nature REVIEWS
DRUG DISCOVERY

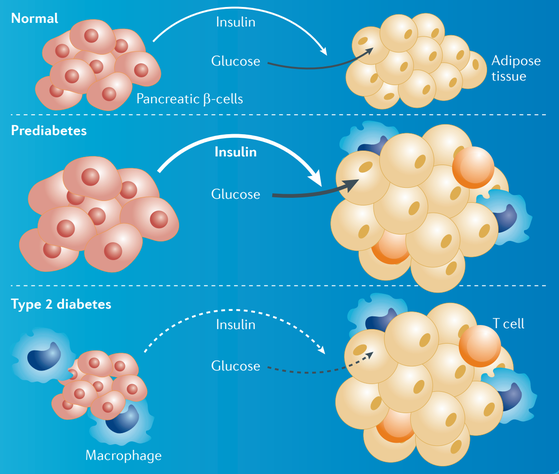
Targeting inflammation in diabetes

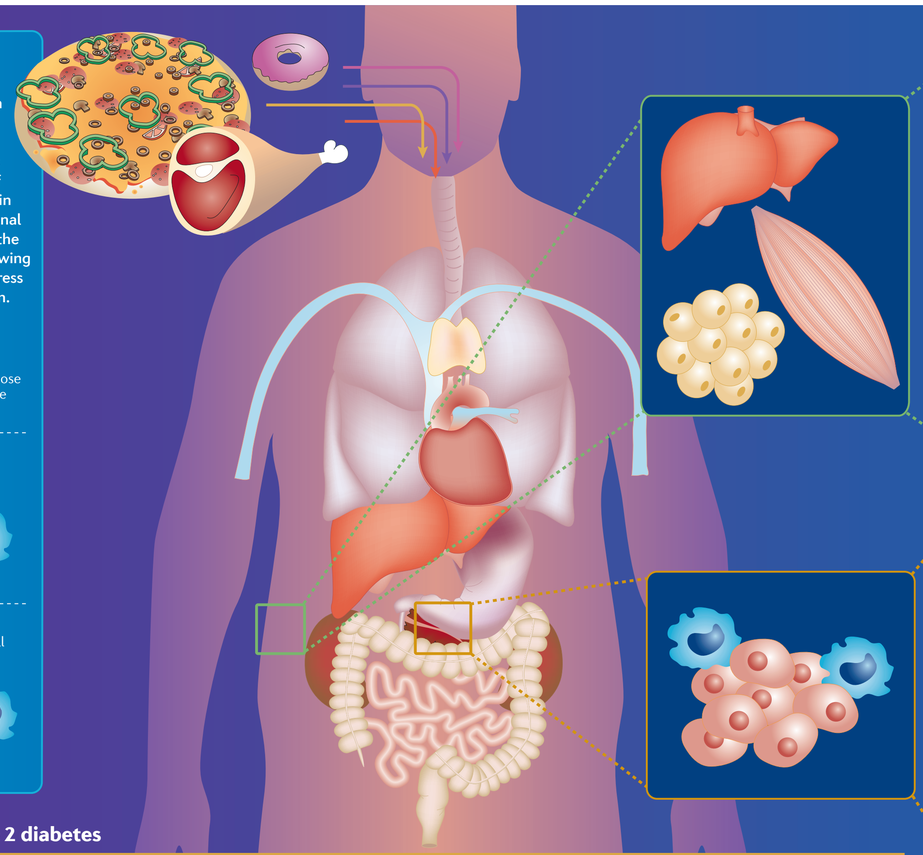
Marc Y. Donath, Elise Dalmas and Marianne Böni-Schnetzler

The immune system is activated in patients with type 2 diabetes. Evidence of these immunological changes includes altered levels of cytokines and chemokines, changes in the numbers and activation states of various leukocyte populations, apoptosis and fibrosis. This is observed in adipose tissue, liver, pancreatic islets and the vasculature. The proposed mechanisms to explain insulin resistance and islet β-cell dysfunction in type 2 diabetes include oxidative stress, ER stress, amyloid deposition in the pancreas, lipotoxicity and glucotoxicity. All of these mechanisms can be caused by overnutrition and induce an inflammatory response. Based on these findings, clinical studies aimed at the modulation of inflammation in patients with type 2 diabetes have been conducted and provide proof of concept that the immune system has an impact on metabolism. Therefore, future treatment of type 2 diabetes and its complications may include anti-inflammatory drugs.

Pathogenesis of the disease

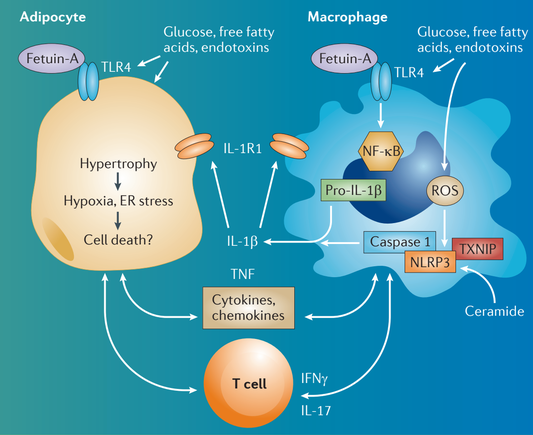
The onset and progression of type 2 diabetes is due to a continuous deterioration of the insulin-secretory capacity of pancreatic β-cells, which does not allow compensation for an increased peripheral insulin demand. Overnutrition and inactivity increase the requirement for insulin to allow glucose disposal into insulin-sensitive tissues. With time, obesity develops and activates the innate immune system with subsequent recruitment of macrophages and T cells, which contributes to the development of insulin resistance. Initially, pancreatic islets may adapt by increasing their functional β-cell mass to provide sufficient insulin to control blood glucose levels in the face of enhanced insulin resistance. Eventually, β-cell compensation fails owing to genetic predisposition, glucotoxicity, lipotoxicity, oxidative stress, ER stress and the formation of amyloid deposits with subsequent islet inflammation.

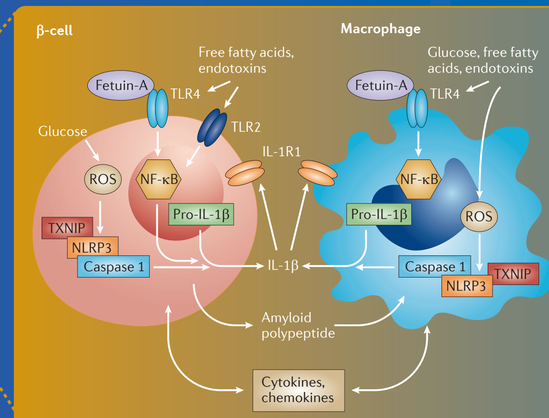




Adipose tissue

Adipocytes store excess nutrients and progressively become hypertrophic. Adipocyte hypertrophy leads to a pro-inflammatory response mainly through hypoxia and ER stress-related mechanisms that may eventually result in cell death. In addition, endotoxins and free fatty acids may activate TLR2 and TLR4 via Fetuin-A recruitment, leading to the production of NF-κB-related pro-inflammatory factors such as IL-1β. The stressed adipocytes will then produce a broad range of cytokines and chemokines — including TNF and MCP1 — that, in turn, promote macrophage and T cell accumulation and activation in adipose tissues. In macrophages, hyperglycaemia-induced TXNIP and lipid species such as ceramides promote the formation of the NLRP3 inflammasome. The NLRP3–caspase 1 complex leads to IL-1β secretion, which fosters chronic inflammation in adipose tissues through auto- and paracrine amplification. Local pro-inflammatory cytokines, including IL-1β, TNF and IFNγ, impair adipogenesis and insulin action, contributing to insulin resistance. Similar alterations are observed in other insulin-sensitive tissues such as muscle and liver.





Islets

Oversupply of nutrients such as free fatty acids and glucose initiates a pro-inflammatory response in pancreatic islets that is governed by IL-1β and leads to insulin secretion failure. Circulating TLR agonists such as lipopolysaccharides from the bacterial cell wall (endotoxins) or free fatty acid bound to Fetuin-A activate TLR2 and TLR4 and induce the expression of pro-inflammatory factors via NF-κB translocation. Glucose and free fatty acids increase islet cell metabolic activity, leading to metabolic stress and elevated ROS formation, which promotes NLRP3 inflammasome and caspase 1 activation, thus enabling the production of mature IL-1β. ER stress, via TXNIP, may also activate the inflammasome. IL-1β autostimulation further amplifies inflammation, engendering a vicious cycle. IL-1β induces various cytokines and chemokines (such as IL-6, IL8, TNF and MCP1) that lead to the attraction and stimulation of macrophages. Macrophages are further stimulated by human islet amyloid polypeptide, which is co-secreted with insulin. IL-1 antagonism and NF-κB modulation dampen insulitis and improve insulin secretion.

Circulation

Obesity-induced type 2 diabetes is recognized as a state of systemic low-grade inflammation that is characterized by an increase in the serum concentrations of acute-phase proteins such as CRP, serum amyloid A and numerous cytokines including IL-6 and IL-1RA. These inflammatory mediators partly originate from the inflamed insulin-sensitive tissues and activated circulating immune cells. Monocytes and T cells mainly harbour a pro-inflammatory phenotype in response to systemic inflammation and chronic hyperglycaemia and/or dyslipidaemia.

Dysregulation of adipocyte-derived mediators is also reported, such as increased levels of free fatty acids or decreased amounts of the insulin-sensitizing adiponectin. Overall, these factors trigger chronic inflammatory responses in the vascular endothelium that enhance immune cell diapedesis to target tissues and further contribute to whole-body inflammation. Eventually, this pathological activation of the immune system may contribute to the long-term complications of diabetes: atherosclerosis, retinopathy, neuropathy and nephropathy.

Clinical studies of anti-inflammatory therapies for type 2 diabetes

Drug; company	Mechanism of action	Development status	Comments	Refs*
Anakinra (Kineret); Biovitrum	IL-R blockade	Phase II; approved for other indications	↓HbA1c, ↓FBG, ↓CRP, ↑insulin secretion; sustained effects for 39 weeks	1–3
Gevokizumab; Servier	IL-1β-specific antibody	Phase II; in Phase III for other indications	↓HbA1c, ↓CRP, ↑insulin secretion; effects statistically significant only at intermediate doses; long-acting, allowing for monthly (or less frequent) dosing	4
Canakinumab (Ilaris); Novartis	IL-1β-specific antibody	Phase III; approved for other indications	↓HbA1c, ↓CRP, ↑insulin secretion; not all effects were statistically significant but study was under-powered owing to low basal HbA1c; long-acting, allowing for monthly (or less frequent) dosing	5,6
LY2189102; Eli Lilly	IL-1β-specific antibody	Phase II	↓HbA1c, ↓CRP, ↑insulin secretion; sustained effects for 24 weeks	7
Salsalate (Mono-Gesic, Salflex, Disalcid, Salsitab); Schwarz Pharma/Elan Pharmaceuticals/3M/Upsher-Smith Laboratories	IKKβ–NF-κB inhibition	Phase III; approved for other indications	↓HbA1c, ↓FBG, ↓CRP, ↑insulin sensitivity, ↑insulin secretion, ↑adiponectin	8–13
CDP571; Celltech Therapeutics	TNF-specific antibody	Phase II	No effect on insulin sensitivity but underpowered and single-dose study (10 patients)	14
Etanercept (Enbrel); Amgen	Soluble TNFR–Fc fusion protein	Phase II; approved for other indications	No effect on insulin sensitivity but underpowered studies (7–10 patients) with a short duration (48 hours to 4 weeks)	15–17
Diacerein; Representaciones e Investigaciones Médicas	Decrease in TNF and IL-1β levels by an unknown mechanism of action	Phase II	↓HbA1c, ↓FBG, ↑insulin secretion	18

*Only published peer-reviewed studies are listed.

Table footnote

Although each study antagonizing the IL-1 system showed improvement of insulin secretion and glycaemia, this was not observed at all doses and some statistical limitations exist. Conversely, studies using TNF blockers were underpowered and of too short a duration to determine in humans the beneficial effects that were observed in animals.

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Abbreviations

CRP, C-reactive protein; ER, endoplasmic reticulum; FBG, fasting blood glucose; HbA1c, glycated haemoglobin; IFNγ, interferon-γ; IKKβ, inhibitor of NF-κB kinase-β; IL-1RA, interleukin-1 receptor antagonist; IL-1β, interleukin-1β; MCP1, monocyte chemoattractant protein 1; NF-κB, nuclear factor-κB; NLRP3, NOD-, LRR- and pyrin domain-containing 3; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumour necrosis factor; TNFR, TNF receptor; TXNIP, thioredoxin-interacting protein.

Further reading

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Competing interests statement

Marc Y. Donath has a patent for the use of IL-1 antagonists in type 2 diabetes.

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Edited by Sarah Crunkhorn; copyedited by Mariam Faruqi; designed by Susanne Harris.

http://www.nature.com/nrd/posters/inflammationtype2diabetes