyrosine residues, which renders it incapable of interacting with pI3K and impairs the entire resulting cascade all the way down to AKT. This results in a decreased translocation of GLUT4 and diminishes glucose absorption while letting lipolysis run free. This leads to more sugars remaining in the blood (**hyperlglycemia**) and more free fatty acids as well due to lipolysis not being inhibited anymore (**hyperlipidemia**).
mTOR/S6K1 pathway A companion signaling pathway resulting from insulin signaling, mToR is activated by AKT and promotes S6K1 and genes involved in the regulation of protein synthesis, survival, and cell growth. S6K1 acts as a regulation loop for insulin signaling by phosphorylating serine/threonine residues on IRS1 when overstimulated by insulin.	The hyperinsulinemia that characterizes insulin resistance leads to an overactivation of mTOR/S6K1, which play their role as a negative feedback regulation loop and further desensitize the cells to insulin. In time, this process aggravates insulin resitance.

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INSULIN SIGNALING

Causes and consequences of insulin resistance

Insulin resistance is symptom of multiple metabolic and cellular processes becoming chronically impaired. The first step toward resistance is the **ectopic accumulation of lipids** in non-fatty tissues such as the muscles and liver. When excessive, the lipids cannot be processed and stored as TAGs (triacylglycerols) and instead accumulates as other metabolites like DAGs (diacylglycerols) and ceramides that induce **lipotoxicity** and affect insulin signaling. These effects are felt at the level of PKCs (Protein Kinase C), which are promoted by such DAGs, and phosphorylate IRS1 on serine/threonine residues, thus inhibiting the downstream signaling from insulin receptors.

In fatty tissues however, lipids are mostly stored as TAGs, but their accumulation becomes so elevated that these tissues are oversaturated to the point that the amount of cellular lipids get in the way of adipocytes' cellular functions. As an answer to this stress, the cells express an array of pro-inflammatory cytokines (TNF-α, IL-6, etc.) that induce and sustain low levels of **chronic inflammation**, with adverse effects on insulin signaling. JNK (c-Jun N-terminal Kinase) and IKKb (IkB Kinase b) in particular are inflammatory kinases that phosphorylate serine/threonine sites on IRS1.

On top of this lipotoxicity and chronic inflammation, cells are also affected by **oxidative stress** coming from ROS (Reactive Oxygen Species), which have deleterious effects on cellular contents and deteriorate intracellular insulin signaling. These ROS can direcly impact the insulin/IRS1/pI3K axis by impairing ISR1 phosphorylation on its tyrosine residues, rendering it less capable of transmitting signals downstream. In the context of obesity, ROS arise due to the excess of fatty acids, which instead of being properly oxidized and removed from cells by mitochondria, are instead allowed to remain and accumulate.

Finally, in line with the oxidative stress, mitochondria are the site of β-oxidation in cells and normally consume fatty acids to make acetyl-CoA for the Krebs cycle. In obese tissues that are already undergoing the effects of lipotoxicity from excessive fatty acids, the cells have reduced protein synthesis abilities and are less capable of generating new and highly functional mitochondria. These are generally less numerous or less maintained, and have less efficient oxidative chains of receptors carrying eletrons from either side of the mitochondrial walls. This **mitochondrial dysfunction** has two adverse effects: the accumulation of more intracellular fatty acids (lipotoxicity) and ROS (oxidative stress), with the aforementionned effects on insulin signaling.

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INSULIN SIGNALING

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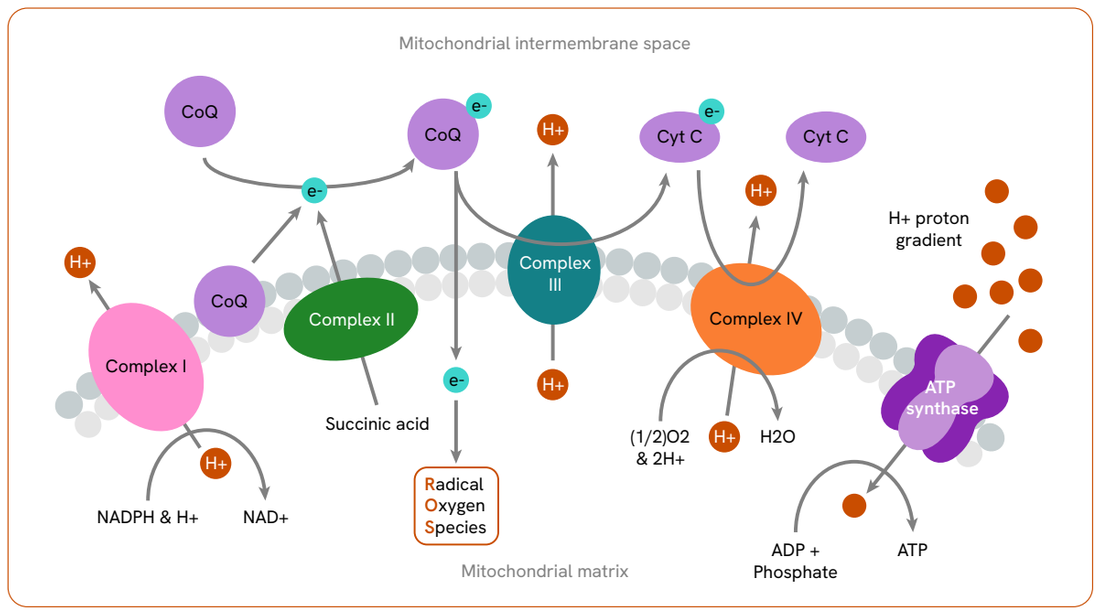

As a way to compensate the diminishing sensitivity of cells to insulin, pancreatic cells increase their production, leading to a state of **hyperinsulinemia**. In most cases however, this is not enough to re-establish normal sensitivity and metabolism, and the levels of glucose in the blood remain too high. This insufficient absorption of glucose is worsened by the neoglucogenesis in the liver, which is no longer repressed by insulin signaling, and can lead to chronic **hyperglycemia** which leads to **type 2 diabetes** in many obese patients.

In addition, insulin resistance fails to repress lipolysis in fatty tissues, which causes high levels of fatty acids to be present in the blood (**dyslipidemia**), with all of its associated risks, such as fatty deposits in arteries, **atherosclerosis, and cardiovascular disorders**. In the liver, a chronic accumulation of lipids is also promoted by insulin resistance and leads to the development of NAFLD (Non-Alcoholic Fatty Liver Disease), then followed by NASH (Non-Alcoholic Steato-Hepatitis) where the liver function becomes impaired. Over time, this condition and chronic inflammation provide a favorable ground for liver fibrosis and, in some cases, even cirrhosis.

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Neuroendocrine regulation of appetite

The neuroendocrine regulation of appetite is a collection of interacting and intersecting signals, pathways, and hormonal transmitters mainly from the central nervous system, digestive system and fatty tissues, which stimulates (orexigenesis) or inhibits (anorexigenesis) appetite and food intake. In the context of obesity, this regulation is often altered and the cause for diet and food intake habits that promote excessive feeding (hyperphagia) and storage of energy as fats. Insulin resistance, oxidative stress, inflammation, and other mechanisms all play a role in this dysregulation and make it especially difficult to manage obese patients. However, due to it being at the root of obesity, the perspective of understanding and developing therapeutic strategies to tackle appetite is a promising one, made even more appealing by the recent success of GLP-1 agonists like Semaglutide.

Key hormones and transmitters

There are multiple transmitters coming from all organs involved in sugar and lipid metabolism that are known to play a role in the regulation of appetite and offer potential research opportuinities for therapeutics against obesity. Their targets in the brain are mainly two populations of neurons located in the hypothalamus region of the brain. First are the **NPY/AgRP neurons** (Neuropeptide Y/Agouti-Related Peptide Neurons), which drive orexigenesis by releasing the appetite-inducing molecules NPY and AgRP. In particular, AgRP is an antagonist inverse of MC4R (Melanocortin-4 Receptor), which inhibits the satiety signals this receptor is responsible for. The second group of neurons are the **POMC/CART** ones (Pro-opiomelanocortin/Cocaine- and Amphetamine-Regulated Transcript), which promote anorexigenesis by inducing satiety via CART and the MC4R agonist α-MSH. Quite logically, the dominance of orexigenic signals over the anorexigenics ones is often at the core of obesity progression, and re-establishing the balance between them is a key area of current research around obesity and related metabolic diseases.

Among the transmitters that impact these neuron populations, **leptin** is a hormone secreted by adipocytes proportionally to how much fat they store. It targets POM/CART neurons to shut down appetite and promote energy spending (anorexigenic signaling). Under normal circumstances, leptin binds its receptor LEPR to activate the **JAK-STAT pathway** where JAK2 (Janus Kinase 2) phosphorylates STAT3 (Signal Transducer and Activator of Transcription 3), translocating it into the nucleus to promote satiey inducing genes like POMC. In obesity settings, the low-level chronic inflammation coming from cytokines like TNF-α and IL-6 causes some anti-inflammatory mediators like SOCS3 (Suppressor of Cytokine Signaling 3) to be activated, which attenuates inflammation-related pathway including JAK-STAT and thus introduces some leptin resistance. As this resistance develops, POM/CART neurons stop reacting to leptin in a proportional way and appetite is more difficult to inhibit, which promotes hyperphagia.

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NEUROENDOCRINE REGULATION OF APPETITE

Key hormones and transmitters

Another hormone that is central to hunger and appetite management is **ghrelin**, which is secreted by the cells from the stomach walls and spikes the appetite (orexigenic signaling). It is generally dubbed the Hunger Hormone due to its propensity to rise prior to meals and drop afterward. Ghrelin targets GHSR (Growth Hormone Secretagogue Receptor) in NPY/AgRP neurons to stimulate appetite, as well as in intestinal and stomach cells to promote the secretion of gastric acids and improve intestinal motility. Following GHSR, the signal goes through **AMPK (AMP-activated Kinase)** which gets activated and promotes the expression of NPY/AgRP. In obese patient, the supression of ghrelin after a meal is often delayed or attenuated, which leads to a long lasting sensation of hunger.

Beyond its roles in sugar and lipid metabolisms and the incidence it has on adipogenesis, **insulin** also intervenes in the regulation of appetite. When binding its IR receptor in the hypothalamus part of the brain, insulin signals through the usual pI3K/AKT pathway and promotes the phosphorylation and inhibition of FoxO1 (Forkhead Box O1), which normally acts as a stimulator of NPY/AgRP. This leads to a promotion of POM/CART neurons over the NYP/AgRP ones, with anorexigenesis as a result. The insulin resistance often observed in conjunction with obesity has an adverse effect on this inhibition and tends to reduce the anorexigenesis signaling and stir the appetite up.

Finally, two intestinal peptides have been identified as especially relevant to the regulation of the appetite: both **PYY (Peptide YY)** and **GLP-1 (Glucagon-Like Peptide 1)** are secreted by intestinal L cells in response to food intake and have anorexigenic affects.

On the one hand, PYY release is particularly sensitive to the ingestion of proteins as they travel the colon, and is expressed in two main forms: PYY1-36 and PYY3-36, the precursor and active forms of the peptide respectively. PYY3-36 mainly acts upon Y2R (Y2 Receptors) in NPY/AgRP neurons, which inhibits said neurons and their orexigenic signaling, leading to a sensation of satiety. As they inhibit these neurons, they also indirectly promote the activity of POMC ones, which acts in conjunction with GLP-1 to promote anorexigenic effects. On the other hand, GLP-1 targets GLP-1R (GLP-1 Receptors) in the pancreas to increase insulin secretion, but also in the POMC neurons, which increase their production of the α-MSH precursor POMC and leads to the activation of MC4R receptor to induce feelings of statiety. Both peptides and their receptors work in tandem to initiate and amplify anorexigenic signals and are highly promising for the therapeutic management of obesity and diabetes, with GLP-1 receptor agonists already being approved for these conditions and PYY peptides showing great potential as well.

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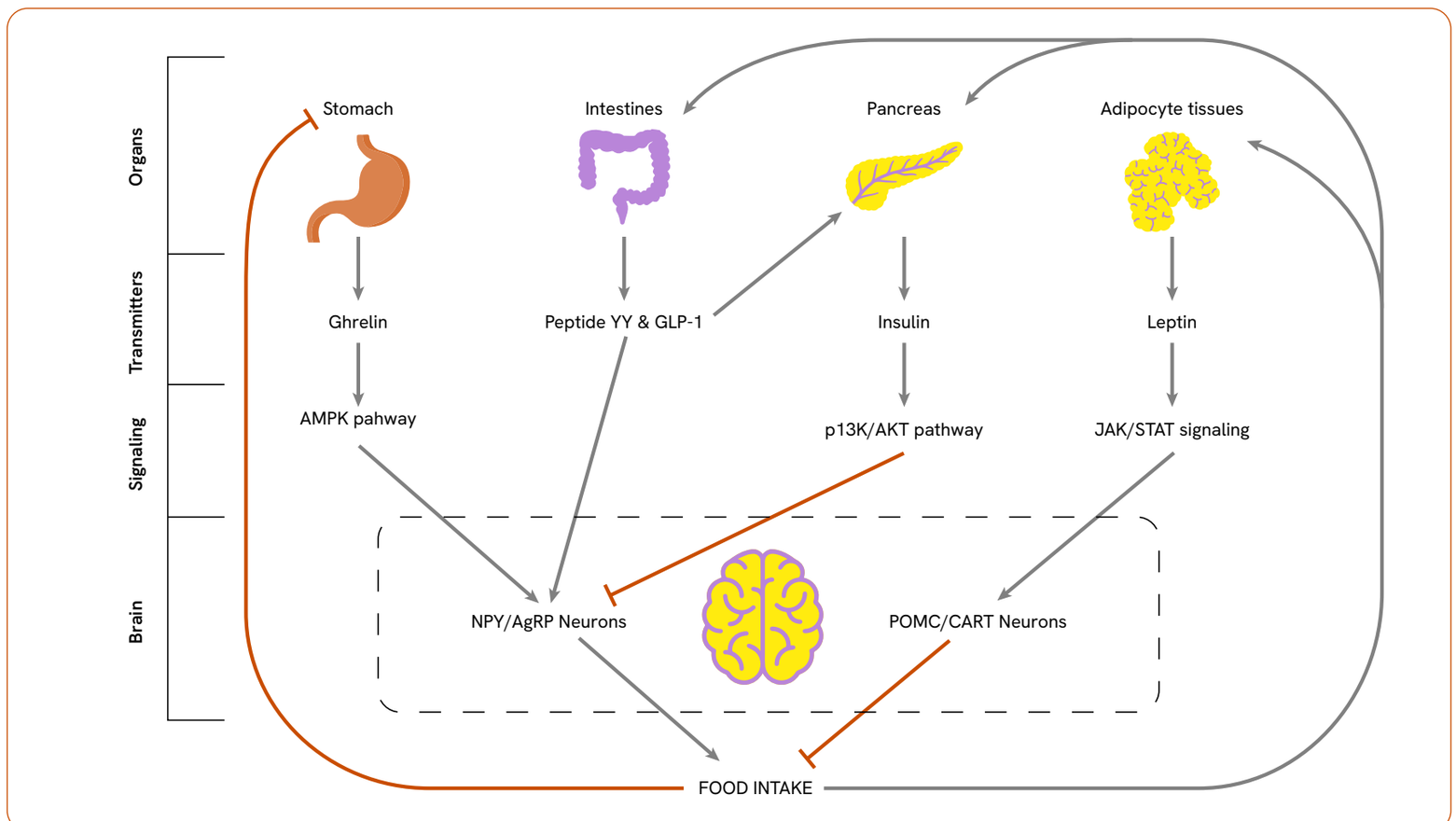

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GPCRs

	HTRF™
cAMP Gi	62AM9PEB
cAMP Gs Dynamic	62AM4PEB
cAMP Gs HiRange	62AM6PEB
IP-One	62IPAKDA
β-arrestin 2 Recruitment	62BDBAR2PEB
GTP / Gi protein binding	62GTPPEG

Beta-Catenin

	HTRF™	AlphaLISA™ *SureFire® Ultra™*
β-Catenin phospho-S37		ALSU-PBCAT-A500
β-Catenin phospho-S675		ALSU-PBCAT-C500
β-Catenin phospho-T41/ S33/37	64CATPEG	
β-Catenin phospho-T41/S45		ALSU-PBCAT-B500
β-Catenin total	64NCAPEG	ALSU-TBCAT-A500

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AKT

	HTRF™	AlphaLISA™ *SureFire® Ultra™*	AlphaLISA™ *SureFire® Ultra™* Multiplex
AKT phospho-S473	64AKSPEG		
AKT phospho-T308	64AKTPEG		
AKT total	64NKTPEG		
AKT1 phospho-S473	63ADK078PEG	ALSU-PAKT1-C500	
AKT1 phospho-S129		ALSU-PAKT1-D500	
AKT1 total	63ADK079PEG	ALSU-TAKT1-B500	
AKT1/2/3 phospho-S473		ALSU-PAKT-B500	
AKT1/2/3 phospho-S473 & AKT1 total			MPSU-PTAKT-M500
AKT1/2/3 phospho-T308		ALSU-PAKT-A500	MPSU-PTAKT-0500
AKT1/2/3 phospho-T450		ALSU-PAKT-C500	MPSU-PTAKT-N500
AKT1/2/3 total		ALSU-TAKT-B500	
AKT2 phospho S473	63ADK080PEG		
AKT2 total	63ADK081PEG		
AKT3 phospho-S473	63ADK082PEG		
AKT3 total	63ADK083PEG		

AMPK

	HTRF™	AlphaLISA™ *SureFire® Ultra™*	AlphaLISA™ *SureFire® Ultra™* Multiplex
AMPK phospho-T172	64MPKPEG		
AMPK total	63ADK060PEG		
AMPKα 1/2 phospho-T172 & total			MPSU-PTAMPK-K500
AMPKα 1/2 total		ALSU-TAMPK-A500	
AMPKα phospho-T172		ALSU-PAMPK-A500	

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c-RAF

	HTRF™
c-Raf phospho-S338	63ADK018PEG
c-RAF phospho-S43	64CRAFS43PEG
c-RAF total	64CRAFTPEG

ERK

	HTRF™	AlphaLISA™ *SureFire® Ultra™*	AlphaLISA™ *SureFire® Ultra™* Multiplex
ERK phospho-T202/Y204	64AERPEG		
ERK total	64NRKPEG		
ERK1/2 phospho-T202/Y204		ALSU-PERK-A500	
ERK1/2 total		ALSU-TERK-A500	MPSU-PTERK-M500

FOXO1

	HTRF™
FOXO1 phospho-S256	64FOXPEG
FOXO1 total	64NFOPEG

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GSK3

	HTRF™	AlphaLISA™ *SureFire® Ultra™*
GSK3α phospho-S21	64GPAPEG	
GSK3α total	64GTAPEG	
GSK3β phospho-S9	64GPBPEG	ALSU-PGS3B-A500
GSK3β total	64GTBPEG	ALSU-TGS3B-A500

Insulin

	HTRF™	AlphaLISA™ *SureFire® Ultra™*	AlphaLISA™ *SureFire® Ultra™* Multiplex
Insulin High Range	62IN1PEG		
Insulin Sensitive	62IN2PEG		
Insulin Serum	62IN3PEB		
IR-β (Insulin Receptor Beta) phospho- T1150/1151 & total			MPSU-PTINR-K500
IR-β (Insulin Receptor Beta) phospho- Y1150/1151	63ADK016PEG		
IR-β (Insulin Receptor Beta) phospho- Y1150/1151		ALSU-PINR-B500	
IR-β (Insulin Receptor Beta) total	63ADK019PEG	ALSU-TINR-A500	
IRS1 phospho Ser312	64IRSPEG		
IRS1 total	64NRSPEG		

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JNK

	HTRF™	AlphaLISA™ *SureFire® Ultra™*
JNK phospho-T183/Y185	64JNKPEG	
JNK1/2 total		ALSU-TJNK-A500
JNK1/3 phospho-T183/Y185		ALSU-PJNK-A500

MEK

	HTRF™	AlphaLISA™ *SureFire® Ultra™*	AlphaLISA™ *SureFire® Ultra™* Multiplex
MEK1 phospho-S218/222	64ME1PEG	ALSU-PMEK1-A500	
MEK1 phospho-S218/222 & total			MPSU-PTMEK1-K500
MEK1 phospho-S298	64MEK1S98PEG		
MEK1 total	64NE1PEG	ALSU-TMEK1-A500	
MEK1/2 phospho-S218/222	64ME2PEG		

MKK4

	HTRF™	AlphaLISA™ *SureFire® Ultra™*
MKK4 phospho-S257	64MK4PEG	ALSU-PMKK4-A500
MKK4 total	64NK4PEG	ALSU-TJNK-A500

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mTOR

	HTRF™	AlphaLISA™ *SureFire® Ultra™*
mTOR phospho S2448	64TORPEG	ALSU-PMTOR-C500
mTOR total		ALSU-TMTOR-B500

p38

	HTRF™	AlphaLISA™ *SureFire® Ultra™*
P38 MAPK phospho T180/Y182	64P38PEG	ALSU-PP38-B500
P38 MAPK total		ALSU-TP38-B500

Ras

	AlphaLISA™ *SureFire® Ultra™*
Ras total	ALSU-TRAS-A500

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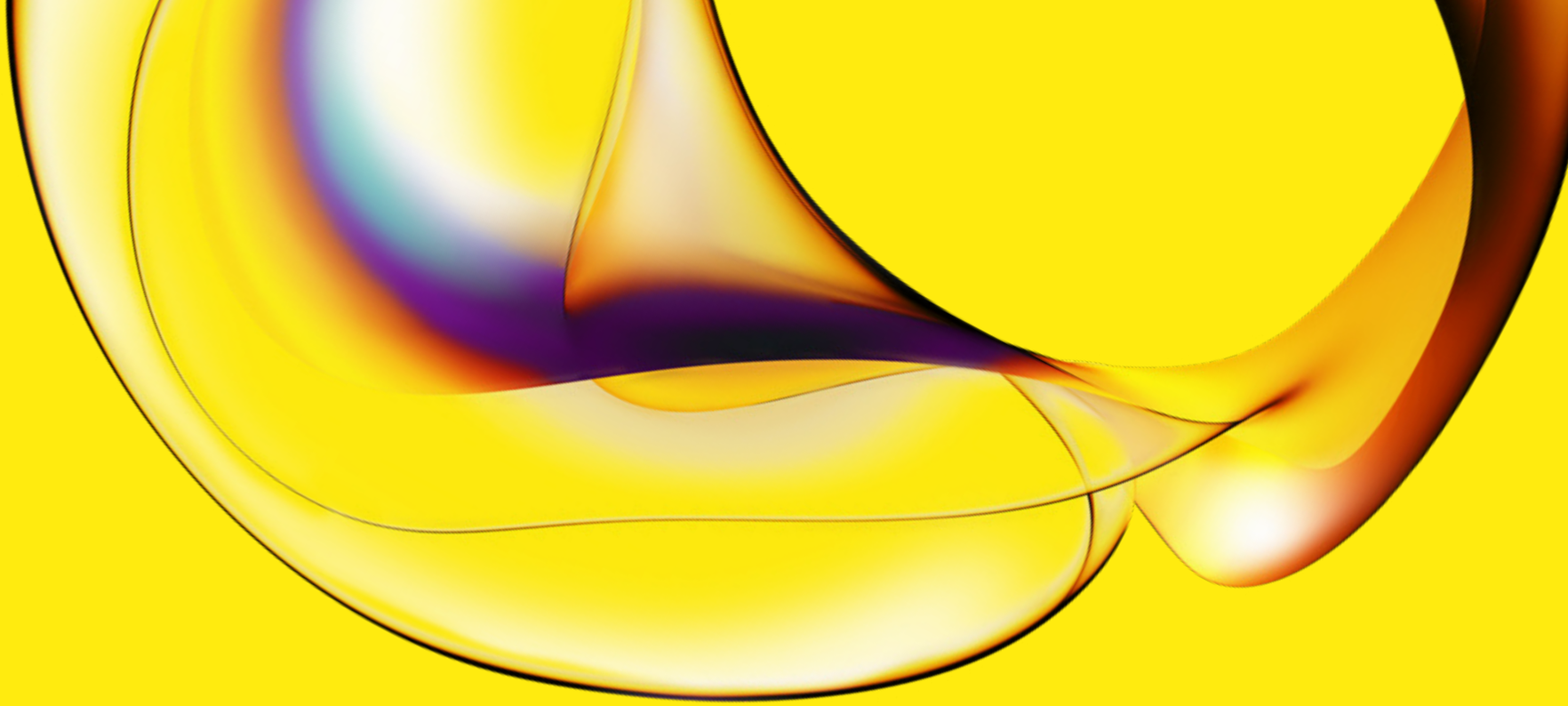

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