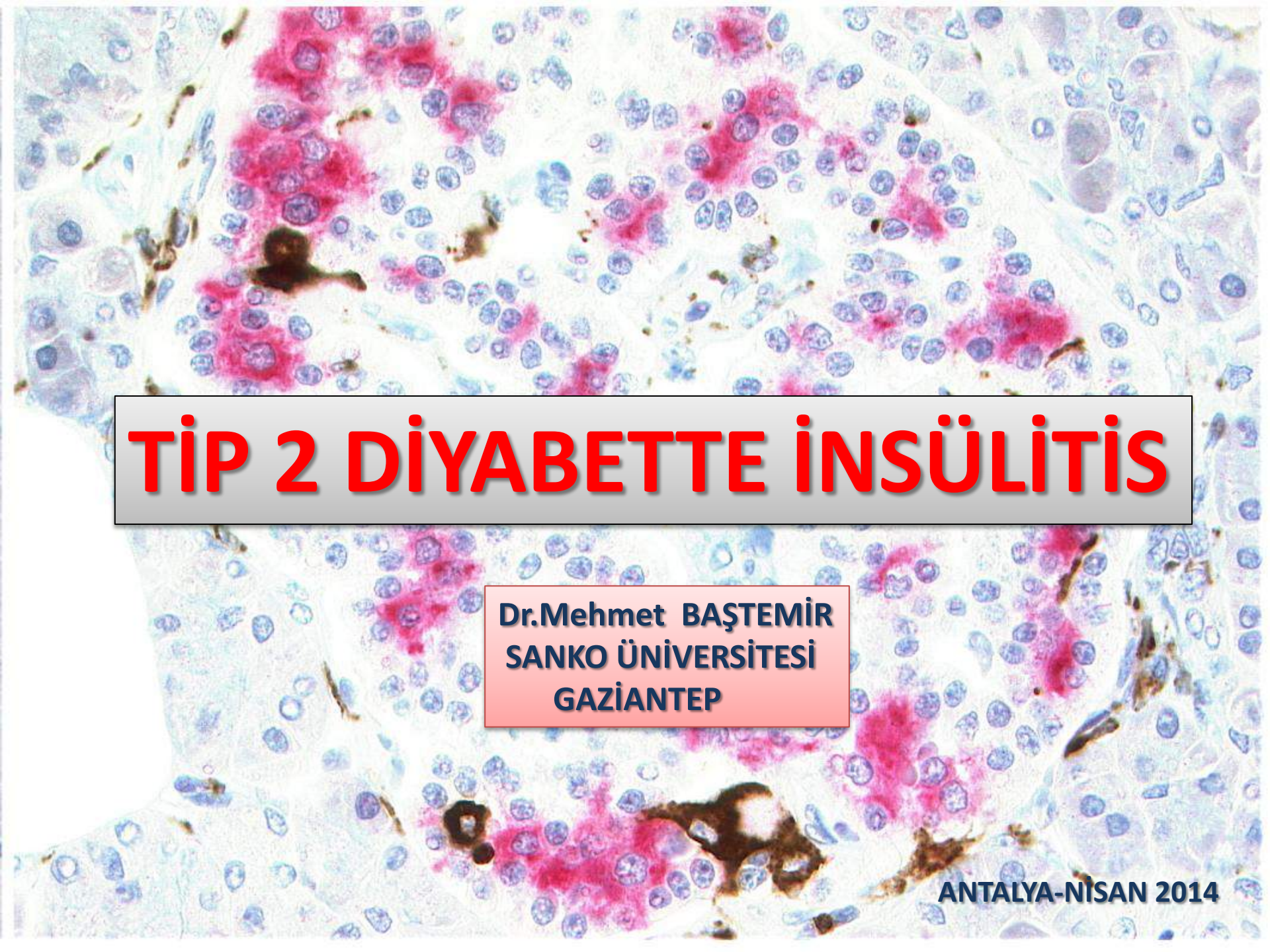
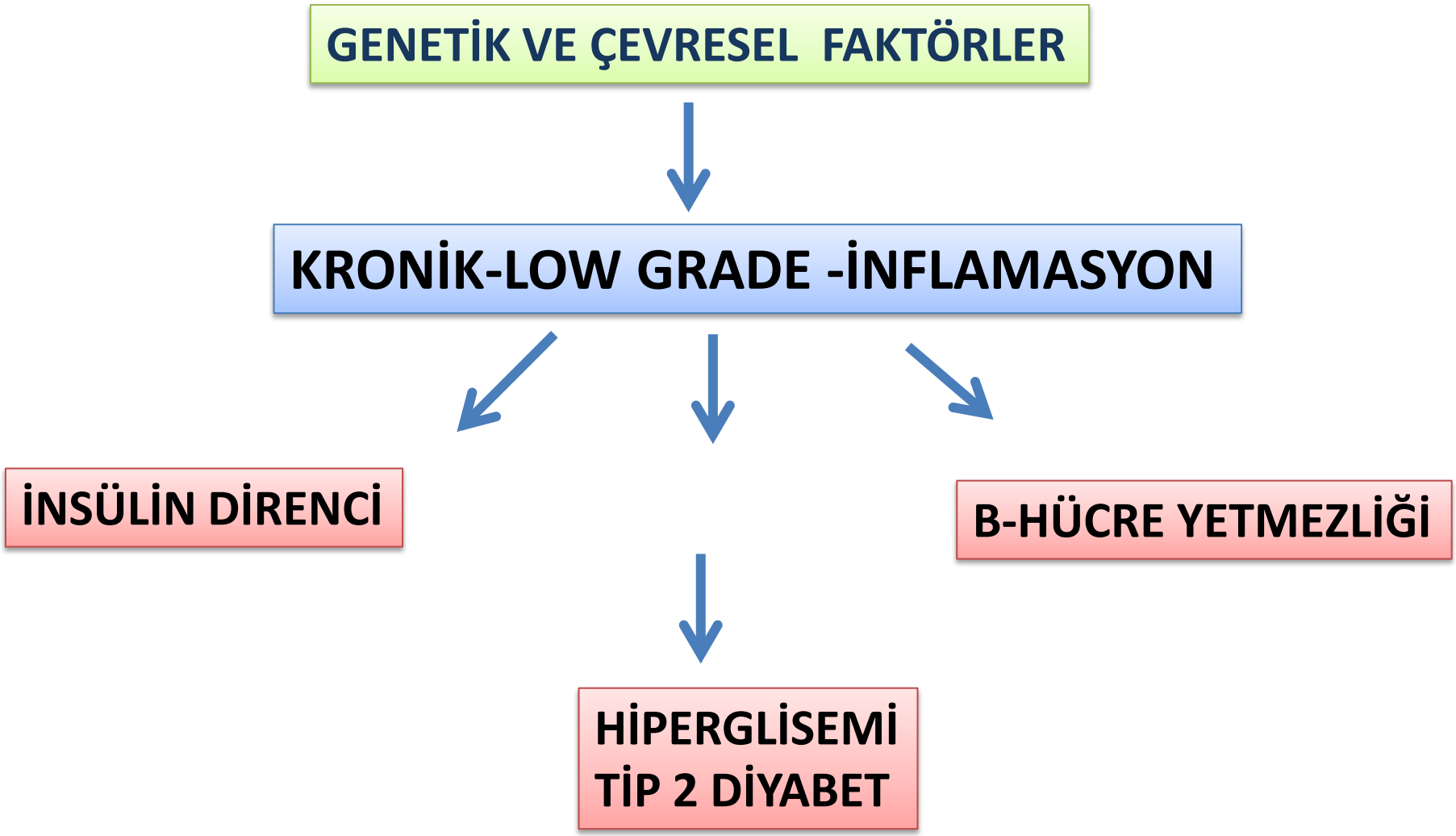


TİP 2 DİYABETTE İNSÜLİTİS

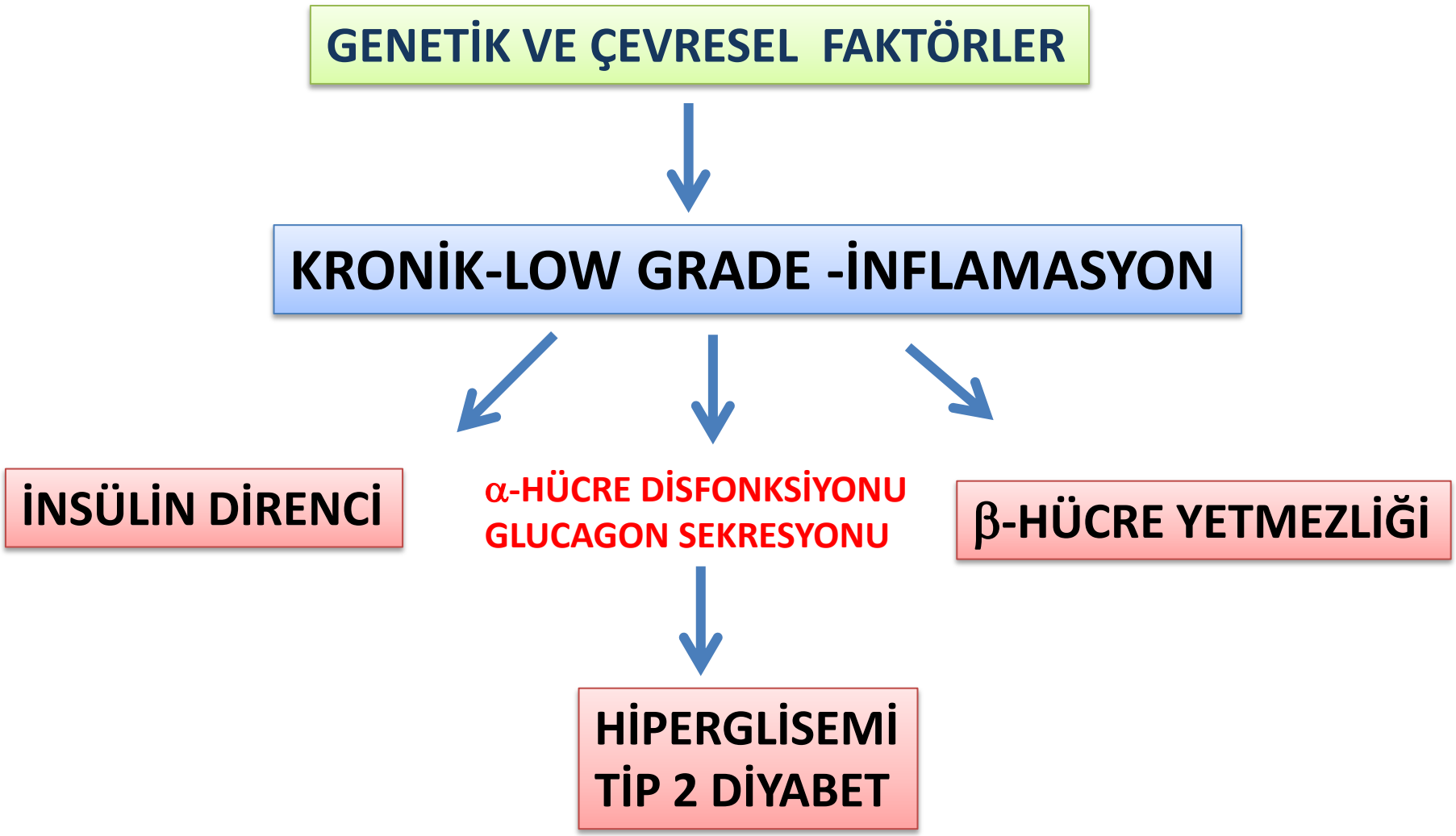
Dr.Mehmet BAŞTEMİR
SANKO ÜNİVERSİTESİ
GAZİANTEP

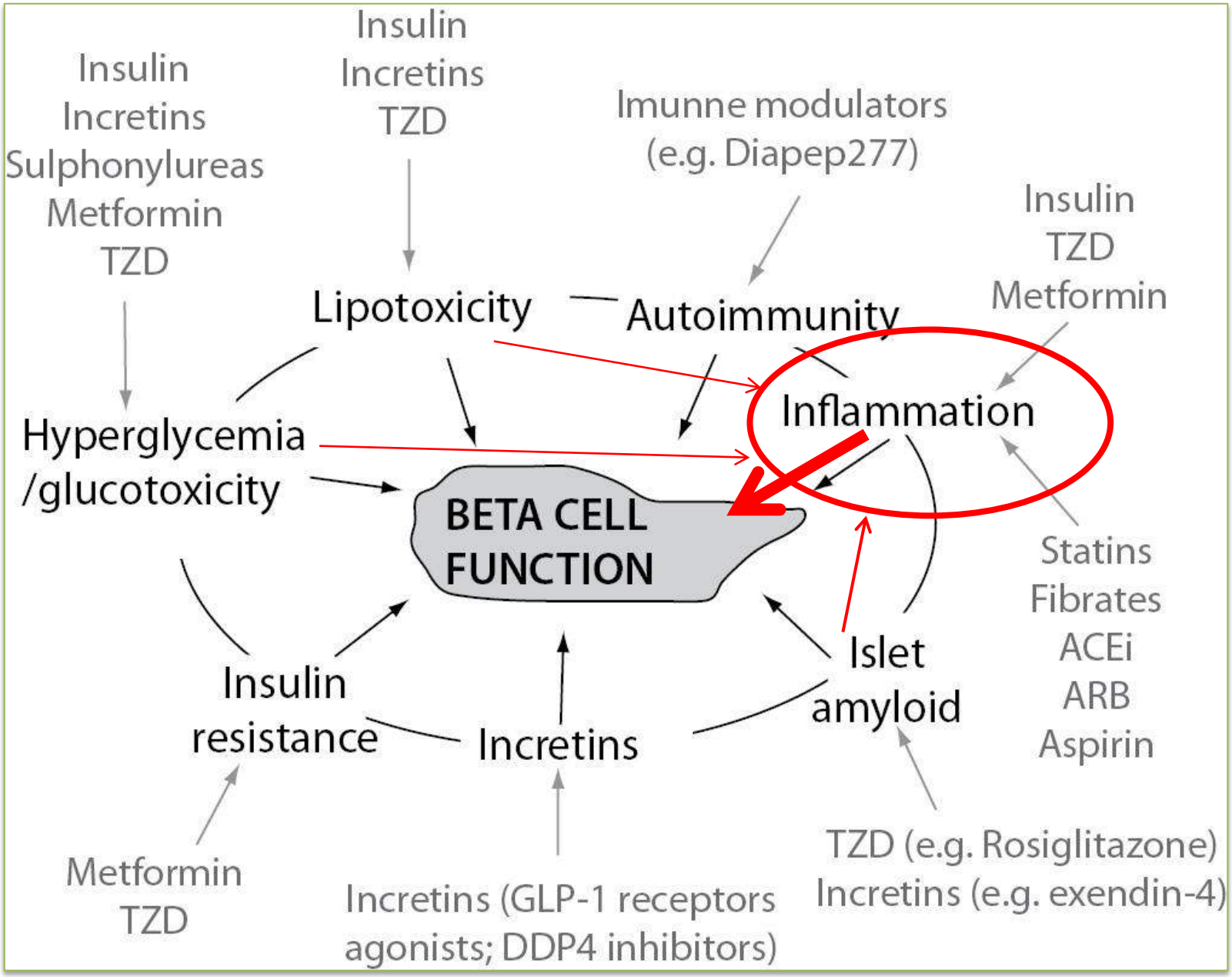
ANTALYA-NİSAN 2014

TİP 2 DİYABETİN PATOGENEZİ



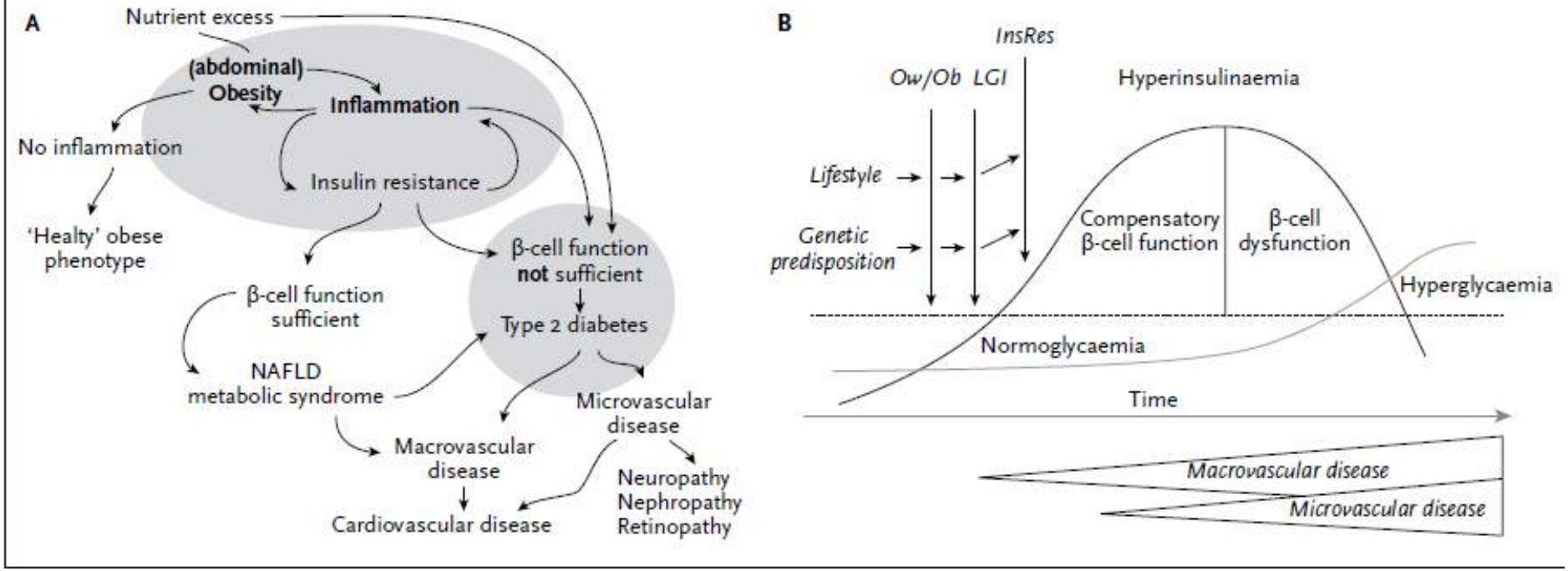
TİP 2 DİYABETİN PATOGENEZİ



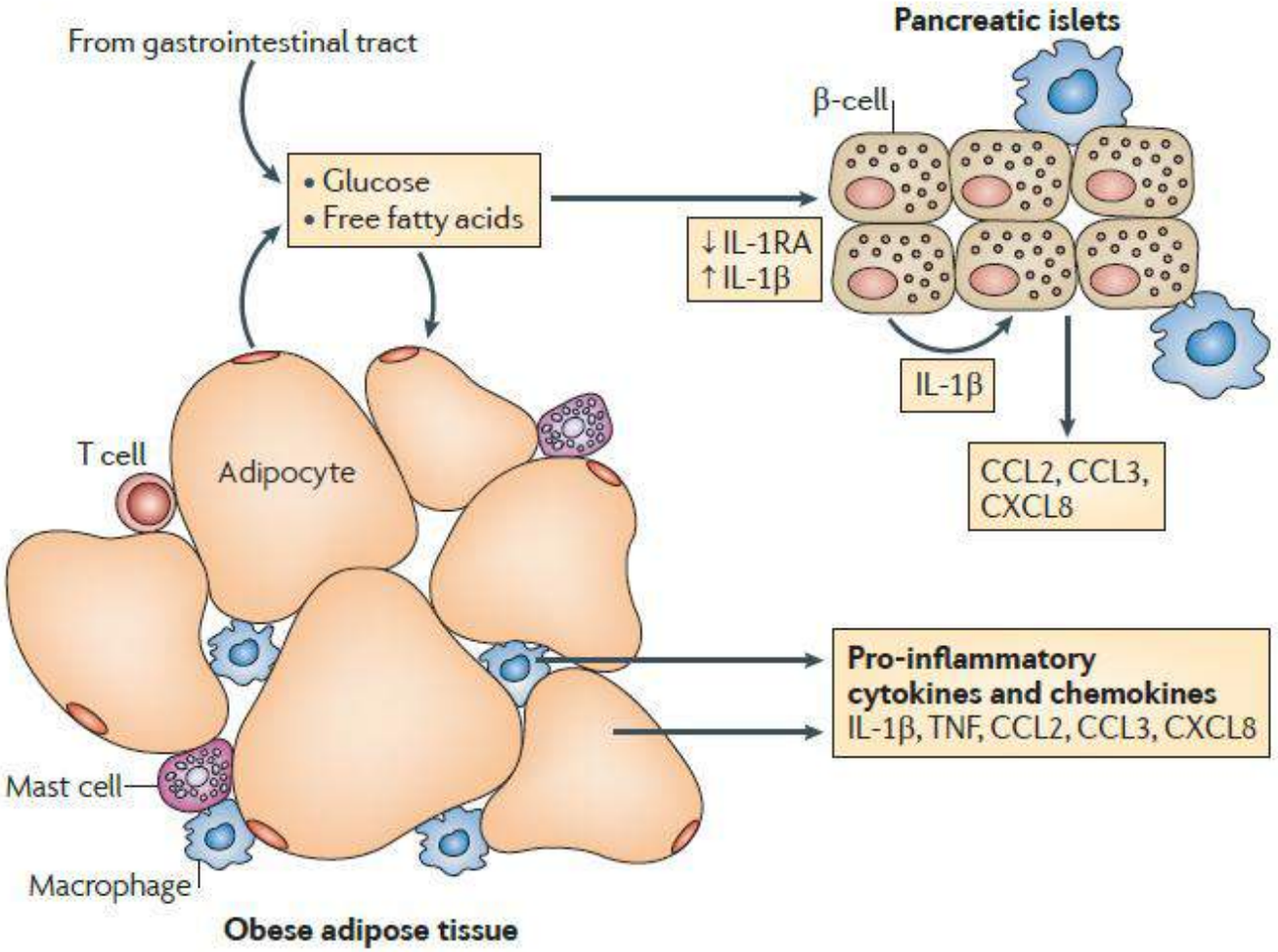

Insulin
Incretins
Sulphonylureas
Metformin
TZD
Insulin
Incretins
TZD
Imunne modulators
(e.g. Diapep277)
Insulin
TZD
Metformin
Lipotoxicity
Autoimmunity
Inflammation
Hyperglycemia
/glucotoxicity
BETA CELL
FUNCTION
Statins
Fibrates
ACEi
ARB
Aspirin
Islet
amyloid
Insulin
resistance
Incretins
Metformin
TZD
Incretins (GLP-1 receptors
agonists; DDP4 inhibitors)
TZD (e.g. Rosiglitazone)
Incretins (e.g. exendin-4)

OBEZİTE –TİP 2 DM İLİŞKİSİ

Figure 1. *Development of insulin resistance and B-cell failure are involved in the development of obesity-associated T2DM*



TİP 2 DM : İNFLAMASYONUN GELİŞİMİ



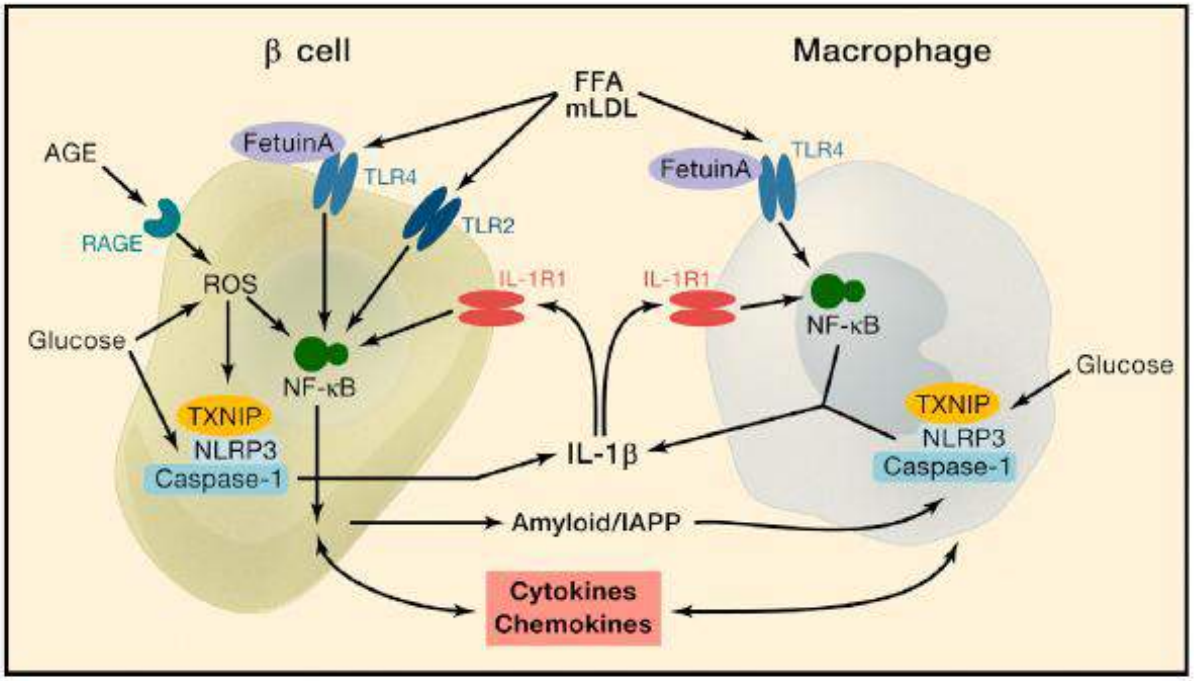


Figure 1. Innate Immune Response to Metabolic Stress in Pancreatic Islets

Increased circulating free fatty acids (FFA), modified LDL (mLDL) particles, and advanced glycation end products (AGE) bind to their cognate receptors (i.e., Toll-like receptor 2 [TLR2], TLR4, and RAGE, respectively), leading to NF-κB activation and the production of various proinflammatory chemokines and cytokines, including the proform of IL-1β. Furthermore, high concentrations of glucose promote the activation of the NLRP3 inflammasome through the recruitment of thioredoxin-interacting protein (TXNIP) in both β cells and macrophages. FFA and AGE, as well as islet-derived islet amyloid polypeptide (IAPP), may also directly trigger the NLRP3 inflammasome complex. Subsequently, pro-IL-1β is processed by the NLRP3-associated caspase-1 and secreted in the microenvironment. In turn, IL-1β sustains autocrine and paracrine activation of both β cells and macrophages, exacerbating the chronic inflammatory responses in the islets.

TİP 2 DM' TE LOKAL ADACIK İNFLAMASYONU

1) FONKSİYON BOZUKLUĞU

2) HÜCRE ÖLÜMÜ/ DOKUNUN YENİDEN YAPILANMASI

3) AMİLOİD DEPOZİSYONU

4) FİBROZİS

5) SİTOKİN VE KEMOKİN ÜRETİMİ

6) MAKROFAJLAR

Tip 2 DM ve İnsülitis

- **Tip 1 DM……otoimmunite**
- **Tip 2 DM……. insülin direnci ve β hücre disfonksiyonu…..β hücre ölümü**
- **Veriler her iki diyabet tipinin adacık inflamasyonuyla karakterize olduğunu göstermekte.**

- **Tip 2 DM: aşırı beslenme ve insülin direnci β hücrelerinin proinflamatuvar mediatörlerin üretimine neden olur. β hücre fonksiyon bozukluğuna, yaşamının kısalmasına ve hatta immün hücrelerin adacıklara yerleşmesine ve inflmasyonun artmasına neden olur.**

- **Tip 2 DM kronik inflamatuvar bir hastalık olarak düşünülebilir. Tip 1 DM ve Tip 2 DM de patogenezde ortak noktalar- benzer mekanizmalar olduğu düşünülmektedir.**

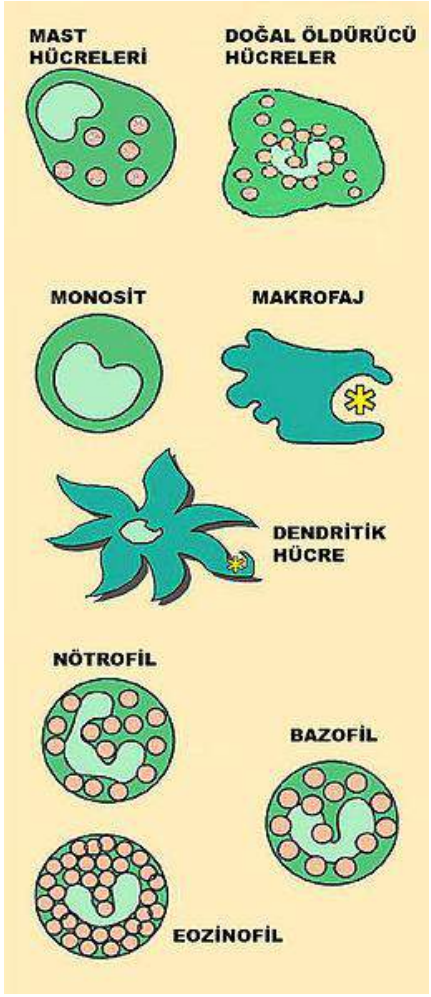
Bağışıklık Sistemi

- Doğuştan gelen bağışıklık sistemi (Innate immunity)
- Edinilmiş bağışıklık sistemi (adaptive immunity)

- Doğuştan gelen bağışıklık sistemi:
  - Non-spesifik savunma mekanizması
  - Hücreler

  - Hücreler, değişken olmayan motifler için değişken olmayan reseptörler eksprese ederler.
  - Memelilerde çok sayıda reseptör ailesi var (pattern-recognition receptors [PRRs]) , örneğin membrana bağlı Toll-like receptors (TLRs) veya sitoplazmik nucleotidebinding oligomerization domain receptors, kısaca, NOD-like receptors (NLRs).

  - Çoğu PRR, özellikle TLR ler nükleer faktör- factor-κB (NF-κB) ve interferon-releasing factor'lerin (IRFs) aktivasyonunu sağlar ve edinilmiş bağışıklık sisteminin aktivasyonu ile direk bir bağlantı kurulmasını sağlar. Bu durum sitokinlerin (örn. İnterfreonların veya interlökinlerin), kemokinlerin üretimlerine ve bunların reseptörlerinin ekspresyonlarına neden olur.



Tip 2 DM de otoinflamasyon

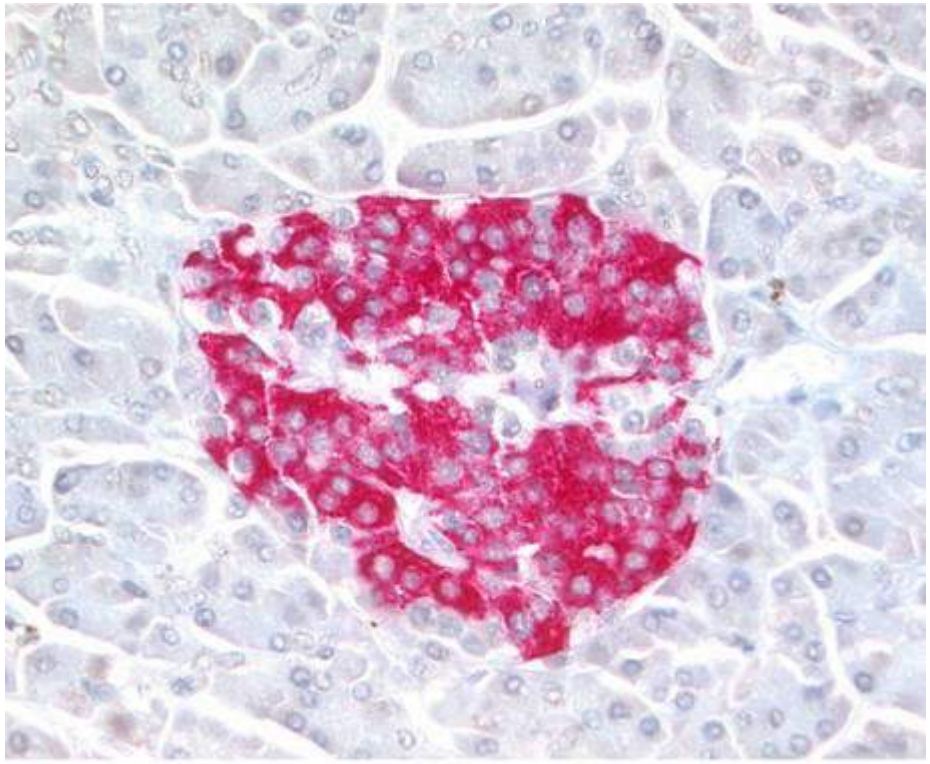
- **Kronik inflamasyon: patofizyolojik faktör….obezite,hiperglisemi ve insülin direnci**
- **Tip 2 DM li hastaların pankreaslarının immün hücrelerle infiltre olduğu gösterildi. Metabolik stres ve obezite β- hücrelerini direk etkilerler ve bu hücreler proinflamatuar yanıtla karşı karşıya kalırlar. Bu durum insülin üretim ve salınımını bozar.**
- **Viseral adipoz dokunun kronik inflamasyonu …proinflamatuar mediatör üretimi…adipoz hücre ve pankreatik adacık hücre etkilenimi**
- **Bu inflamasyon proinflamatuar proteinlerin (C-reactive protein (CRP), TNF-α, IL-6 ve IL-1β gibi) aşırı eksperyonuna neden olur.**
- **Bu proinflamatuar moleküller doğal bağışıklık sistemi hücrelerini aktive ederler…pankeas adacıklarında monosit ve makrofaj populasyonunda artış…doku hasarı..pankreas, adipoz doku ve vasküler yapı da**
- **Tip 2 DM hayvan modellerinde ve Tip 2 DM li insan pankreas adacıklarında histolojik çalışmalarda T hücre ve B hücre belirgin değildir.**
- **Brooks-Worrell ve ark. Fenotipik Tip 2 DM hastalarında adacık proteinlerine T hücre reaktivitesi tesbit etmişler. Bozulmuş β- hücre fonksiyonu ile çok güçlü korelasyon tesbit etmişler (otoantikor pozitif).**

Brooks-Worrell B, Palmer JP.. Clin Exp Immunol. 2012;167:40-46

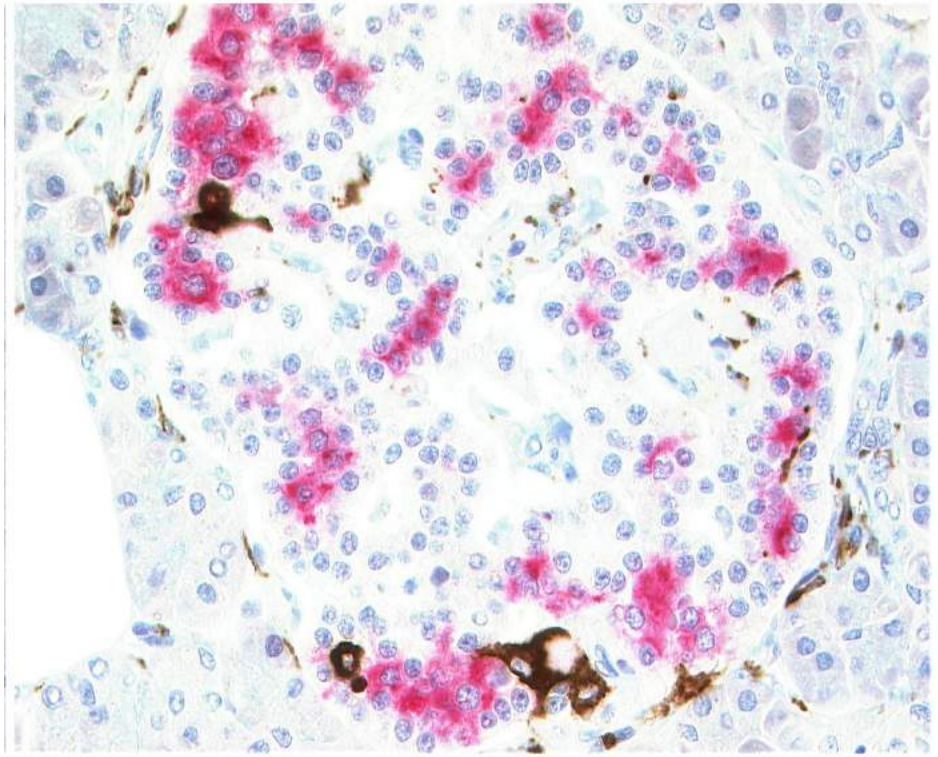
TİP DİYABETTE İNSULİTİS

İnsan pankreası

Kontrol



Tİp 2 diyabet



insulin

CD68

J. Ehses et al. Diabetes 56: 2356-2370

Original Article

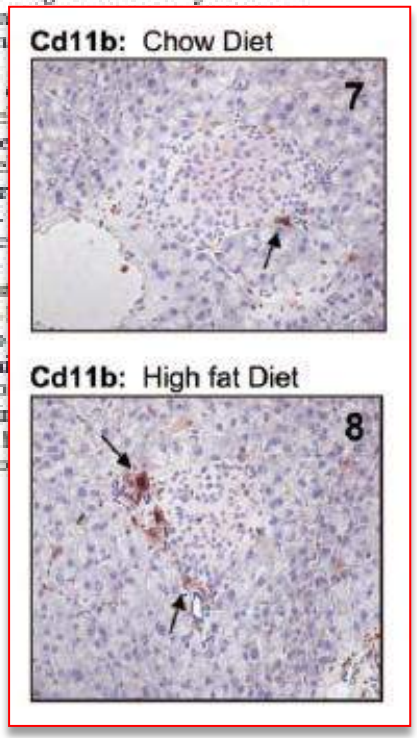
Increased Number of Islet-Associated Macrophages in Type 2 Diabetes

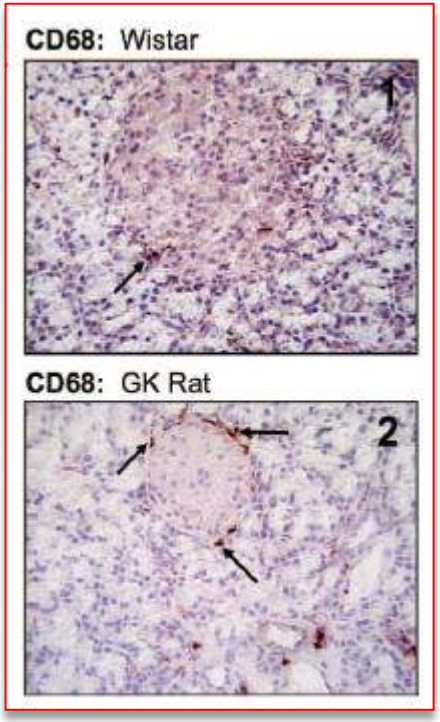
Jan A. Ehses,[1] Aurel Perren,[2] Elisabeth Eppler,[3] Pascale Ribaux,[4] John A. Pospisilik,[5] Ranit Maor-Cahn,[1] Xavier Gueripel,[2] Helga Ellingsgaard,[1] Marten K.J. Schneider,[6] Gregoire Biollaz,[7] Adriano Fontana,[7] Manfred Reinecke,[3] Francoise Homo-Delarche,[8] and Marc Y. Donath[1]

Activation of the innate immune system in obesity is a risk factor for the development of type 2 diabetes. The aim of the current study was to investigate the notion that increased numbers of macrophages exist in the islets of type 2 diabetes patients and that this may be explained by a dysregulation of islet-derived inflammatory factors. Increased islet-associated immune cells were observed in human type 2 diabetic patients, high-fat–fed C57BL/6J mice, the GK rat, and the *db/db* mouse. When cultured islets were exposed to a type 2 diabetic milieu or when islets were isolated from high-fat–fed mice, increased islet-derived inflammatory factors were produced and released, including interleukin (IL)-6, IL-8, chemokine KC, granulocyte colony-stimulating factor, and macrophage inflammatory protein 1α. The specificity of this response was investigated by direct comparison to nonislet pancreatic tissue and β-cell lines and was not mimicked by the induction of islet cell death. Further, this inflammatory response was found to be biologically functional, as conditioned medium from human islets exposed to a type 2 diabetic milieu could induce increased migration of monocytes and neutrophils. This migration was blocked by IL-8 neutralization, and IL-8 was localized to the human pancreatic α-cell. Therefore, islet-derived inflammatory factors are regulated by a type 2 diabetic milieu and may contribute to the macrophage infiltration of pancreatic islets that we observe in type 2 diabetes. *Diabetes* 56:2356–2370, 2007

Activation of the innate immune system has long been reported in obesity, insulin resistance, and type 2 diabetics and is characterized by increased circulating levels of acute-phase proteins and of cytokines and chemokines (1–5). However, the notion that excess circulating nutrients may stimulate the β-cell to produce chem
and immune cell infiltration h
type 2 diabetic patients.

One of the most classical
nology is the CXC family e
(CXCL8) (6). IL-8 is produce
and endothelial and epithe
associated with infections, gr
cancer, and atherosclerosis.
neutrophils, the chemotactic
tant in mediating monocyte
does not express IL-8. Ins
homolog of IL-8 is thought to
Gro-α in the rat), which also
granulocyte and monocyte mi
thought to be an ortholog o
levels of IL-8 are elevated i
(10,11), in whom IL-8 has
insulin resistance and athero





JLB

Article

Accumulation of M1-like macrophages in type 2 diabetic islets is followed by a systemic shift in macrophage polarization

Helena Cucak, Lars Groth Grunnet,† and Alexander Rosendahl*,‡*

*Department of Diabetes Complication Biology and †Islet Biology, Hagedorn Research Institute, Novo Nordisk A/S, Måløv, Denmark

RECEIVED FEBRUARY 11, 2013; REVISED JULY 18, 2013; ACCEPTED AUGUST 20, 2013. DOI: 10.1189/jlb.0213075

ABSTRACT

Human T2D is characterized by a low-grade systemic inflammation, loss of β-cells, and diminished insulin production. Local islet immunity is still poorly understood, and hence, we evaluated macrophage subpopulations in pancreati… model of T2… disease, on… in the diabe… in the nondi… islet residen… pared with … nounced re… macrophag… jority of the … CD68⁺F4/8…

Introduction

The global prevalence of T2D is steadily growing and has been shown to be linked to lifestyle changes associated with obesity. The numbers of estimated T2D cases are reaching epidemiological levels, with 285 million people considered to have T2D … people … is a … Periph… …s been … with an … [3]. … and … their … blood

In summary, our results show that proinflammatory M1-like galectin-3^{+} CD80/CD86^{low} macrophages invade diabetic islets. Moreover, the innate immunity matures in a diabetes-dependent manner from an initial proinflammatory toward a profibrotic phenotype, supporting the concept that T2D is an inflammatory disease. *J. Leukoc. Biol.* **95: 149–160; 2014.**

TİP 2 DM ADACIKLARINDA MAKROFAJ POLARİTESİ

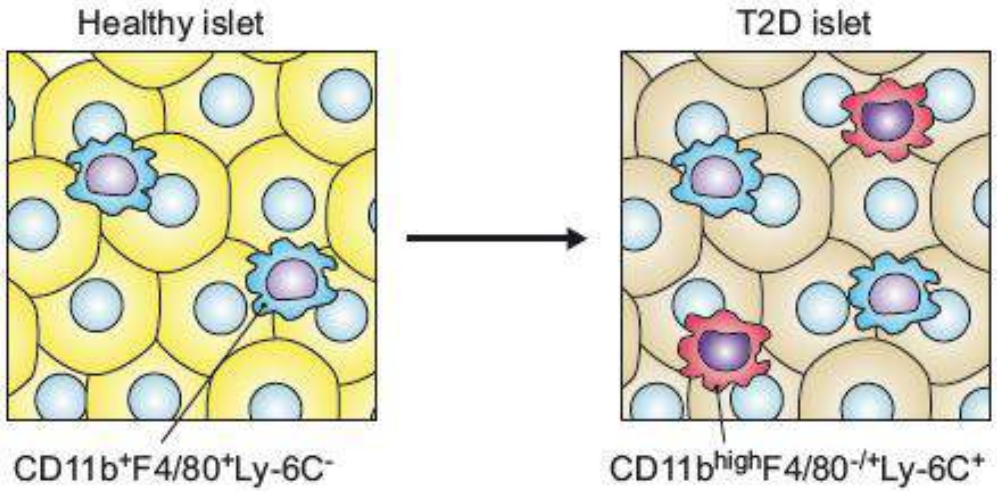


Figure 2. Islet macrophage polarity in type 2 diabetes (T2D). The majority of resident macrophages in healthy islets exhibit $CD11b^{+}F4/80^{+}Ly\text{-}6C^{-}$. In T2D islets $CD11b^{high}F4/80^{-/+}Ly\text{-}6C^{+}$ monocytes/macrophages accumulate.

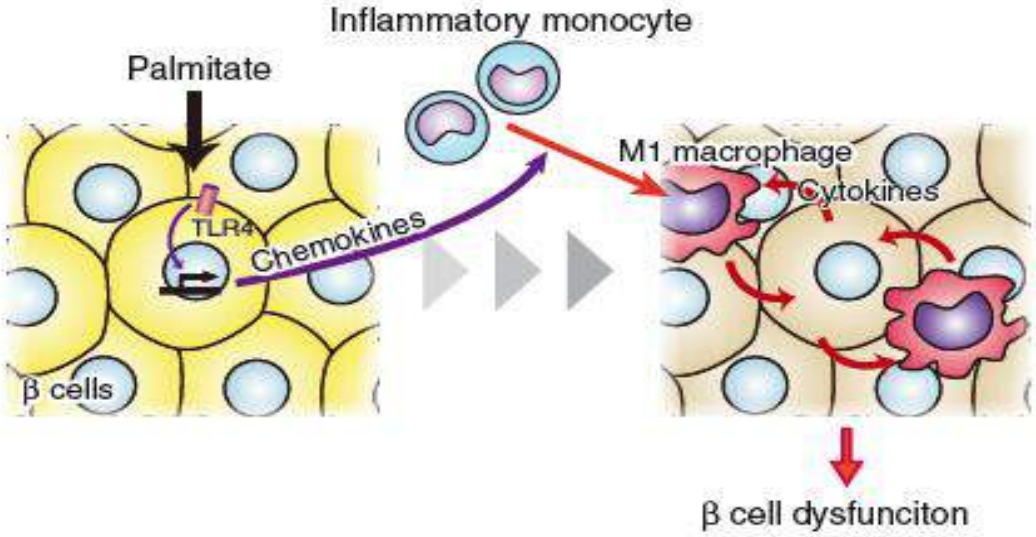


Figure 3. Palmitate-TLR4 pathway leading to islet inflammation and β-cell dysfunction. Palmitate induces β-cell dysfunction *in vivo* at least partly by activating inflammatory processes in islets. β-Cells sense palmitate via the TLR4/MyD88 pathway and recruit inflammatory monocytes to islets by producing chemokines. The recruited monocytes differentiate into M1 macrophages that play a pivotal role in β-cell dysfunction induced by palmitate.

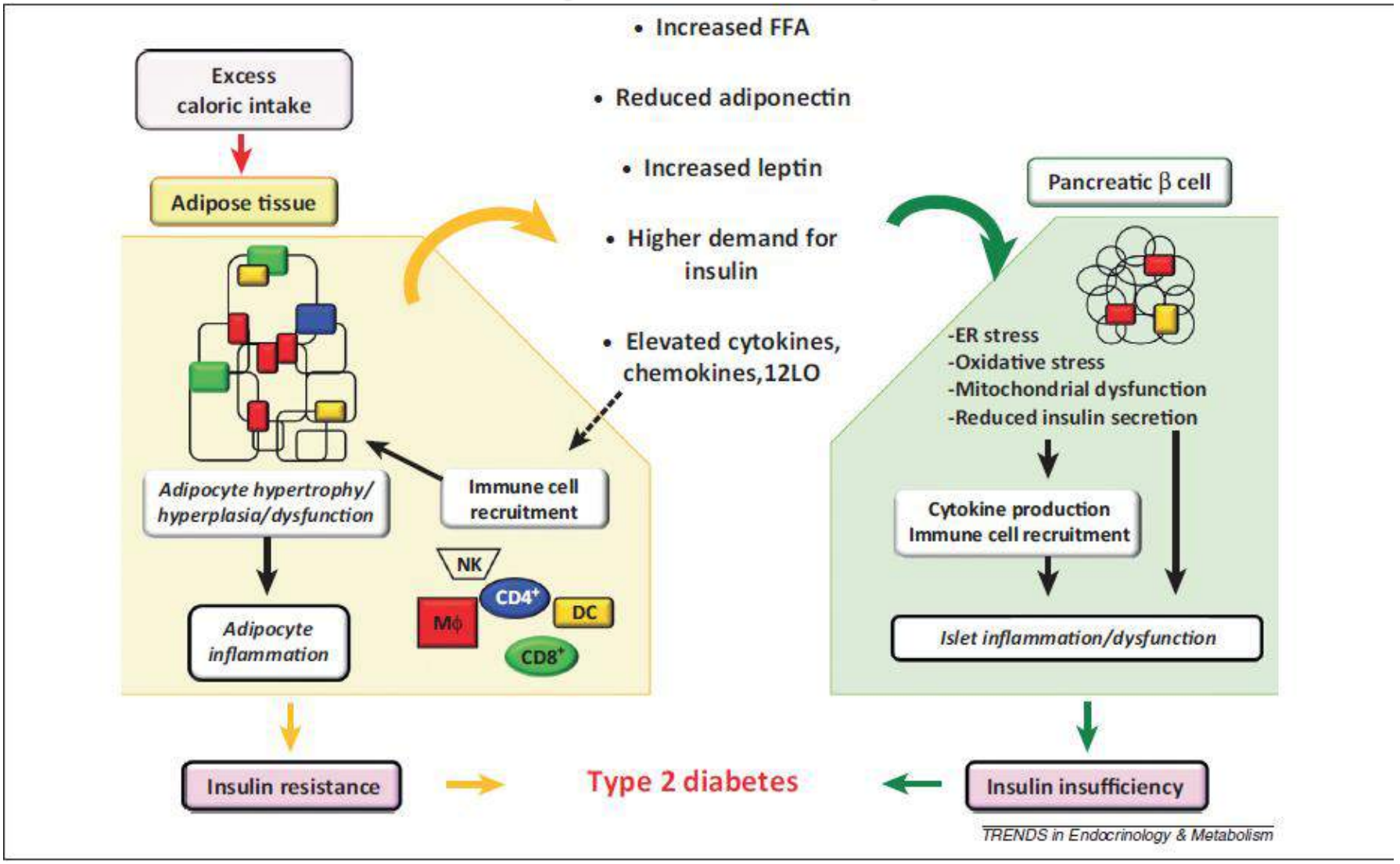
Tip 2 DM'de inflamasyonda rol oynayan aktörler:

- Adipoz dokunu rolü
- Endoplazmik retikulum stresi adacık inflamasyonunu indükler.
- IL-6 ve ekzersiz: bir miyokinin pro – ve antiinflamatuar özellikleri ile rolü
- IL-1: bir master sitokindir ve inflamatuar yanıtı tetikler ve arttırır.
- NF-κB nin santral rolü
- Lipoksijenaz, sitokine maruziyet üzerine stresin potansiyel mediatörüdür

ADİPOZ DOKUNUN ROLÜ

- Adipositte obezite ilişkili metabolik değişiklikler kronik inflamasyonla ilişkili..
- İmmünolojik mediatör oluşumu, immün hücre aktivasyonu ve göçü
- İnflame adipoz doku proinflamatuvar adipokinlerin üretimini arttırır (TNF, leptin, IL-6, CC-kemokin ligand2 ve diğerleri.)
- MCP-1 makrofajların dokuya göçüne neden olur ve makrofaj infiltrasyonu olur. M1 makrofajlar , TNF, IL-6 ve NO üretirler.
- Proinflamatuar CD4+T hücreleri adipoz dokuda CD8+ T hücre gelişimini stimule eder ve hücre ve yabancı maddelerin lizizine neden olur.
- Antiinflamatuar sitokinlerin (IL-10 ve SCRP-5) düzeyleri azalır.
- IL-10 ve SCRP-5 , TNF-α yı inhibe eder, NF-κB aktivasyonunu azaltır ve makrofaj köpük hücre gelişimini geciktirir Bu antiiflamatuar sitokinlerin azalması patolojik duruma karşı korunmayı engeller.
- Sonuç olarak adipoz doku inflamasyonu adacıklarda metabolik strese neden olur ve immün hücrelerin bu bölgeye göçü adacık inflamasyonuna neden olur.

Obezitede adipoz dokunun fonksiyonel bozukluğu B-hücre inflamasyonunu ve Tip 2 DM'i tetikler



Endoplazmik retikulum stresi adacık inflamasyonunu indükler

- Pankreatik β-hücresi fizyolojik olarak endoplazmik retikulum stresi ile karşı karşıya kalır bu durum insülin sentez ve sekresyonunda fluktasyon gösteren ihtiyaç durumunda endoplazmik retikulumun kapasitesini ayarlamak için gereklidir.

- Bu stresi ortadan kaldırmak için ER bir sinyal kaskadını (unfolded protein response (UPR) tetikler. ER fonksiyonunun adaptasyonunu ve yeniden kazanılmasını sağlar.
- Üç farklı UPR sensörü var:
  - protein kinase RNA (PKR)-like ER kinase (PERK)…global protein sentezini azaltır. ER' un iş yükü azalır
  - inositol-requiring enzyme-1α (IRE1α)….
  - activating transcription factor 6 (ATF6)……ER biyogenezinde hatalı protein yıkımında görev alır.
- Eğer bu sistem bozulursa apopitoz tetiklenir.
- Artan glikoz, FFA ve insülin sentez ihtiyacı β-hücre ve adipositlerde oksidatif ve ER stresine neden olur. Bu durum adacıklarda inflamasyona ve insülin direncine neden olur.

- Uzun süreli ve aşırı β-hücre UPR si Tip 2 DM de β-hücre disfonksiyonuna ve hücre ölümüne neden olur.

İNFLAMASYONU BAŞLATANLAR

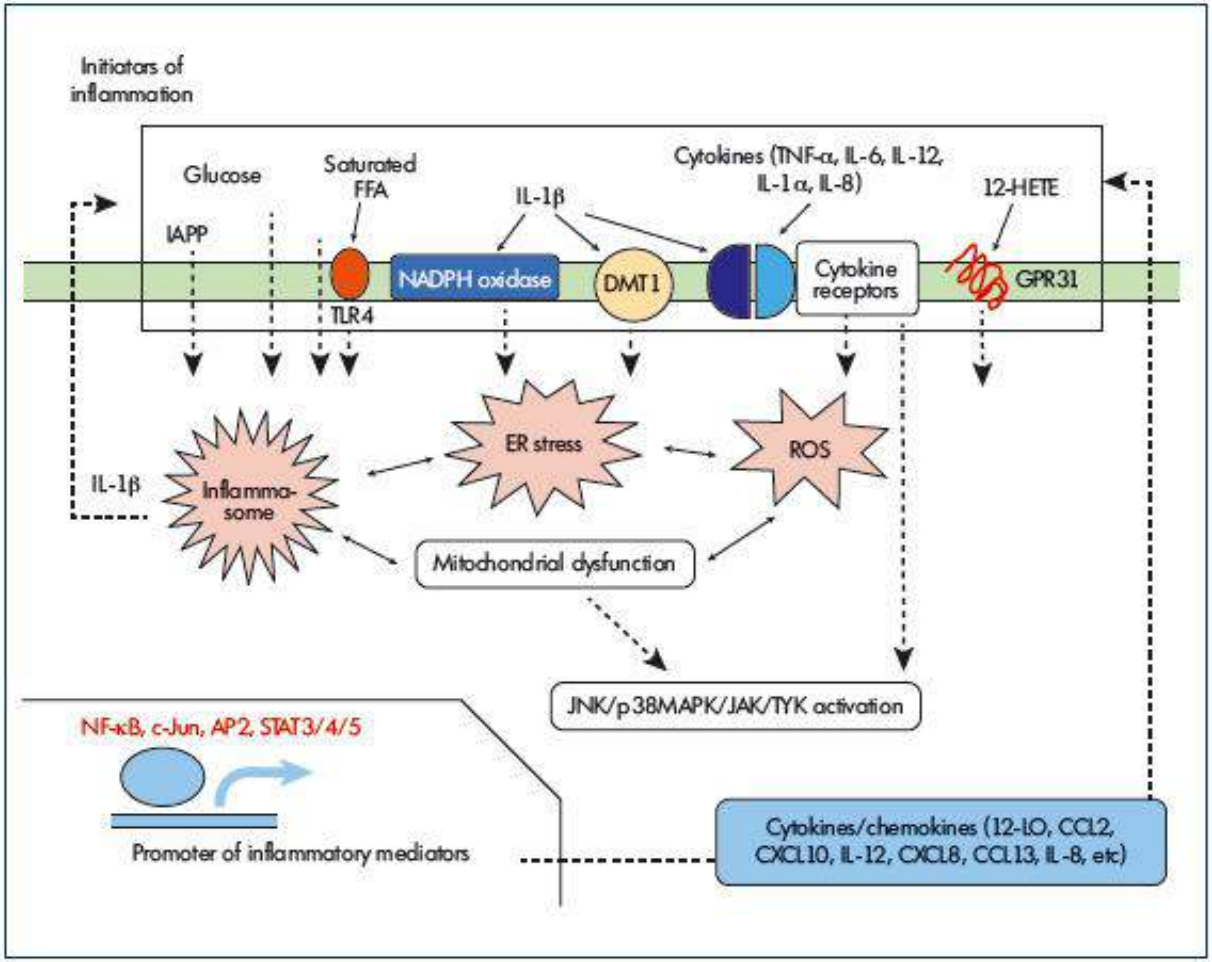
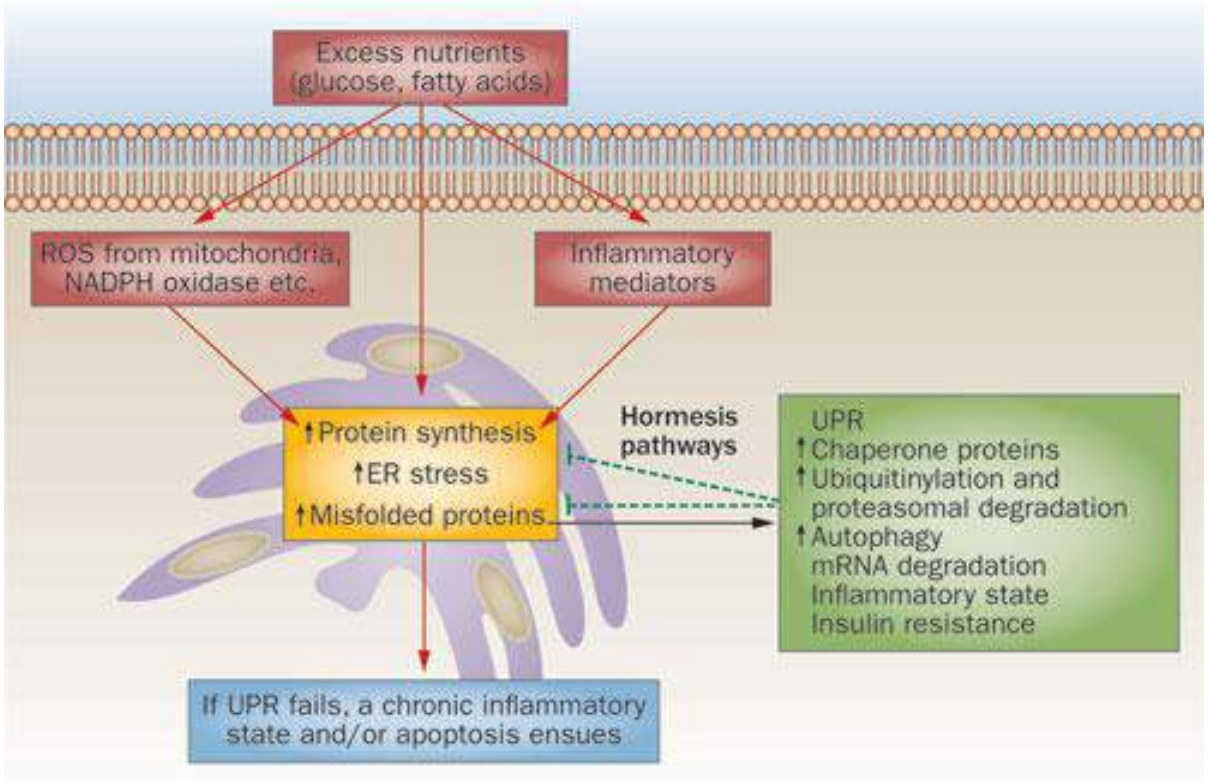


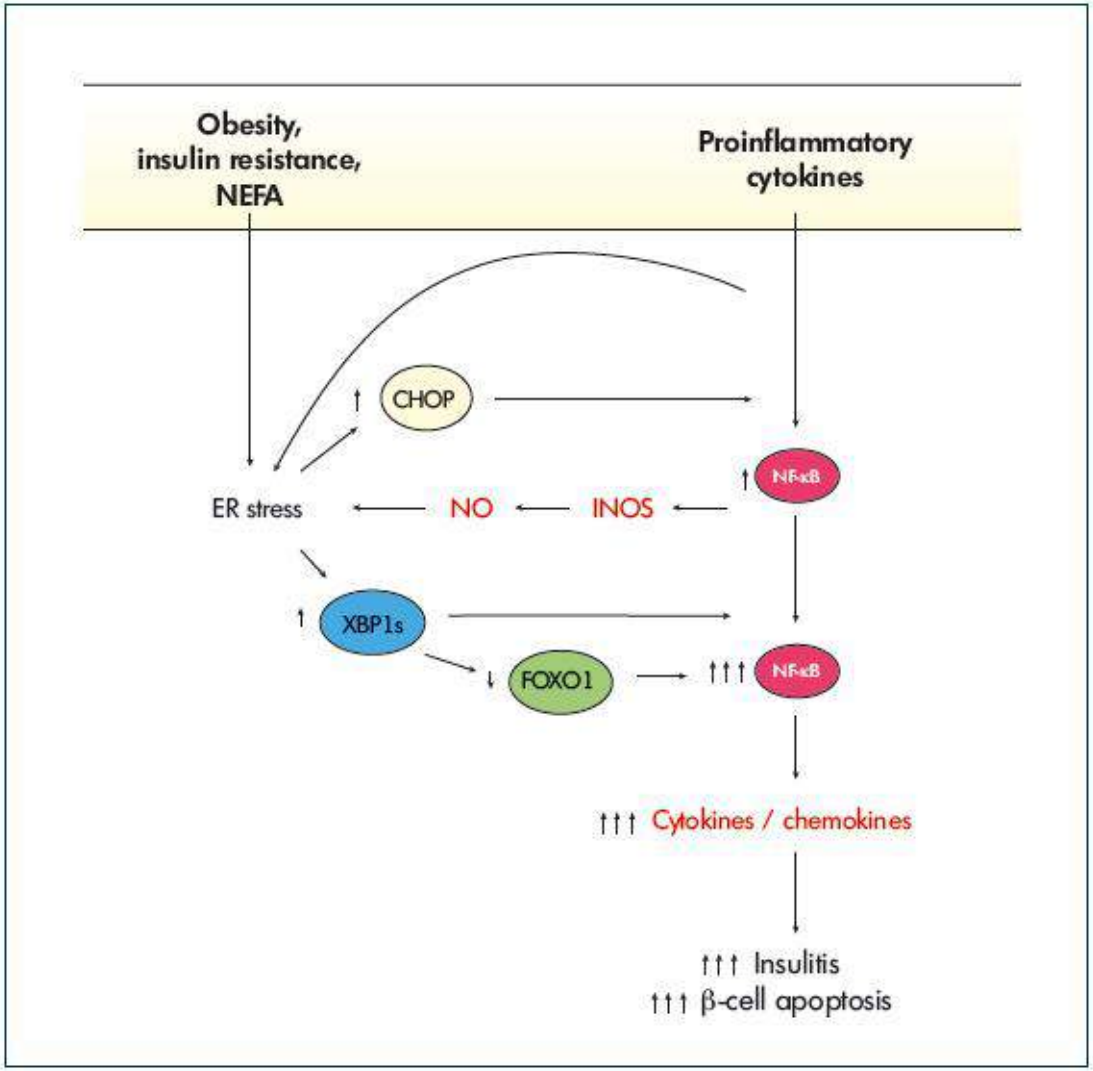
Figure 3 The unfolded protein response—a hormetic response to endoplasmic reticulum stress



Kolb, H. & Eizirik, D. L. (2011) Resistance to type 2 diabetes mellitus: a matter of hormesis?
Nat. Rev. Endocrinol. doi:10.1038/nrendo.2011.158

nature REVIEWS ENDOCRINOLOGY

Pankreatik β-hücrede unfolded protein response (UPR) ve inflamasyon arasındaki ilişki



IL-1: bir master sitokin olarak inflamatuar yanıtı tetikler ve arttırır-1

- Düşük dozlarda IL-1β , pankreatik adacıklarda insülin sekresyonu iyileştirir ve β hücre replikasyonunu arttırır ve β-hücre apopitozunu azaltır.
- Metabolik strese bağlı olarak yüksek seviyede IL-1β β hücre proliferasyonunu bozar ve β hücre disfonksiyonuna neden olur.
- Sature yağ asiti palmitat insan pankreatik hücrelerinde ER stresini , NF-κB aktivasyonunu ve sitokinlerin upregülasyonunun (IL-1β, TNF, ve IL-6) ekspresyonunu indükler.
- Doğal bağışıklık sistemindeki pek çok stimulus (örn. sitokinler.. TNF-α, IL1-α, IL-1β) veya TLR ligandları ile fagositik hücrelerin stimulasyonu NF-κB nın aktivasyonunu ve pro-IL-1β' nin upregülasyonunu indükler.

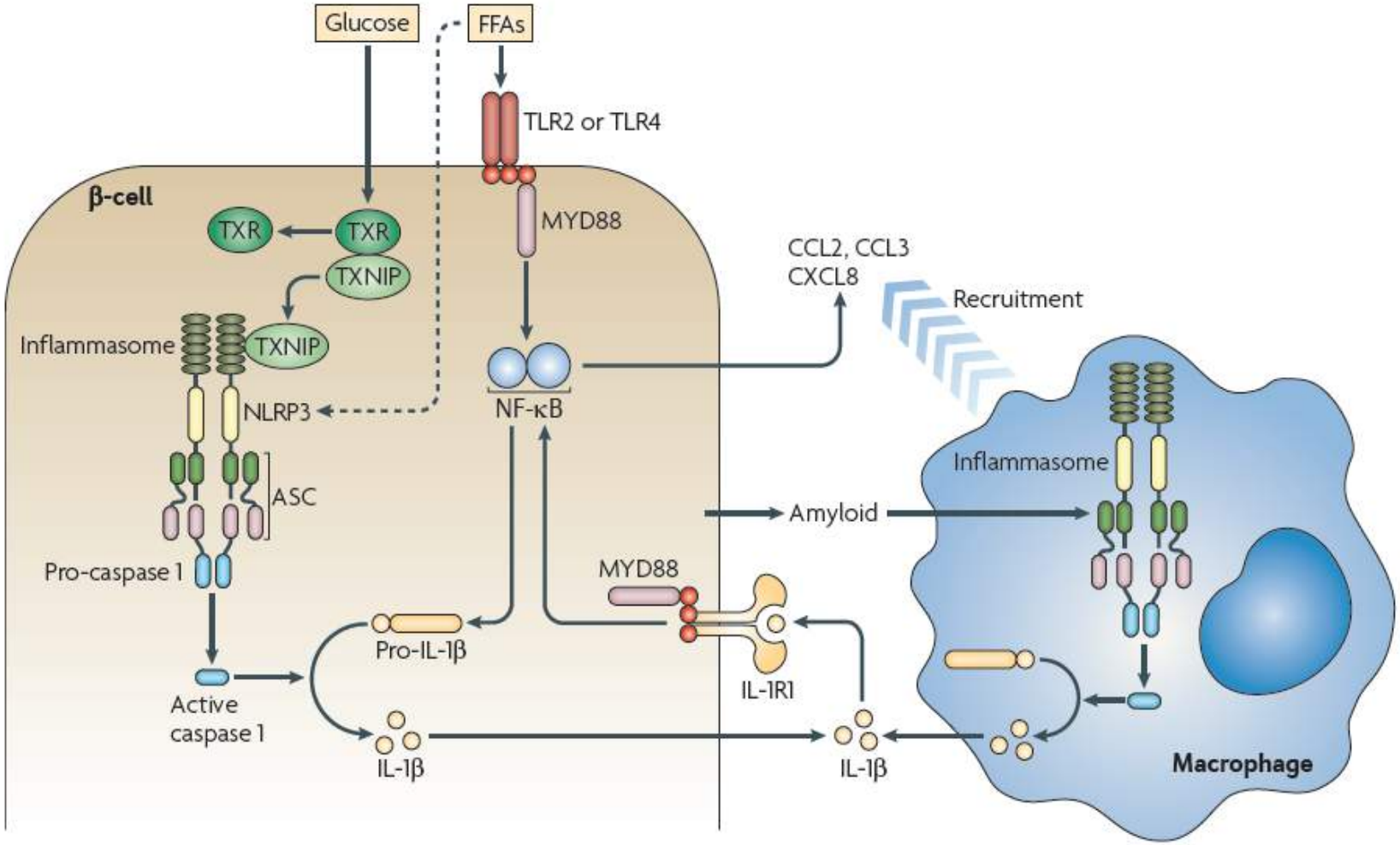


Figure 2 | **Interleukin-1β-induced inflammation in islets of patients with type 2 diabetes.**

IL-1: bir master sitokin olarak inflamatuar yanıtı tetikler ve arttırır-2

- **IL-1β, NF-κB aktivasyonu ile çok sayıda sitokin ve kemokinlerin (CC-chemokine ligand 2 (CCL2), CCL3, and CXC-chemokine ligand 8 (CXCL8)) üretimini indükler.**
- **FFA' lerin indüklediği Toll-like receptor 2 (TLR2) veya TLR4 aktivasyonu ile bu durum desteklenir ve makrofajların ilgili bölgeye göçüne neden olur.**
- **FFA'ler NLRP3 inflamazomunu direk olarak aktive edebilir.**
- **Adacık kökenli amiloid göç ile gelen makrofajları aktive edebilir ve bunu NLRP3 inflamazomu aracılığı ile yapar. IL-1β üretimini arttırır. IL-1β, IL-1 receptor type 1 (IL-1R1) ile otostimülasyon döngüsünü arttırır.**

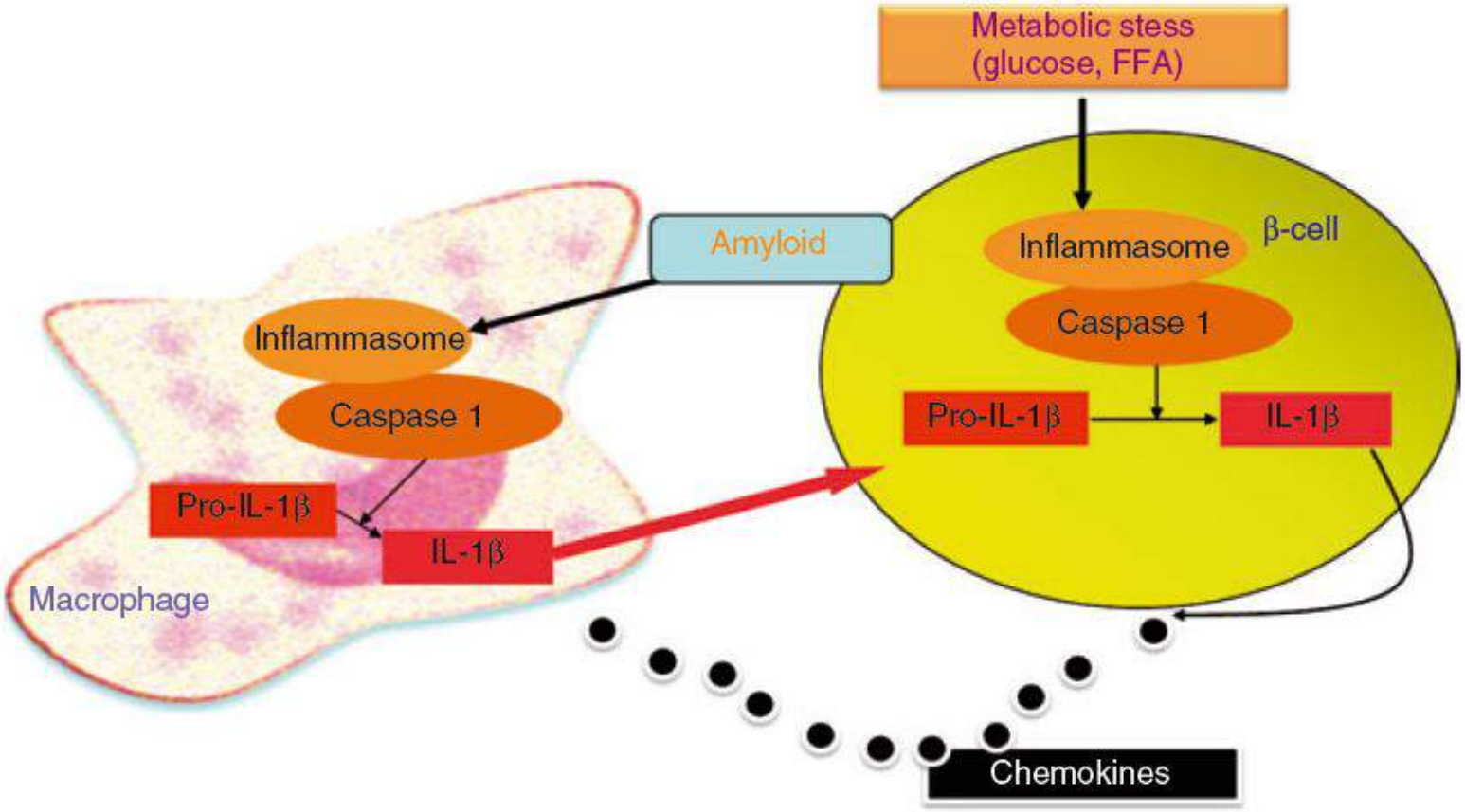
IL-1: bir master sitokin olarak inflamatuar yanıtı tetikler ve arttırır-3

- İnflamazom çok sayıda proteinin bir araya gelmesi ile oluşan kompleks bir yapıdır ve doğal bağışıklık sisteminin aktivasyonunun yönlendirilmesinde anahtar bir rol oynar; çeşitli metabolik bozukluklar ile aktive olabilir(pankreatik adacıklarda glikoz ve hIAPP ve adipoz dokuda lipopolysakkarit, FFA ve seramidler..diyabetik hastada)

- B hücresinde thioredoxin-interacting protein (TXNIP), ER stresi ve inflamasyon arasında kritik bir bağdır. , ER stresorleri ile aktive olur ve NLRP3 ile IL-1β üretimi tetiklenir.

- Bir kez sekrete edildikten sonra IL-1β hedef hücrede, IL-1 receptor I (IL-1R1)' e bağlanır. Bu proçes doğal antagonisti IL-1Ra (IL-1F3) ile inhibe olur.

TİP 2 DİYABETTE ADACIK İNFLAMASYONU



Downloaded on April 21, 2014. The Journal of Clinical Investigation. More information at www.jci.org/articles/view/15318

Glucose-induced β cell production of IL-1β contributes to glucotoxicity in human pancreatic islets

Kathrin Maedler,[1] Pavel Sergeev,[1] Frédéric Ris,[2,3] José Oberholzer,[3] Helen I. Joller-Jemelka,[4] Giatgen A. Spinas,[1] Nurit Kaiser,[5] Philippe A. Halban,[2] and Marc Y. Donath[1]

[1]Division of Endocrinology and Diabetes, University Hospital, Zurich, Switzerland
[2]Louis-Jeantet Research Laboratories, University of Geneva Medical Center, Geneva, Switzerland
[3]Division of Surgical Research, Department of Surgery, University of Geneva Medical Center, Geneva, Switzerland
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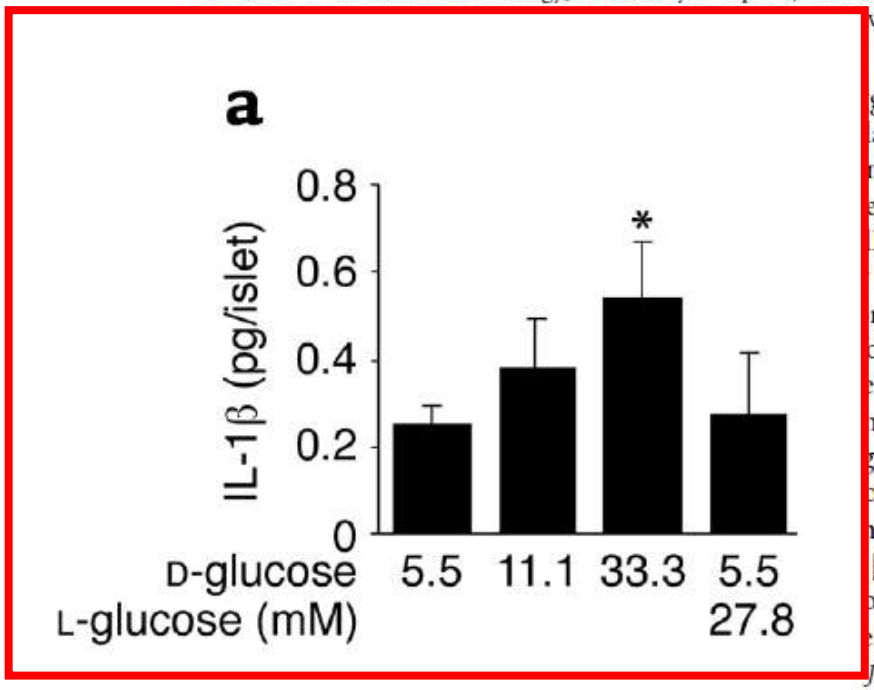
versity – Hadassah Medical Center, Jerusalem, Israel



gested to be detrimental to pancreatic β cells, caus-
ammatory cytokine acting during the autoimmune
nction and promotes Fas-triggered apoptosis in part
ecently, we have shown that increased glucose con-
l apoptosis in human islets. The aim of the present
mediate the deleterious effects of high glucose on
ndiabetic organ donors to high glucose levels result-
ollowed by NF-κB activation, Fas upregulation, DNA
IL-1 receptor antagonist protected cultured human
nselves were identified as the islet cellular source of
β cells were observed in pancreatic sections of type
ol subjects. Similarly, IL-1β was induced in β cells of
nt of diabetes. Treatment of the animals with phlo-
β cell expression of IL-1β. These findings implicate
of glucotoxicity in type 2 diabetes and identify the
ll mass and function in this condition.

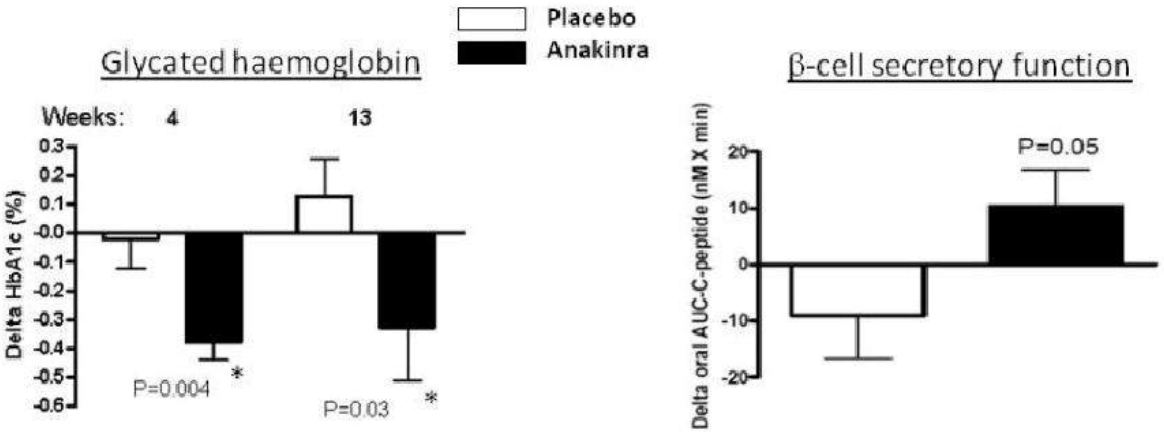
J. Clin. Invest. **110**:851–860 (2002). doi:10.1172/JCI200215318.

The NEW ENGLAND JOURNAL of MEDICINE

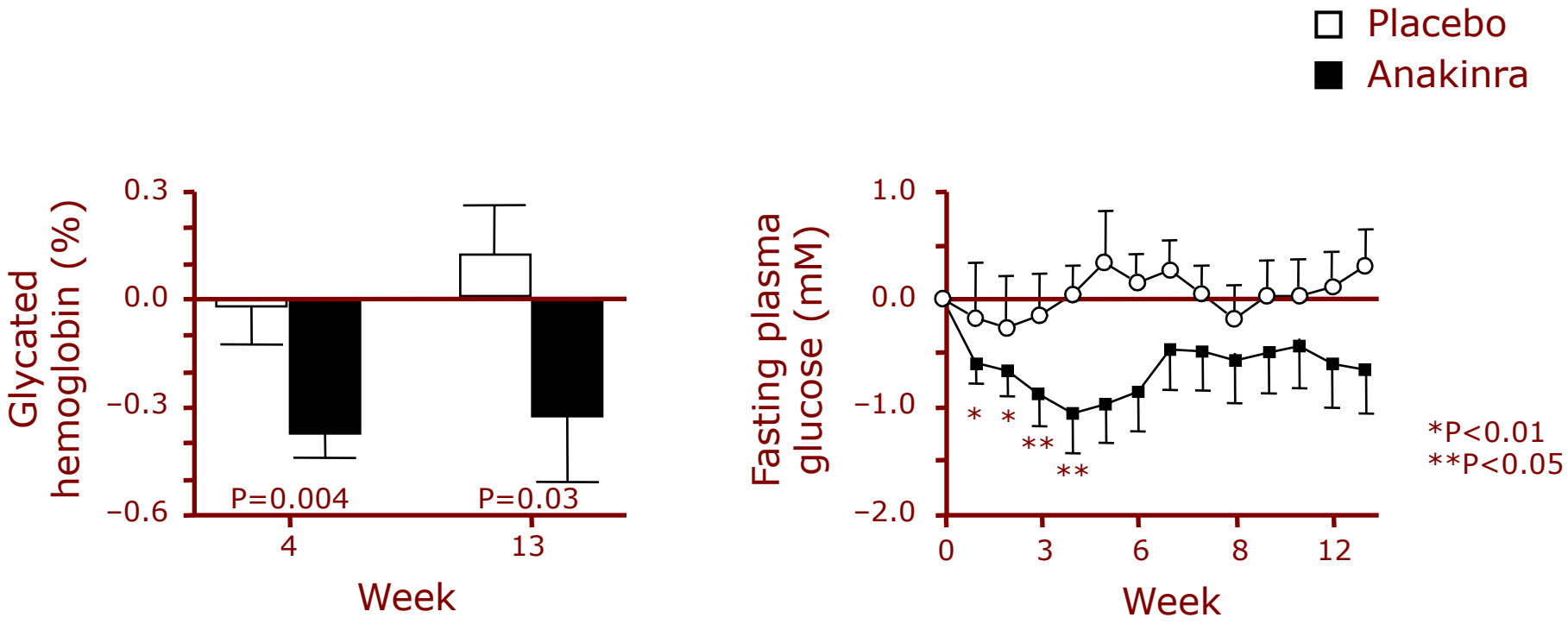
ORIGINAL ARTICLE

Interleukin-1–Receptor Antagonist in Type 2 Diabetes Mellitus

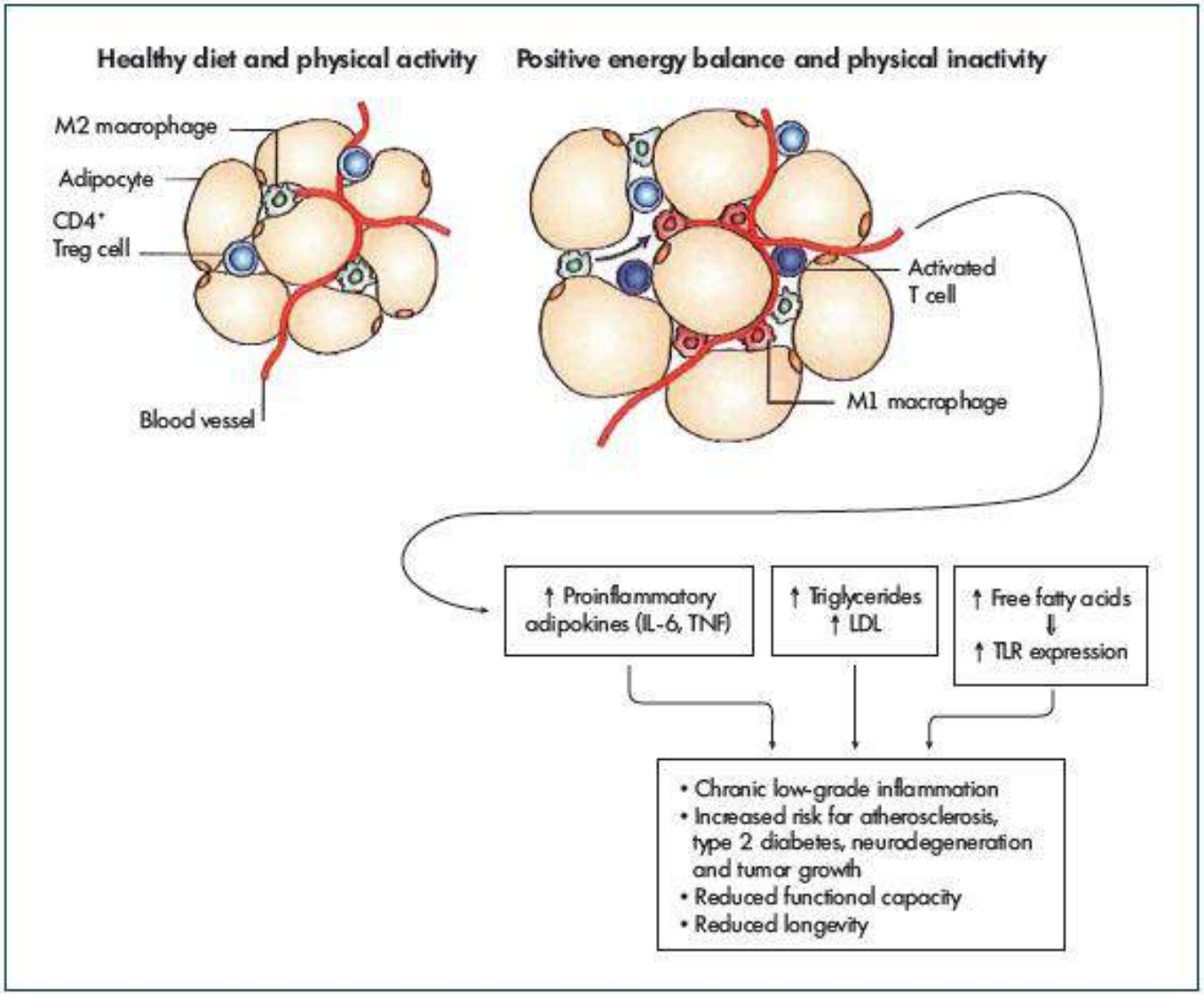
Claus M. Larsen, M.D., Mirjam Faulenbach, M.D., Allan Vaag, M.D., Ph.D., Aage Vølund, M.Sc., Jan A. Ehses, Ph.D., Burkhardt Seifert, Ph.D., Thomas Mandrup-Poulsen, M.D., Ph.D., and Marc Y. Donath, M.D.



Primary endpoint: change in HbA_{1c} at 13 weeks



Diyet ve fiziksel aktivitenin inflamasyon ve hastalık üzerine etkisi

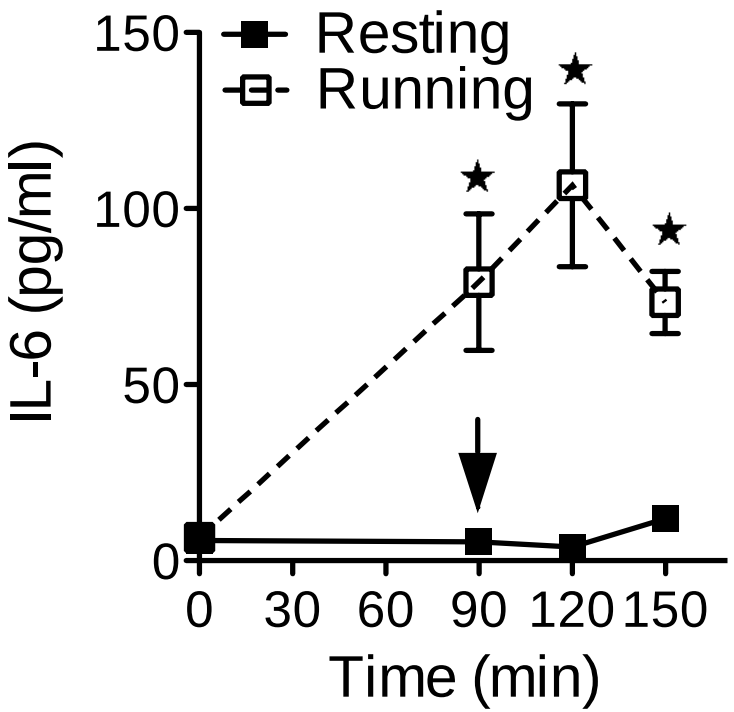


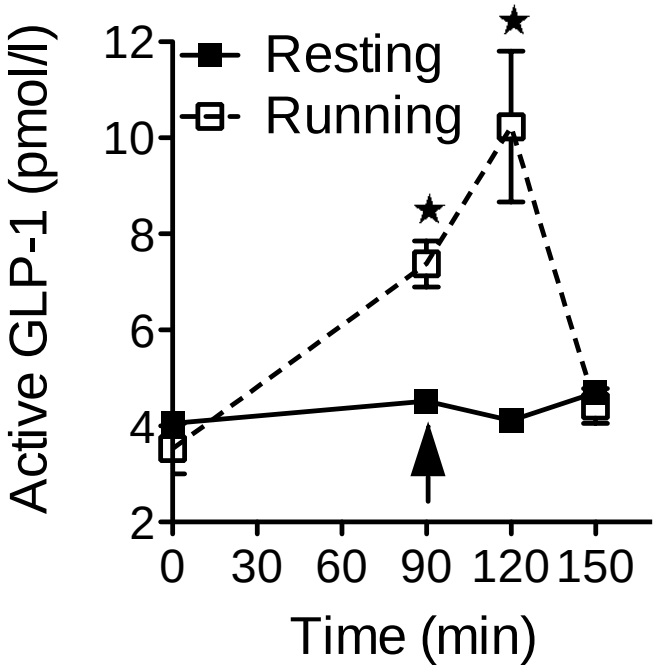
EGZERSİZ

IL-6

OBEZİTE

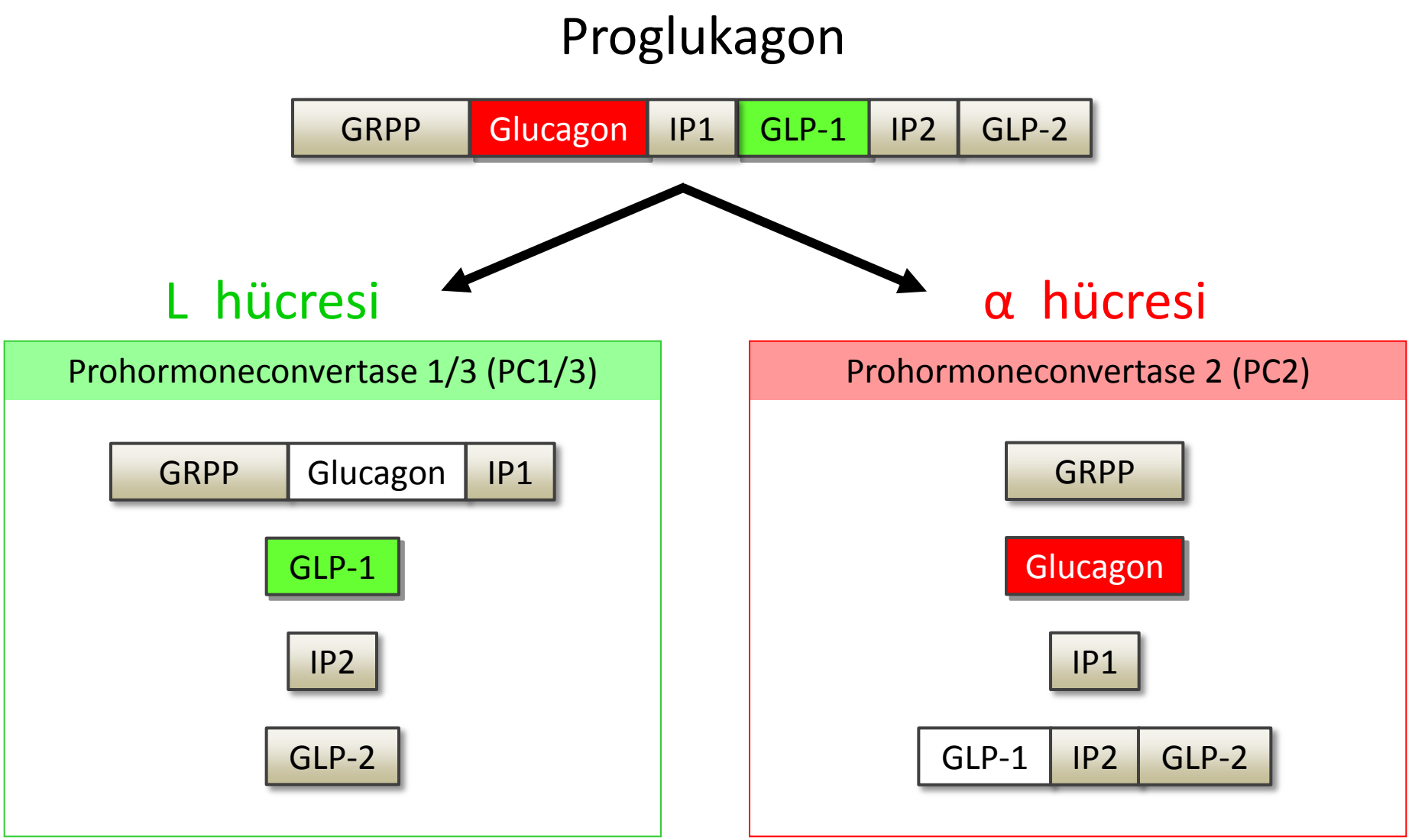
Egzersizin indüklediği GLP-1 IL-6 bağımlıdır.





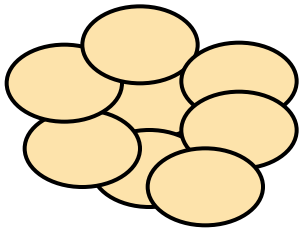
Ellingsgaard et al. *Nat Med* 2011; 17:1481-9.

Proglukagon işlenmesi…



ADİPOZ DOKU

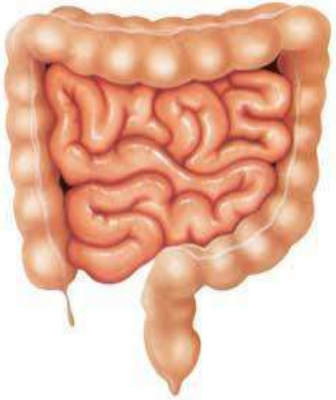
İSKELET KASI



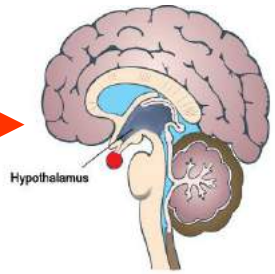
IL-6

İNTESTİN

PANKREATİK ADACIK



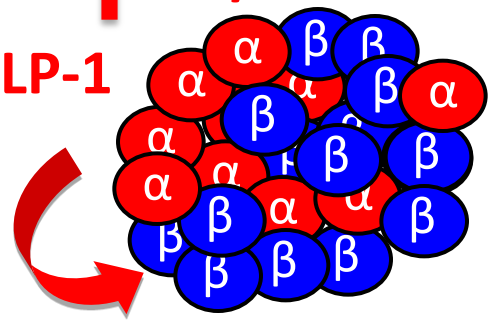
↑GLP-1



DOYGUNLUK

↑PC1/3

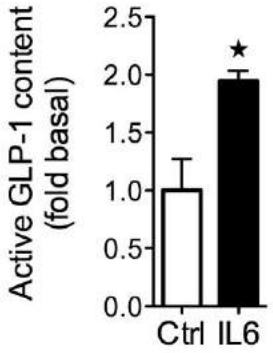
↑GLP-1

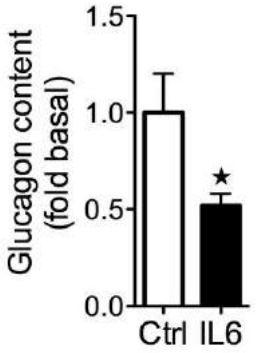


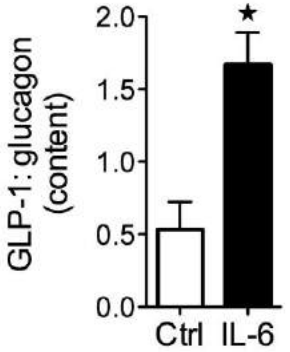
↑β fonksiyonu ve survi

Ellingsgaard et al. *Nat Med* 2011; 17:1481-9.

IL-6 insan α hücrelerinde GLP-1 i arttırır.







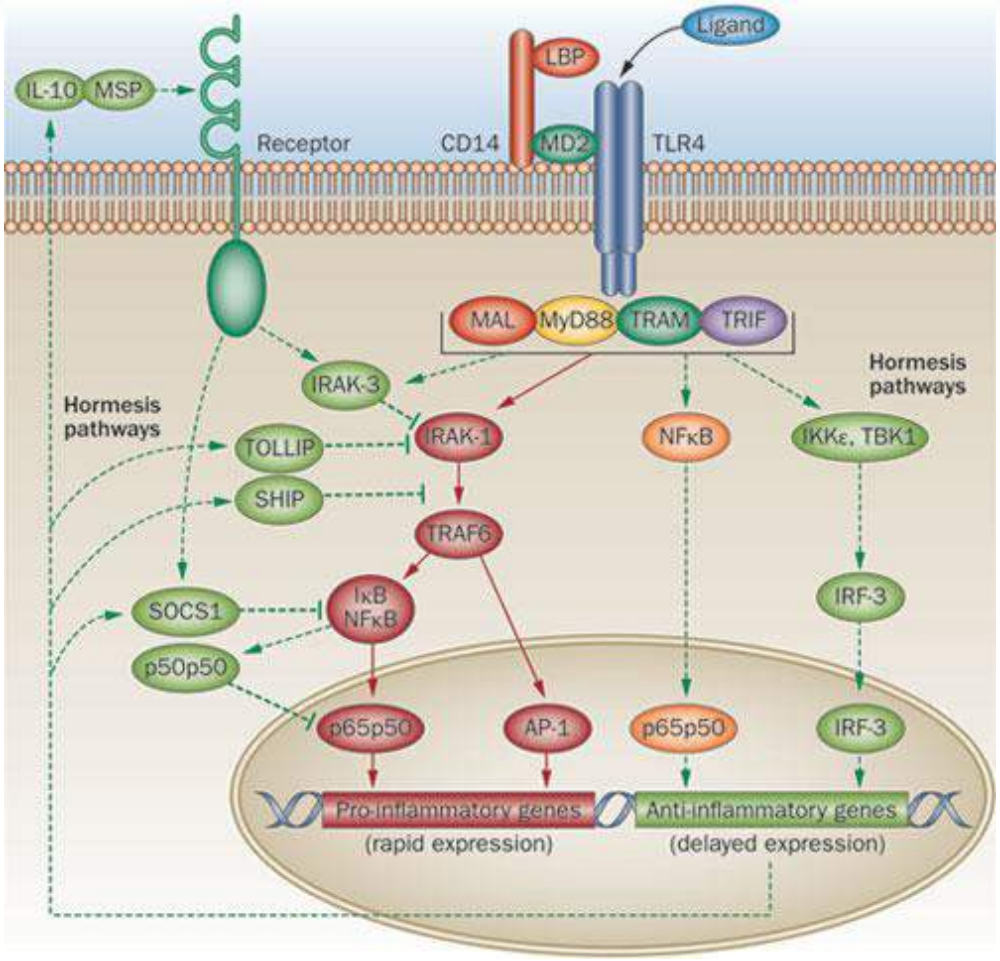
Ellingsgaard et al. *Nat Med* 2011; 17:1481-9.

Toll-like reseptör 2 ve 4 ve NLRP3

- Toll-like reseptör 2 ve 4 ve NLRP3 (Nucleotide-binding oligomerization domain, Leucine-rich Repeat and Pyrin domain containing 3) inflamasom'u Tip2 DM de adacık inflamasyonunu tetiklerler ve bu tetikleyicilerin makrofajları aktive etmesi adacık hücrelerinin disfonksiyonuna aracılık eder.
- Bu reseptörleri hedef alan terapotik yaklaşımlar hiperglisemiyi düzeltebilir ve beta hücrelerini koruyabilir.

Immunology and Cell Biology , (4 February 2014) | doi:10.1038/icb.2014.4

Figure 1 Hormetic response to signaling via TLR4



Kolb, H. & Eizirik, D. L. (2011) Resistance to type 2 diabetes mellitus: a matter of hormesis? *Nat. Rev. Endocrinol.* doi:10.1038/nrendo.2011.158

nature REVIEWS ENDOCRINOLOGY

NLRP3

- **Yapılan bir çalışmada adacık hücrelerinde NLRP3, ASC ve caspase-1 ekspresyonu gösterildi. *NLRP3*-knockout adacık hücrelerinde IL-1β salınımının azaldığı gösterildi. *NLRP3*-knockout farelerde yüksek yağlı diyet sonrası glikoz profillerinin iyi olduğu ve bunun azalmış IL-1β salınımına bağlı olduğu ileri sürülmüş.**

- **Bir çalışmada NLRP3' ün insan adacık amiloid polipeptid (IAPP) tarafından aktive edildiği gösterilmiş. İnsan IAPP si amiloidojenik fakat farelerin IAAP si değil (amino asit dizilimi farklı).**

Zhou R, Tardivel A, Thorens B, et al. Nat Immunol 2010;11:136–140.
Masters SL, Dunne A, Subramanian SL et al. Nat Immunol 2010;11:897–904

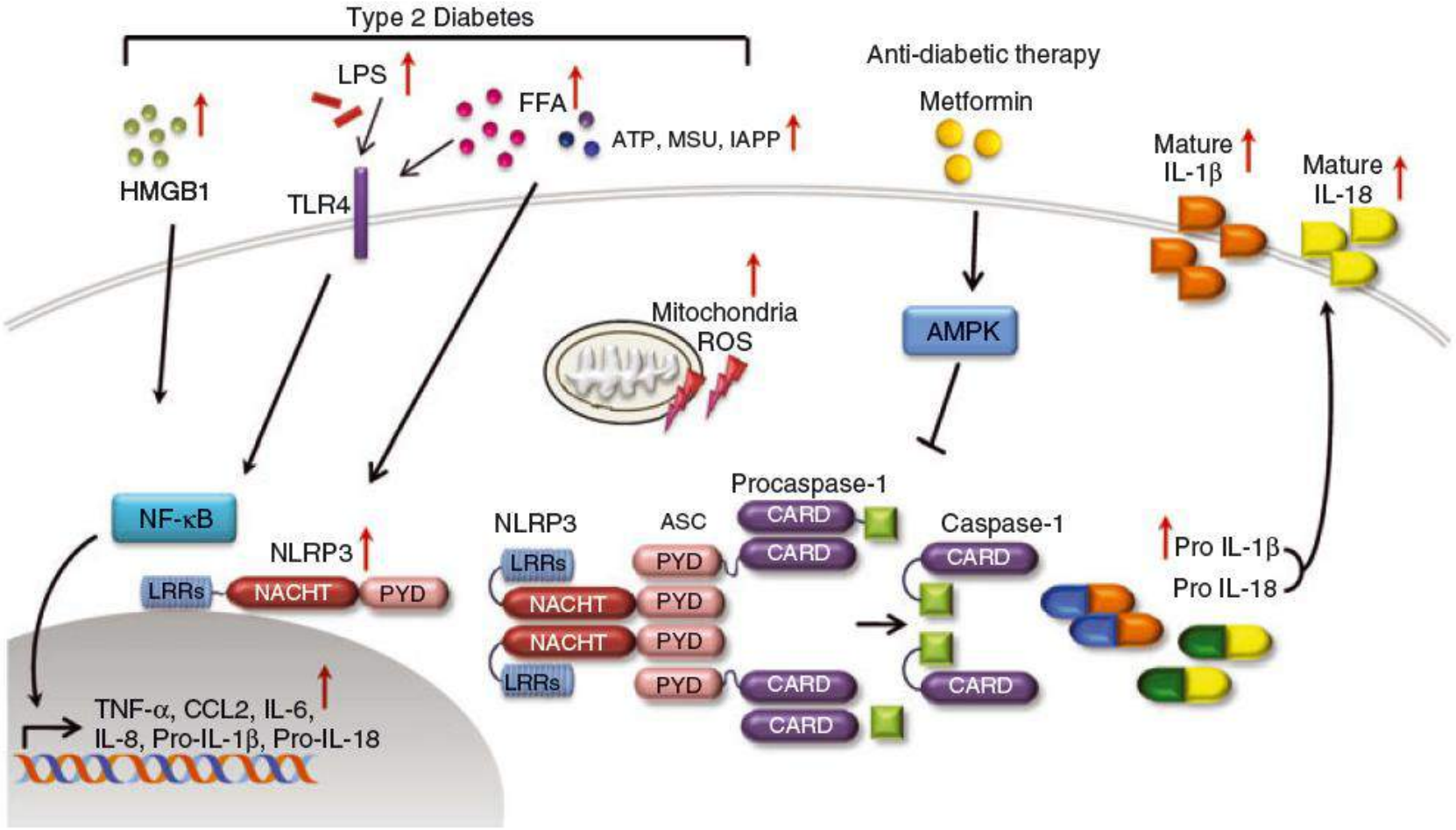


Figure 2. Enhanced activation of NLRP3 inflammasomes in type 2 diabetes (T2D) myeloid cells. In drug-naïve T2D, NLRP3 inflammasomes are activated by diverse obesity-associated alarm molecules. In monocyte-derived Mφs, basal NLRP3 and ASC protein levels, as well as proinflammatory cytokines, are elevated when compared with those of controls. In addition, caspase-1 cleavage and interleukin (IL)-1β maturation are upregulated in the Mφs of T2D patients. Elevated mitochondrial reactive oxygen species (ROS) may contribute to increased activation of NLRP3 inflammasomes in myeloid cells from these patients. Free fatty acids (FFAs) may activate NLRP3 in conjunction with lipopolysaccharide (LPS), a TLR4 agonist, by an unknown mechanism. Treatment of T2D with metformin for 2 months significantly improves clinical parameters, and inhibits inflammasome activation or production of mature IL-1β. The activation of the AMPK pathway by metformin may modulate NLRP3 inflammasome activation through unknown mechanisms.

Am J Physiol Endocrinol Metab 301: E83–E90, 2011.
First published April 26, 2011; doi:10.1152/ajpendo.00603.2010.

Protection from diabetes development by single-chain antibody-mediated delivery of a NF-κB inhibitor specifically to β-cells in vivo

Sandra Ueberberg,[1] Timo Deutschbein,[1] Harald H. Klein,[1] Johannes W. Dietrich,[1] Sara Akinturk,[2] Nora Prochnow,[2] Ralph Schirrmacher,[3] and Stephan Schneider[1,4]

[1]*Department of Internal Medicine I, Division of Endocrinology and Metabolism, Berufsgenossenschaftliches University Hospital Bergmannsheil;* [2]*Department of Neuroanatomy and Molecular Brain Research, Ruhr-University, Bochum, Germany;* [3]*Department of Neurology and Neurosurgery, Lady Davis Institute for Medical Research, McGill University, Montreal, Quebec, Canada; and* [4]*Medical Department II, Diabetology and Endocrinology, St. Vinzenz Hospital, Cologne, Germany*

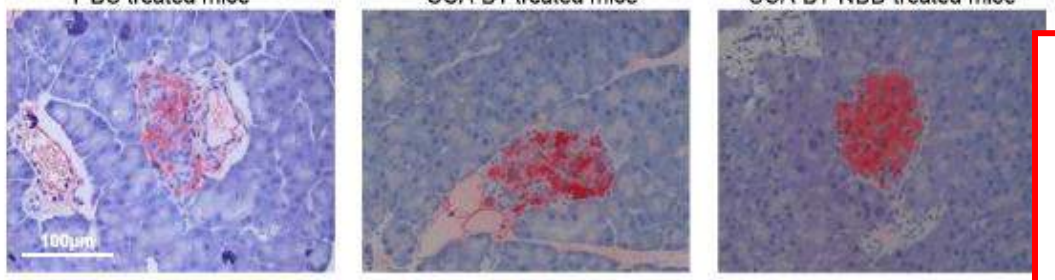
Submitted 29 October 2010; accepted in final form 15 April 2011

Ueberberg S, Deutschbein T, Klein HH, Dietrich JW, Akinturk S, Prochnow N, Schirrmacher R, Schneider S. Protection from

with anakinra improved islet function in patients with type 2 diabetes (2).

st of the NF-κB complex is bound to two κBβ), and the cytoplasmatic regulatory al modifier (NEMO) prevents the NF-κB nslocation to the nucleus as well as its

β-CELL PROTECTION BY SCA-NBD FUSION PROTEIN



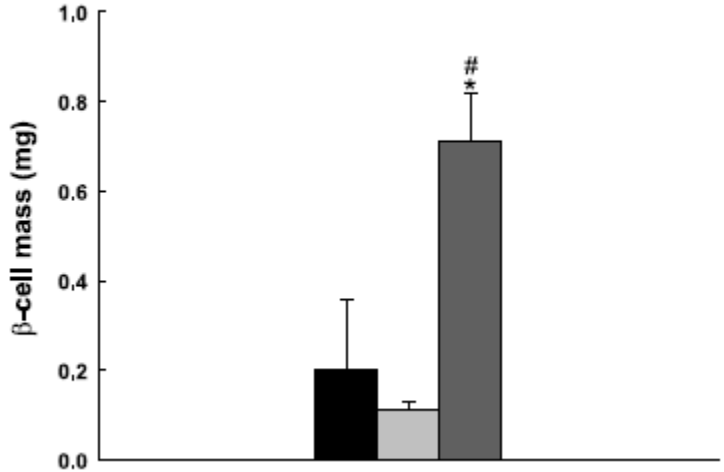
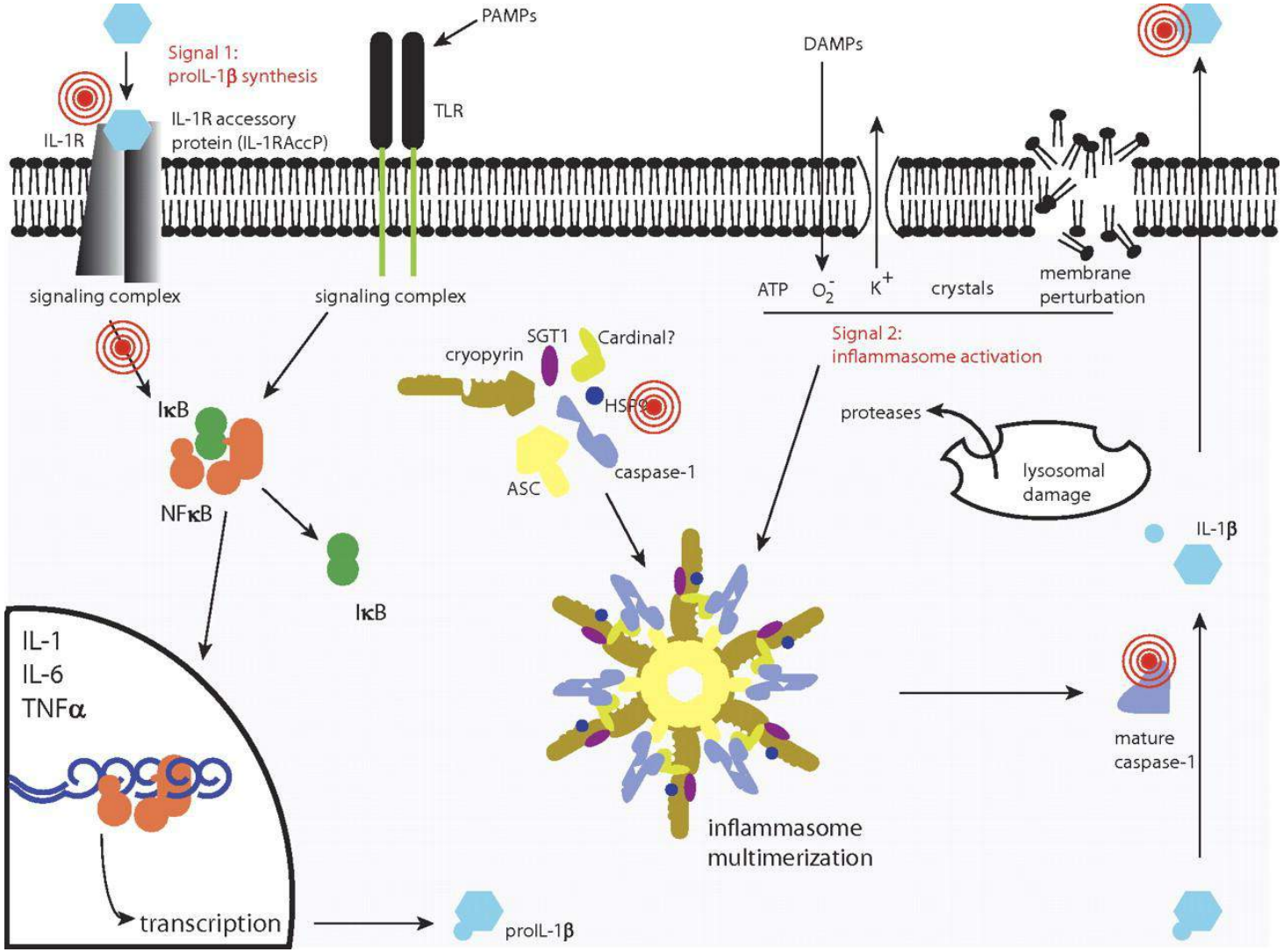


Fig. 6. *A*: histological sections of the pancreas in a PBS-, SCA B1-, or SCA B1 NBD-treated mouse 28 days after the last injection of STZ stained for insulin (red). *B*: pancreatic β-cell mass of CD mice treated with PBS (black bars; $n = 10$), SCA B1 (gray bars; $n = 10$), or SCA B1-NBD (dark gray bars; $n = 10$) 28 days after the last injection of STZ. Data are

TİP 2 DM TEDAVİSİNDE ANTİ-İNFLAMATUVAR YAKLAŞIM



Doherty T A et al. J Leukoc Biol 2011;90:37-47

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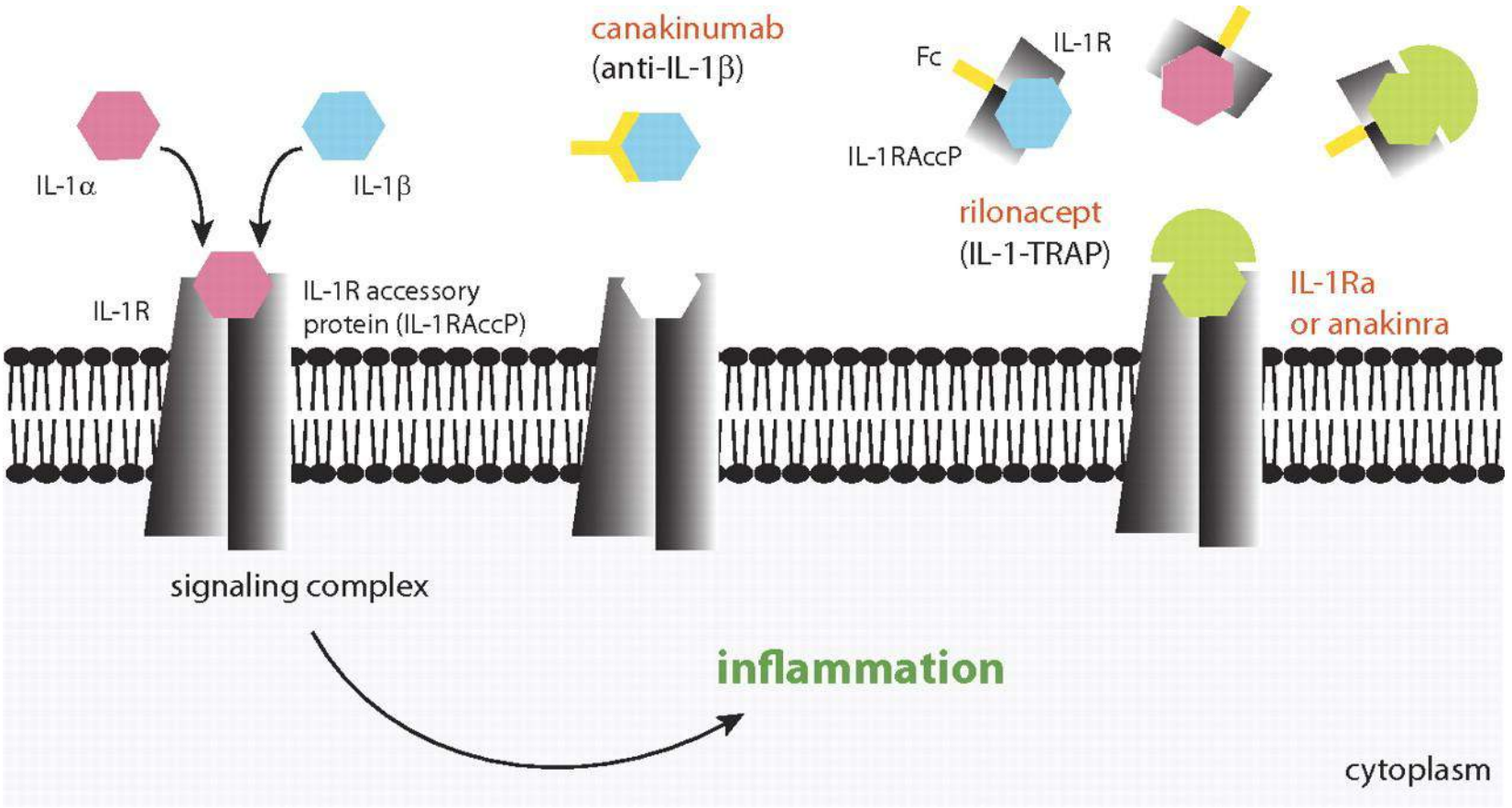
Current mechanisms of IL-1-targeted therapy.



Doherty T A et al. J Leukoc Biol 2011;90:37-47

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TİP 2 DM TEDAVİSİNDE ANTİ-İNFLAMATUVAR YAKLAŞIM

Table 1. Clinical Studies Using Anti-Inflammatory Approaches to Treat Patients with Type 2 Diabetes

Mechanism	Drug	Treatment Duration	Main Findings	Remarks/Limits	Source
IL-1 receptor blockade	anakinra (kineret)	13 weeks	HbA1c ↓; CRP ↓; insulin secretion ↑	dose not adapted to body weight	Larsen et al., 2007
IL-1 receptor blockade	anakinra (kineret)	follow up for 39 weeks	sustained CRP ↓; insulin secretion ↑; insulin requirement ↓	follow-up study of the one above (Larsen et al., 2007)	Larsen et al., 2009
IL-1 receptor blockade	anakinra (kineret)	4 weeks	insulin secretion ↑; insulin sensitivity unchanged	prediabetic patients; underpowered study (13 patients) and short duration	van Asseldonk et al., 2011
IL-1β antagonsim	single dose of anti-IL-1β antibody (gevokizumab)	13 weeks	HbA1c ↓; CRP ↓; insulin secretion ↑	–	Cavelti-Weder et al., 2012
IL-1β antagonsim	anti-IL-1β antibody (canakinumab)	4 weeks	insulin secretion ↑; CRP ↓	short duration	Rissanen et al., 2012
IL-1β antagonsim	anti-IL-1β antibody (canakinumab)	16 weeks	CRP ↓; HbA1c ↓; insulin secretion ↑ (not statistically significant)	underpowered for low basal HbA1c	Ridker et al., 2012
IL-1β antagonsim	anti-IL-1β antibody (LY2189102)	12 weeks and follow up for 24 weeks	HbA1c ↓; CRP ↓; insulin secretion ↑	further improvement of HbA1c at week 24	Sloan-Lancaster et al., 2013

Table 1. Clinical Studies Using Anti-Inflammatory Approaches to Treat Patients with Type 2 Diabetes

Mechanism	Drug	Treatment Duration	Main Findings	Remarks/Limits	Source
IKK-β-NF-κB inhibition	salsalate	4 weeks	FBG ↓; CRP ↓; insulin sensitivity ↑; adiponectin ↑	short duration	Fleischman et al., 2008
IKK-β-NF-κB inhibition	salsalate	2–4 weeks	FBG ↓; CRP ↓; adiponectin ↑	short duration	Goldfine et al., 2008
IKK-β-NF-κB inhibition	salsalate	1 week	FBG ↓; insulin ↑; CRP ↓	short duration	Koska et al., 2009
IKK-β-NF-κB inhibition	salsalate	12 weeks	HbA1c ↓; FBG ↓; triglyceride ↓; Adiponectin ↑	–	Goldfine et al., 2010
IKK-β-NF-κB inhibition	salsalate	12 weeks	HbA1c ↓; FBG ↓; insulin secretion ↑; triglyceride ↓	drug-naive patient; strong effects on gylcemia	Faqhihimani et al., 2011
IKK-β-NF-κB inhibition	salsalate	12 weeks	FBG ↓; adiponectin ↑	prediabetic patients	Goldfine et al., 2013

Table 1. Clinical Studies Using Anti-Inflammatory Approaches to Treat Patients with Type 2 Diabetes

Mechanism	Drug	Treatment Duration	Main Findings	Remarks/Limits	Source
TNF-α antagonism	single dose of anti-TNF-α antibody (CDP571)	4 weeks	no effect on insulin sensitivity	underpowered study (ten patients) and short duration	Ofei et al., 1996
TNF-α antagonism	single dose of soluble TNF- Receptor: Fc fusion protein (Ro 45-2081)	48 hours	no effect on insulin sensitivity	underpowered study (seven patients) and short duration	Paquot et al., 2000
TNF-α antagonism	soluble TNF- receptor: Fc fusion protein (etanercept)	4 weeks	CRP ↓; insulin secretion ↑; no effect on insulin sensitivity	underpowered study (ten patients) and short duration	Dominguez et al., 2005
TNF-α antagonism	soluble TNF- receptor: Fc fusion protein (etanercept)	4 weeks	CRP ↓, adiponectine ↑; LDL ↓; no effect on insulin sensitivity	short duration	Bernstein et al., 2006
Decrease of TNF-α and IL-1β by an unknown mechanism of action	diacerein	8.5 weeks	HbA1c ↓; FBG ↓; insulin secretion ↑	drug-naive patient; strong effects on gylcemia	Ramos-Zavala et al., 2011