

TIP 2 DİYABETTE İNSÜLİTİS

Dr.Mehmet BAŞTEMİR
SANKO ÜNİVERSİTESİ
GAZİANTEP

ANTALYA-NİSAN 2014

TIP 2 DİYABETİN PATOGENEZİ

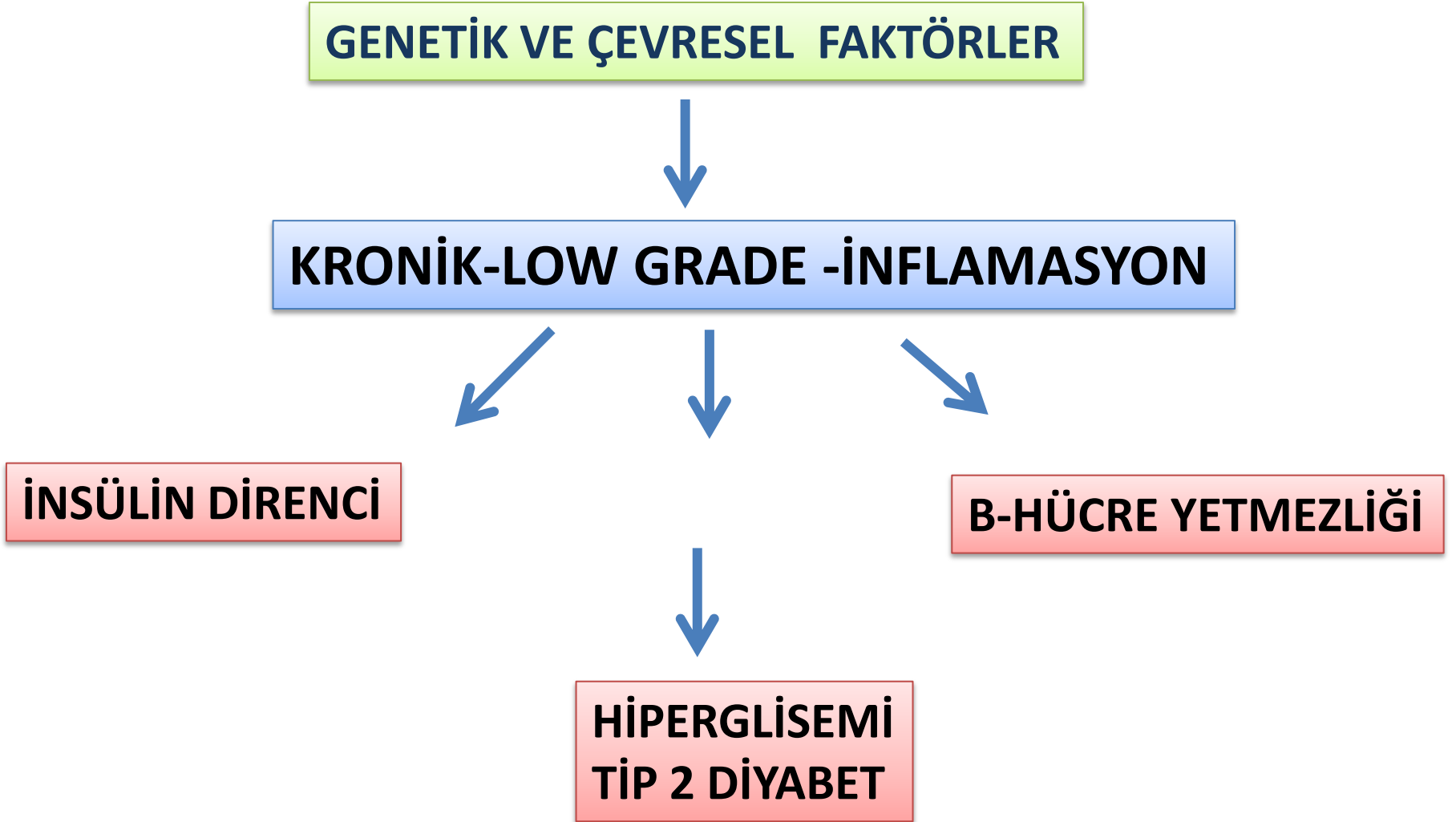
GENETİK VE ÇEVRESEL FAKTÖRLER

KRONİK-LOW GRADE -İNFLAMASYON

İNSÜLİN DİRENCİ

B-HÜCRE YETMEZLİĞİ

HİPERGLİSEMİ
TIP 2 DİYABET



TIP 2 DİYABETİN PATOGENEZİ

GENETİK VE ÇEVRESEL FAKTÖRLER

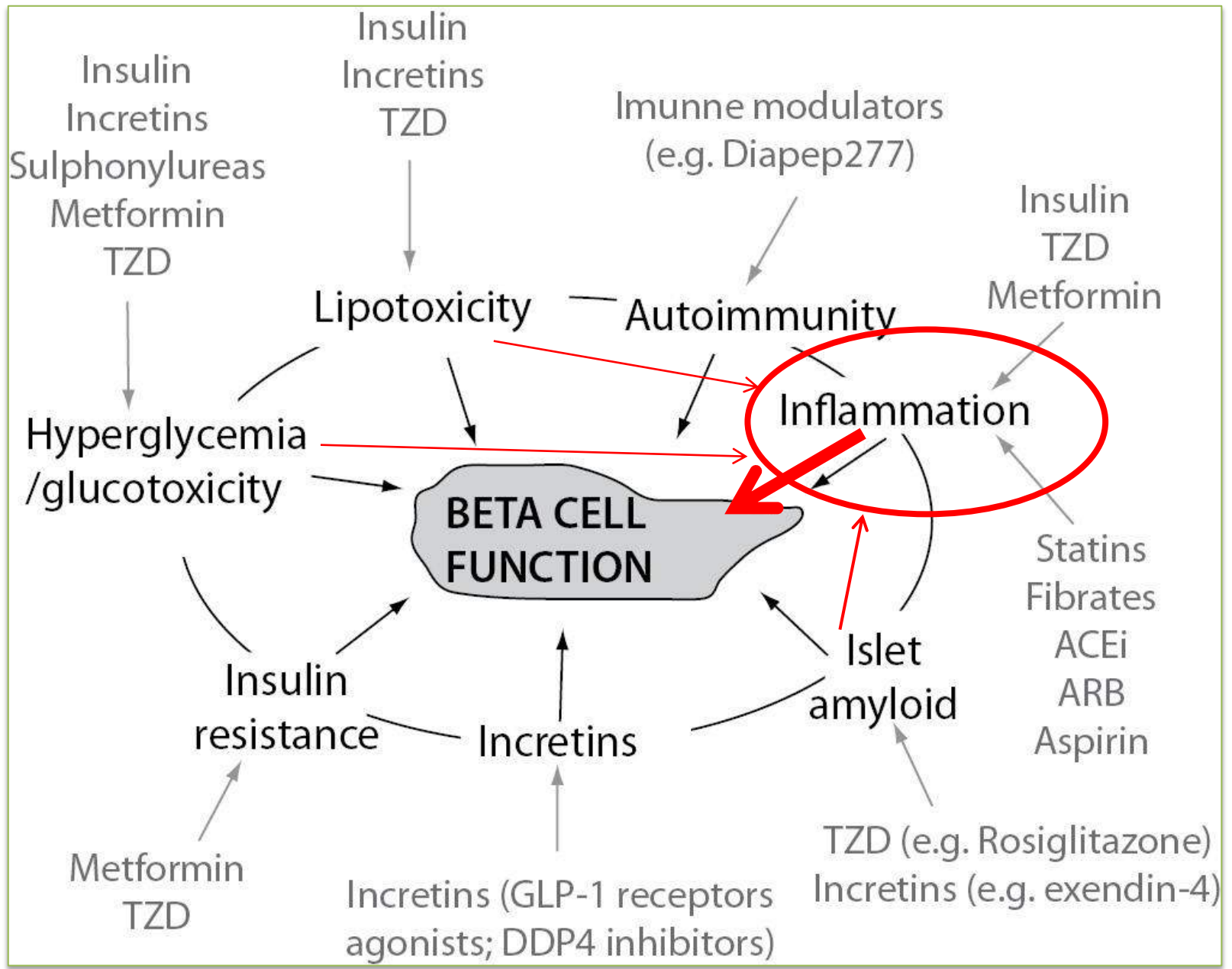
KRONİK-LOW GRADE -İNFLAMASYON

İNSÜLİN DİRENCİ

α -HÜCRE DİSFONKSİYONU
GLUCAGON SEKRESYONU

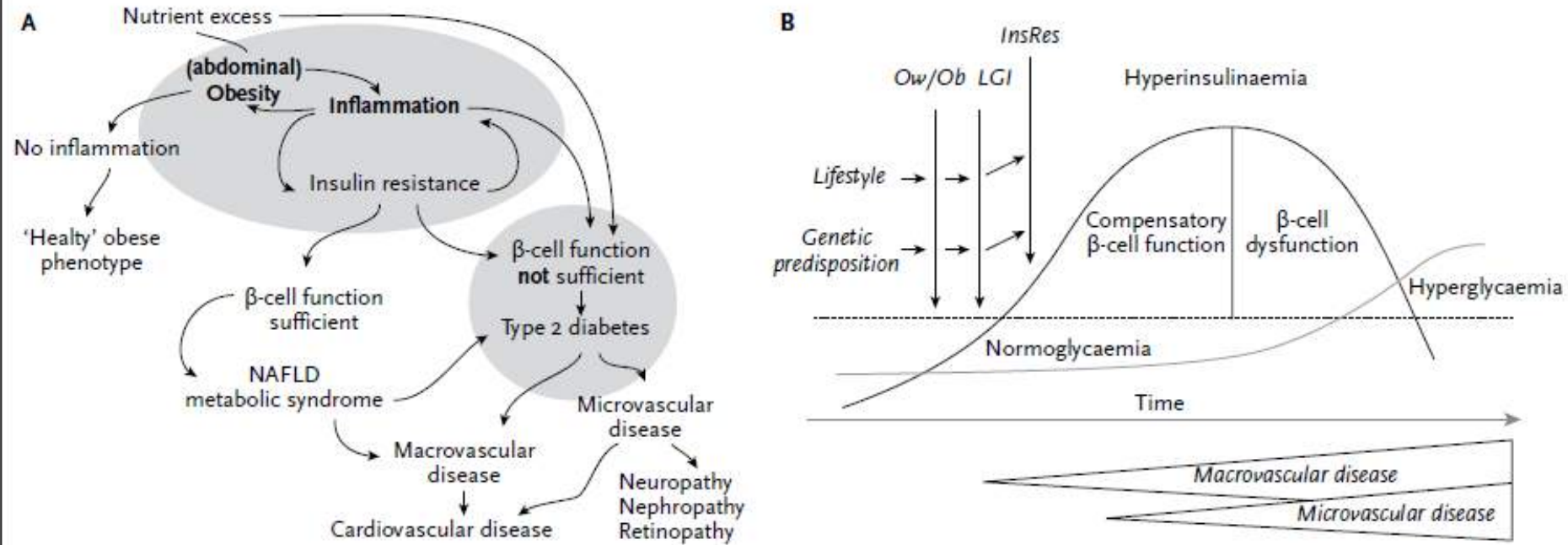
β -HÜCRE YETMEZLİĞİ

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TIP 2 DİYABET

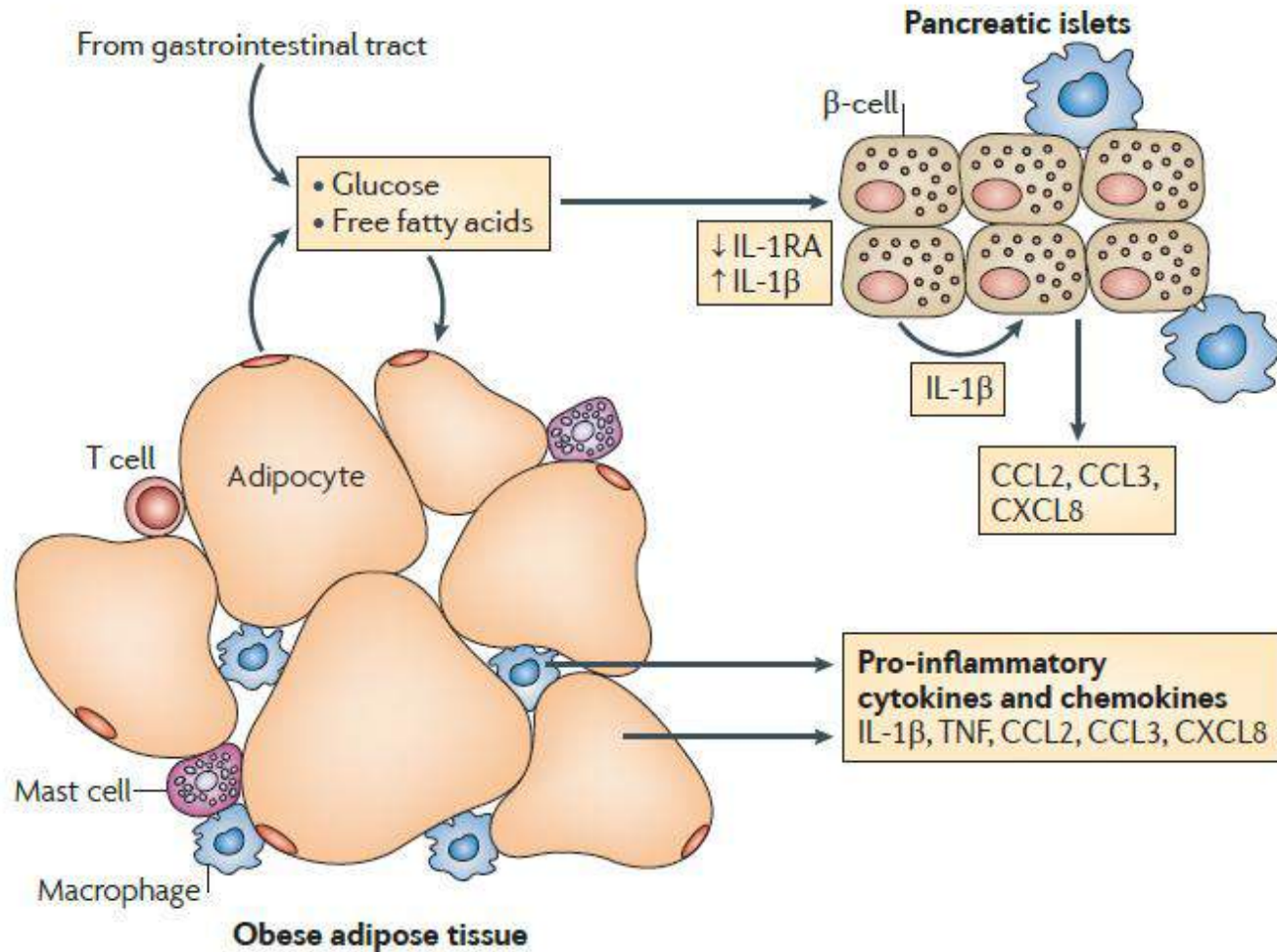


OBEZİTE –TİP 2 DM İLİŞKİSİ

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



TİP 2 DM : İNFLAMASYONUN GELİŞİMİ



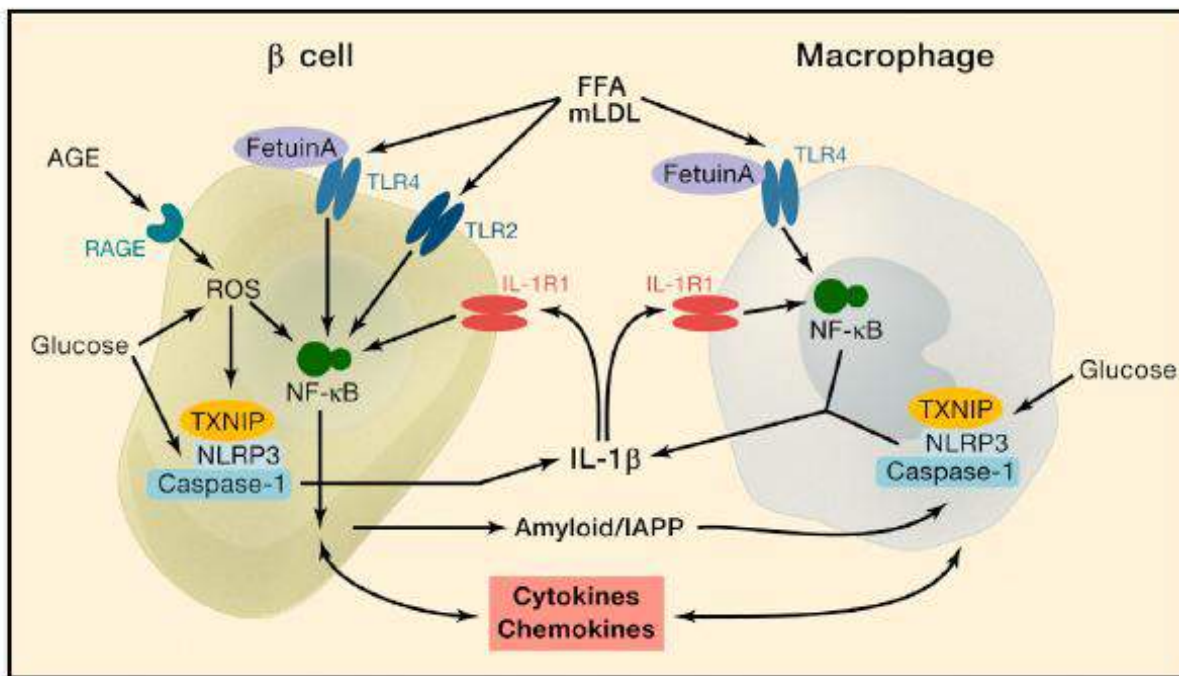


Figure 1. Innate Immune Response to Metabolic Stress in Pancreatic Islets

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- κ B activation and the production of various proinflammatory chemokines and cytokines, including the proform of IL-1 β . 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-1 β is processed by the NLRP3-associated caspase-1 and secreted in the microenvironment. In turn, IL-1 β 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

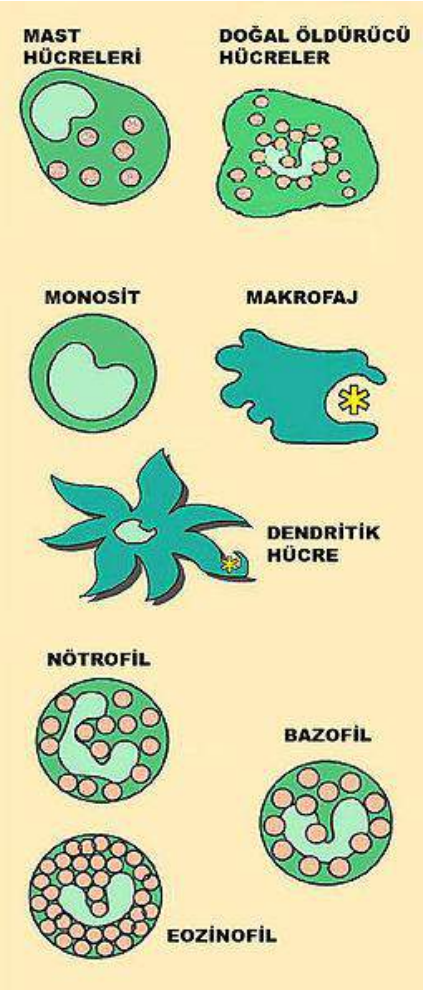
6) MAKROFAJLAR

Tip 2 DM ve İnsülitis

- Tip 1 DM.....otoimmunitite
- Tip 2 DM..... insülin direnci ve β hücre disfonksiyonu..... **β hücre ölümü**
- Veriler her iki diyabet tipinin adacık inflamasyonu ile karakterize olduğunu göstermektedir.
- Tip 2 DM: aşırı beslenme ve insülin direnci β hücrelerinin proinflamatuvar mediyatörlerin üretimine neden olur. β hücre fonksiyon bozukluğuna, yaşamının kısalmasına ve hatta immün hücrelerin adacıklara yerleşmesine ve inflamasyonun artmasına neden olur.
- Tip 2 DM kronik inflamatuvar bir hastalık olarak düşünülebilir. Tip 1 DM ve Tip 2 DM de patogeneizde 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- κ B (NF- κ B) 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.



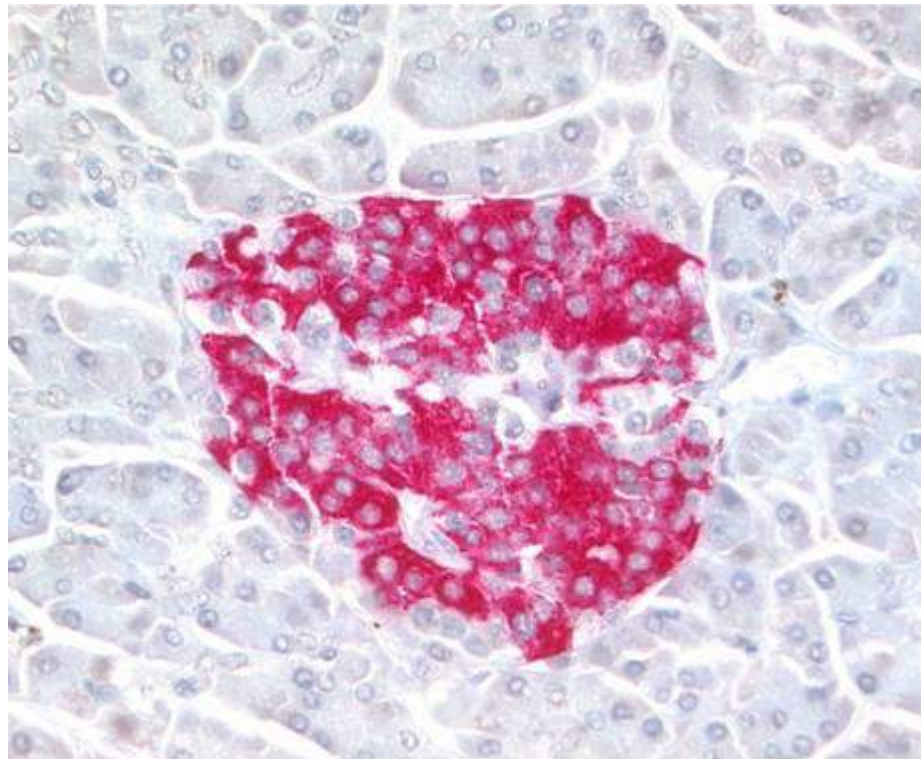
Tip 2 DM de otoinflamasyon

- **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 **proinflamatuvar** yanıtla karşı karşıya kalırlar. Bu durum insülin üretim ve salınımını bozar.
- Viseral adipoz dokunun kronik inflamasyonu ...proinflamatuvar mediatör üretimi...adipoz hücre ve pankreatik adacık hücre etkilenimi
- Bu inflamasyon proinflamatuvar proteinlerin (**C-reactive protein (CRP), TNF- α , IL-6 ve IL-1 β** gibi) aşırı ekspresyonuna neden olur.
- Bu proinflamatuvar moleküller **doğal bağışıklık sistemi hücrelerini** aktive ederler...pankreas 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).

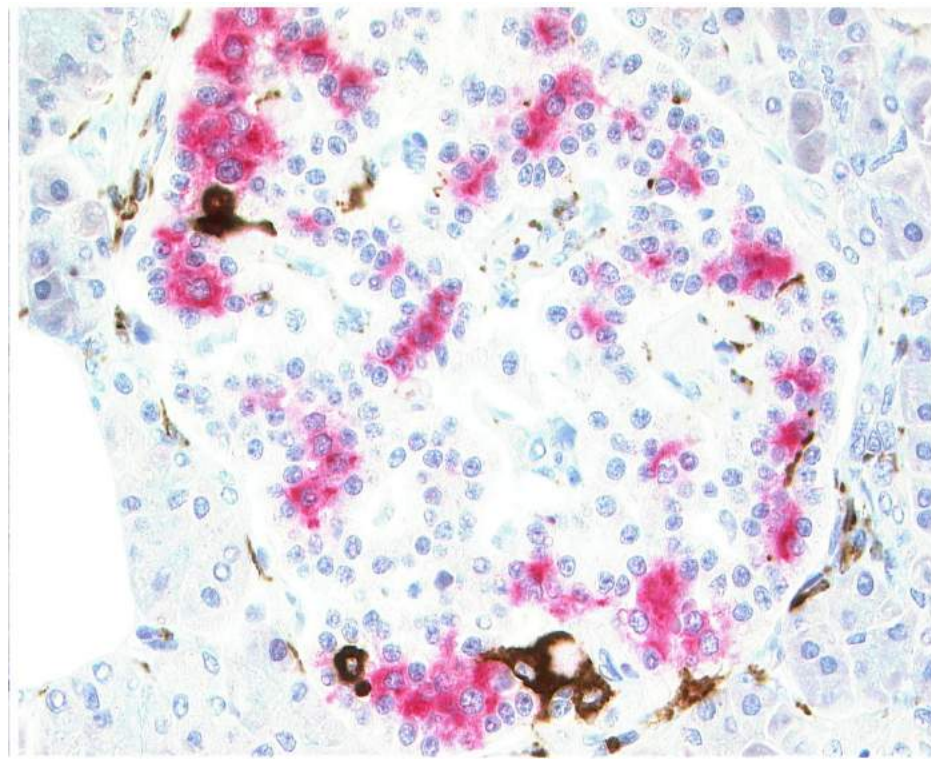
TİP DİYABETTE İNSULİTİS

İnsan pankreası

Kontrol



Tip 2 diyabet



 insulin

 CD68

Increased Number of Islet-Associated Macrophages in Type 2 Diabetes

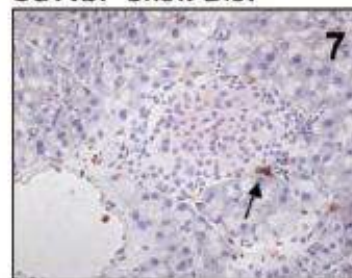
Jan A. Ehses,¹ Aurel Perren,² Elisabeth Eppler,³ Pascale Ribaux,⁴ John A. Pospisilik,⁵ Ranit Maor-Cahn,¹ Xavier Guericel,² Helga Ellingsgaard,¹ Marten K.J. Schneider,⁶ Gregoire Biollaz,⁷ Adriano Fontana,⁷ Manfred Reinecke,³ Francoise Homo-Delarche,⁸ and Marc Y. Donath¹

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 1 α . 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* 56:2354–2370, 2007

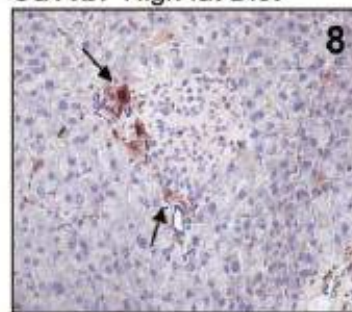
Activation of the innate immune system has long been reported in obesity, insulin resistance, and type 2 diabetes and is characterized by increased circulating levels of acute-phase proteins and of cytokines and chemokines (1–5). However, the notion that excess circulating nutrients may stimulate the β -cell to produce chemokines and immune cell infiltration has not been reported in type 2 diabetic patients.

One of the most classical chemokines in immunology is the CXC family member CXCL8 (IL-8) (6). IL-8 is produced by endothelial and epithelial cells and is associated with infections, granuloma formation, cancer, and atherosclerosis. In mice, neutrophils, the chemotactic target of IL-8, does not express IL-8. Its ortholog in the rat, Gro- α (the rat homolog of IL-8) is thought to be an ortholog of IL-8 in the rat, which also granulocyte and monocyte chemoattractant (10,11), in whom IL-8 has been associated with insulin resistance and athero-

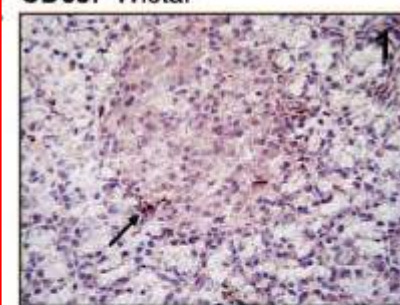
Cd11b: Chow Diet



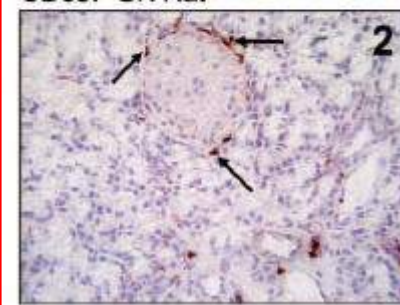
Cd11b: High fat Diet



CD68: Wistar



CD68: GK Rat



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

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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 pancreatic islets from a mouse model of T2D. In the diabetic islets, the majority of the CD68⁺ F4/80⁺ macrophages were M1-like, whereas in the nondiabetic islets, the majority of the CD68⁺ F4/80⁺ macrophages were M2-like. 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.

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

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.

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TİP 2 DM ADACIKLARINDA MAKROFAJ POLARİTESİ

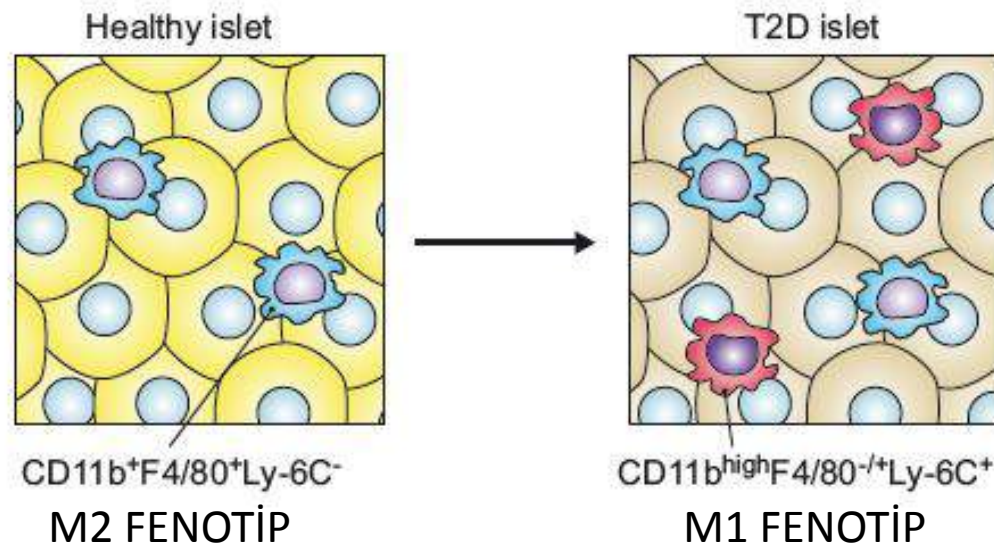


Figure 2. Islet macrophage polarity in type 2 diabetes (T2D). The majority of resident macrophages in healthy islets exhibit CD11b⁺F4/80⁺Ly-6C⁻. In T2D islets CD11b^{high}F4/80^{-/+}Ly-6C⁺ monocytes/macrophages accumulate.

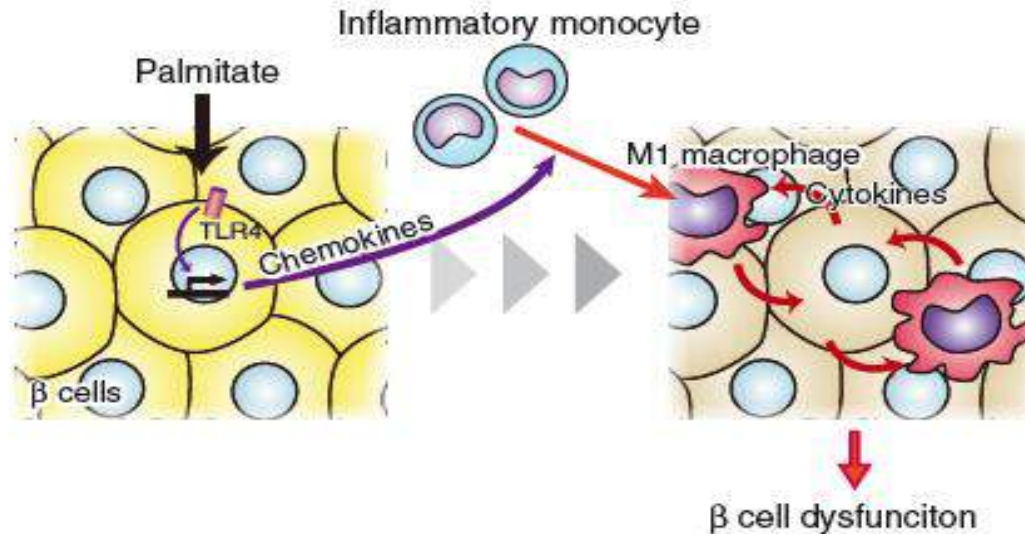


Figure 3. Palmitate-TLR4 pathway leading to islet inflammation and β -cell dysfunction. Palmitate induces β -cell dysfunction *in vivo* at least partly by activating inflammatory processes in islets. β -Cells sense palmitate via the TLR4/MyD88 pathway and recruit inflammatory monocytes to islets by producing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

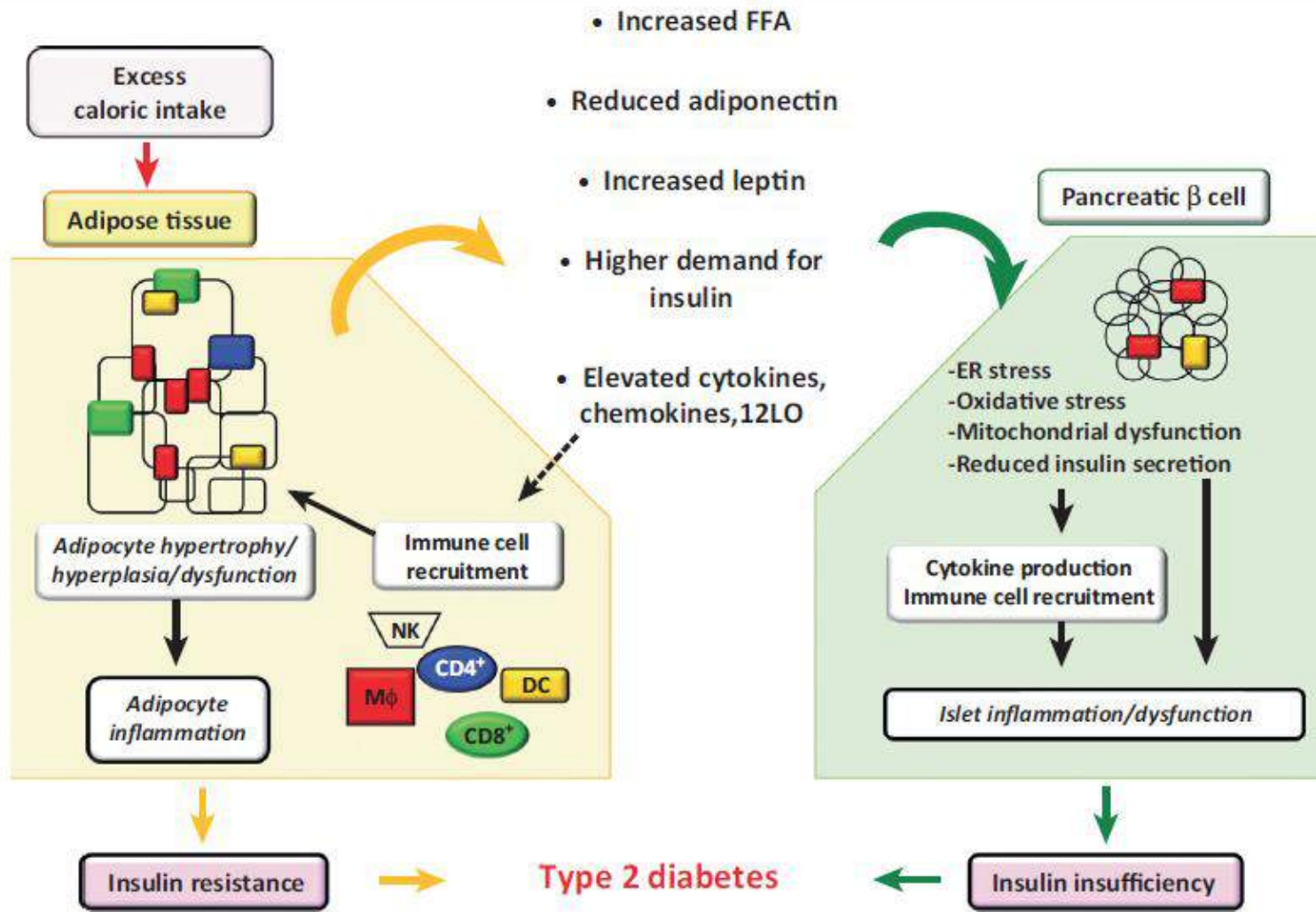
Tip 2 DM'de inflamasyonda rol oynayan aktörler:

- **Adipoz dokunu rolü**
- **Endoplazmik retikulum stresi adacık inflamasyonunu indükler.**
- **IL-6 ve ekzersiz: bir miyokinin pro – ve antiinflamatuvar özellikleri ile rolü**
- **IL-1: bir master sitokindir ve inflamatuvar 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 artırır (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.**
- Proinflamatuvar CD4+T hücreleri adipoz dokuda CD8+ T hücre gelişimini stimüle eder ve hücre ve yabancı maddelerin lizisine neden olur.
- **Antiinflamatuvar sitokinlerin (IL-10 ve SCRP-5) düzeyleri azalır.**
- IL-10 ve SCRP-5 , TNF- α yı inhibe eder, NF- κ B aktivasyonunu azaltır ve makrofaj köpük hücre gelişimini geciktirir Bu antiinflamatuvar 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 -hücreyi 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-1 α (IRE1 α)**....
 - **activating transcription factor 6 (ATF6)**.....ER biyogenezinde hatalı protein yıkımında görev alır.
- Eğer bu sistem bozulursa apoptoz 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

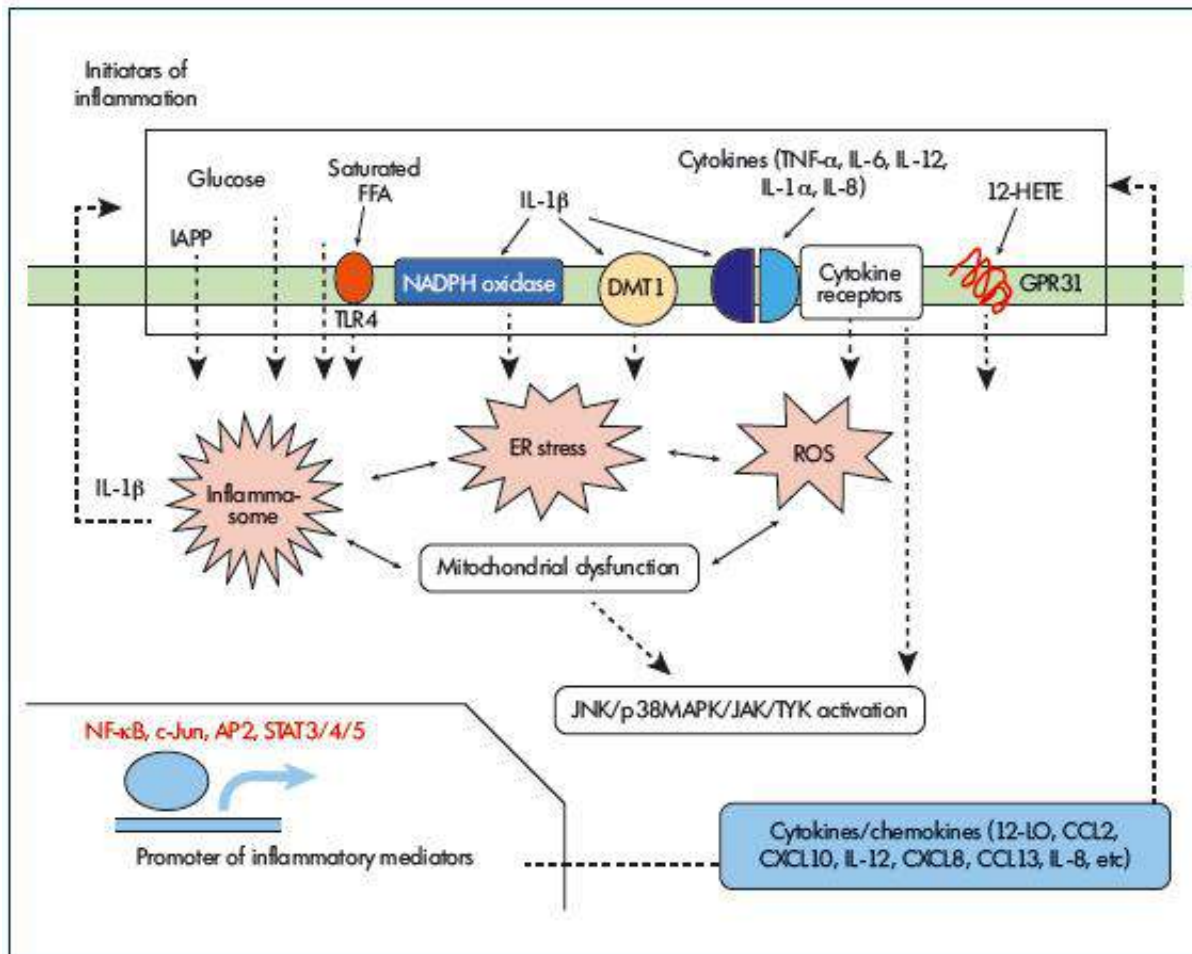
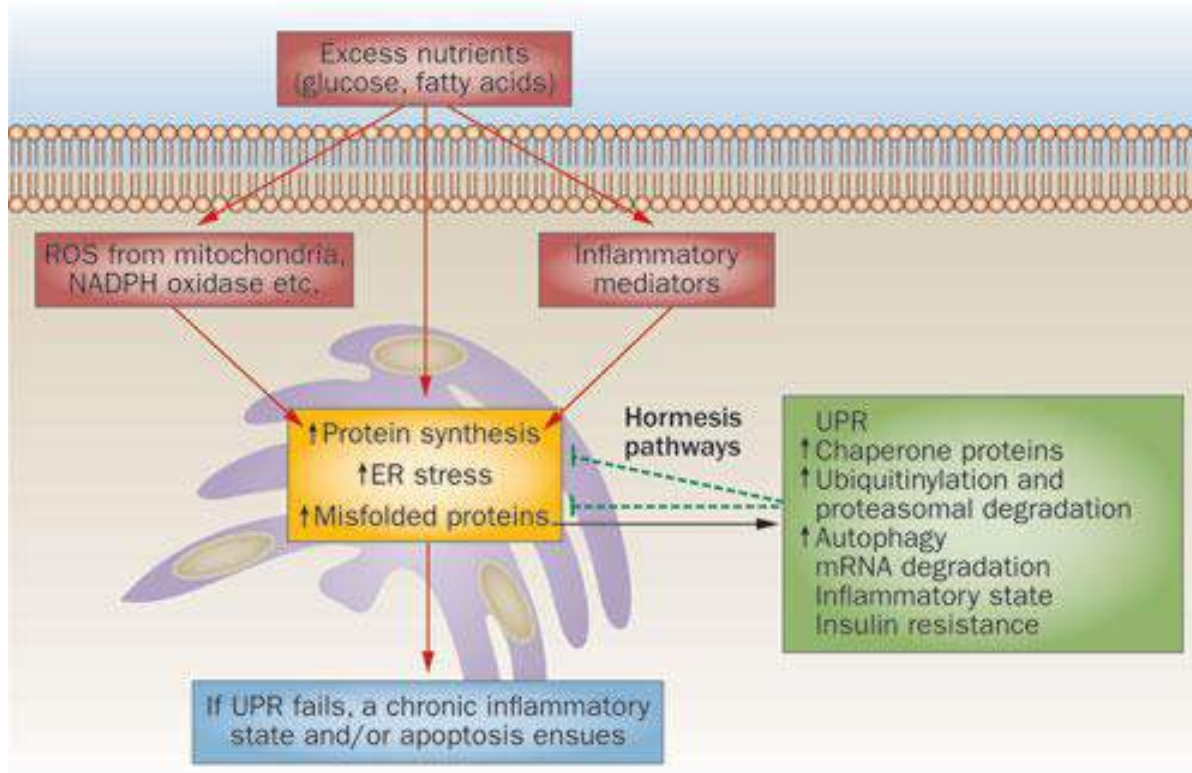
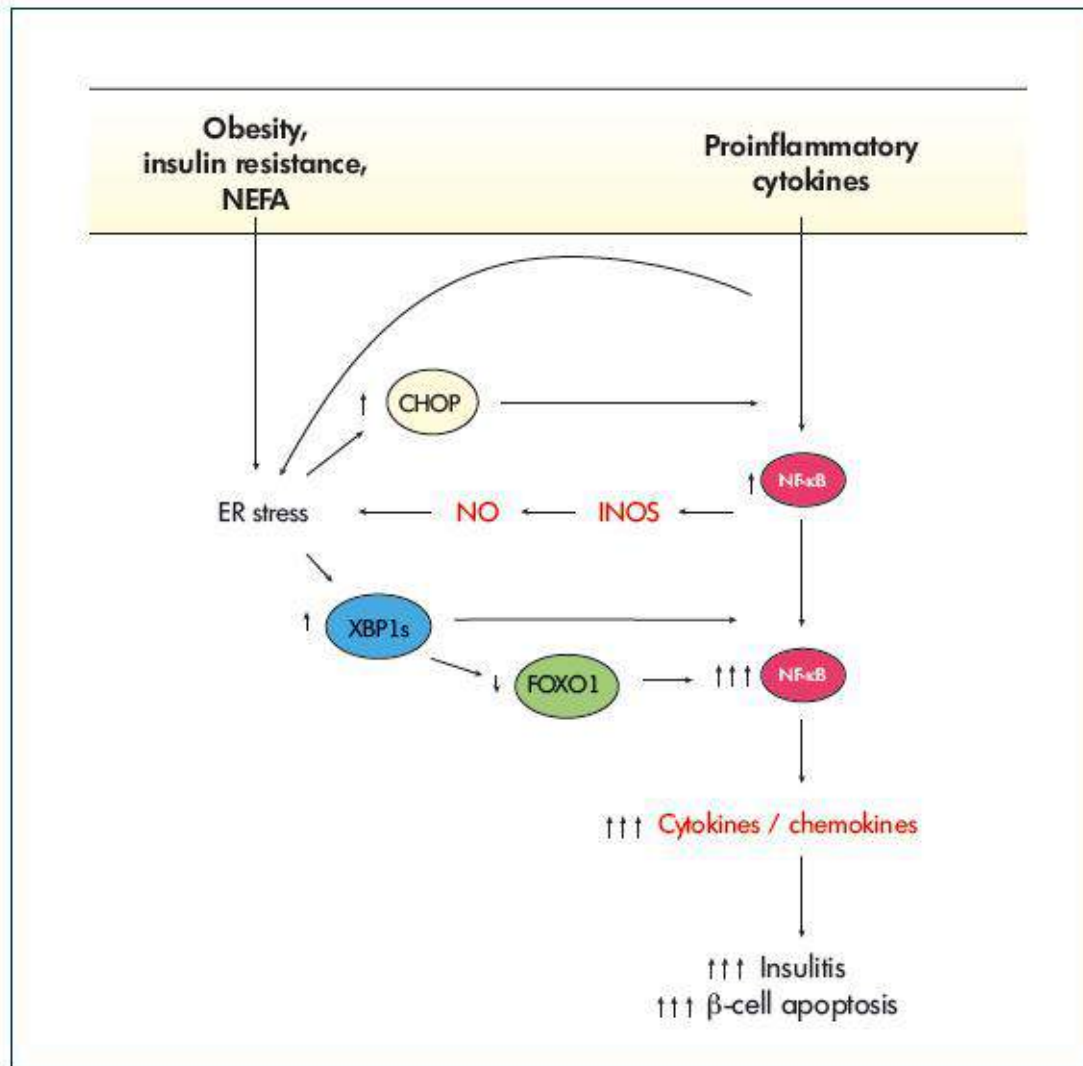


Figure 3 The unfolded protein response—a hormetic response to endoplasmic reticulum stress



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

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



IL-1: bir master sitokin olarak inflamatuvar yanıtı tetikler ve artırır-1

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

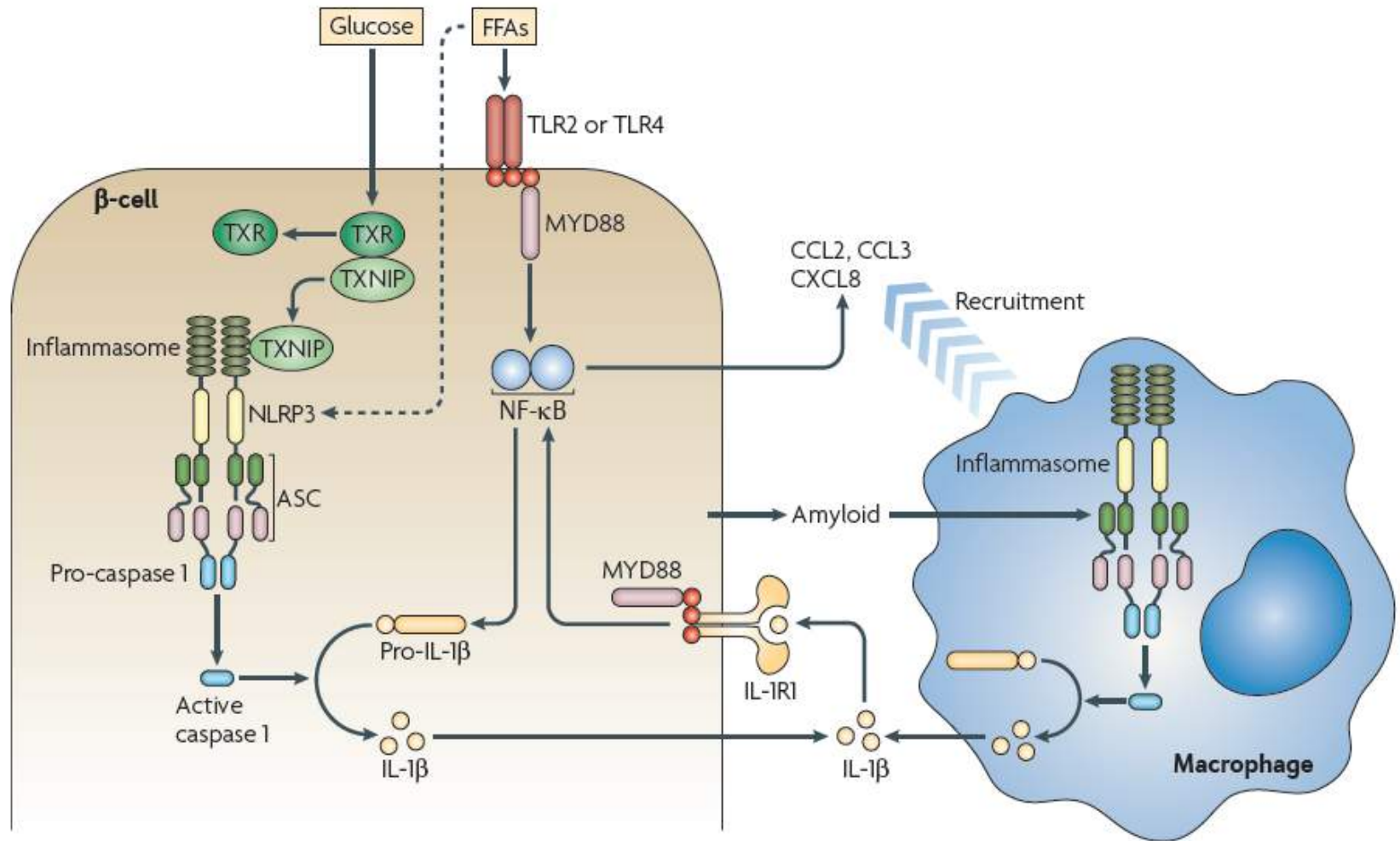


Figure 2 | Interleukin-1β-induced inflammation in islets of patients with type 2 diabetes.

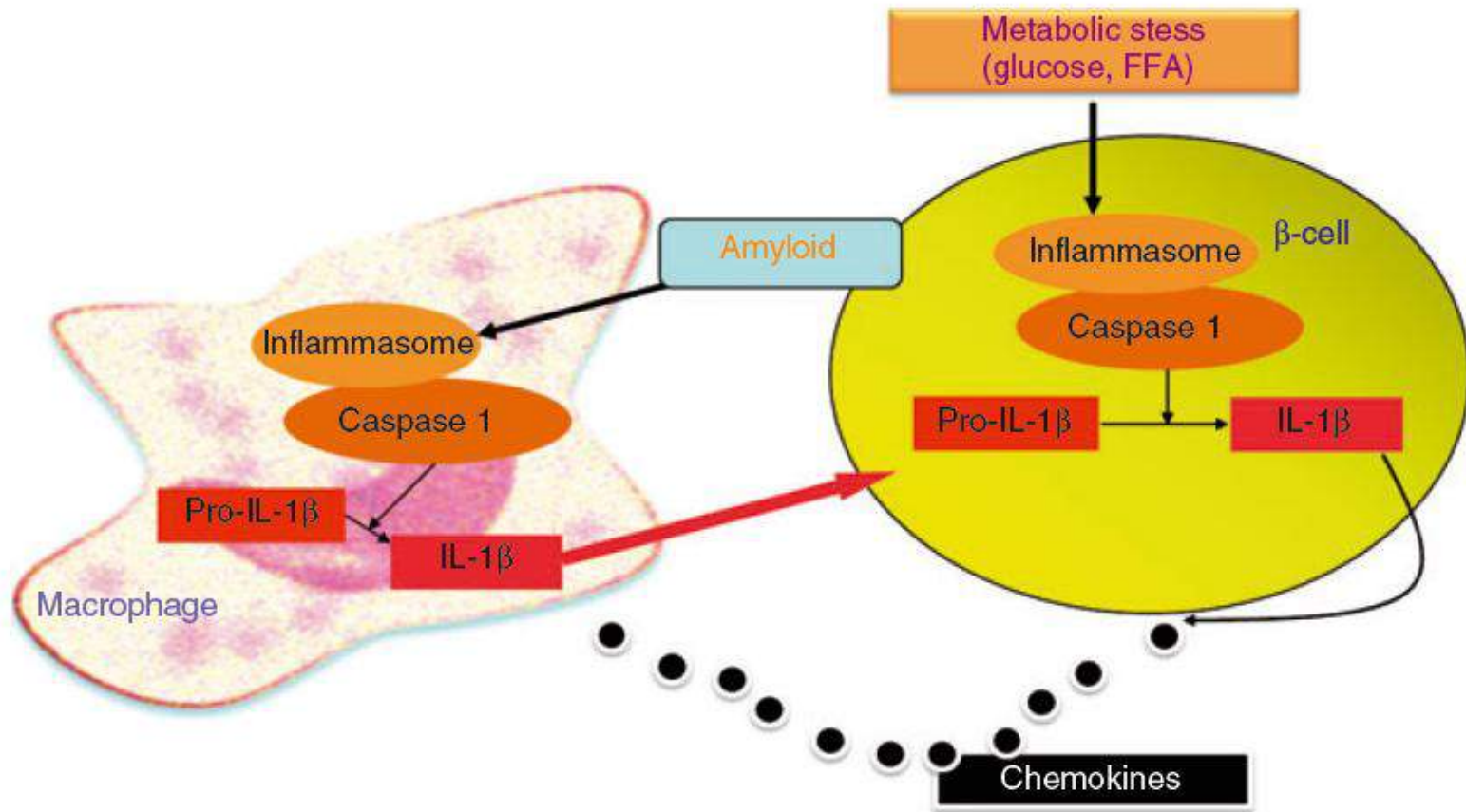
IL-1: bir master sitokin olarak inflamatuvar yanıtı tetikler ve artırır-2

- **IL-1 β** , NF- κ B 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-1 β üretimini artırır. IL-1 β , IL-1 receptor type 1 (IL-1R1) ile otostimülasyon döngüsünü artırır.

IL-1: bir master sitokin olarak inflamatuvar yanıtı tetikler ve artırır-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 hücrelerinde thioredoxin-interacting protein (TXNIP), ER stresi ve inflamasyon arasında kritik bir bağlantıdır. , ER stresörleri ile aktive olur ve NLRP3 ile IL-1 β üretimi tetiklenir.
- Bir kez sekrete edildikten sonra IL-1 β hedef hücrede, IL-1 receptor I (IL-1R1)' e bağlanır. Bu süreç doğal antagonisti IL-1Ra (IL-1F3) ile inhibe olur.

TİP 2 DİYABETTE ADACIK İNFLAMASYONU



Glucose-induced β cell production of IL-1 β 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. Donath¹

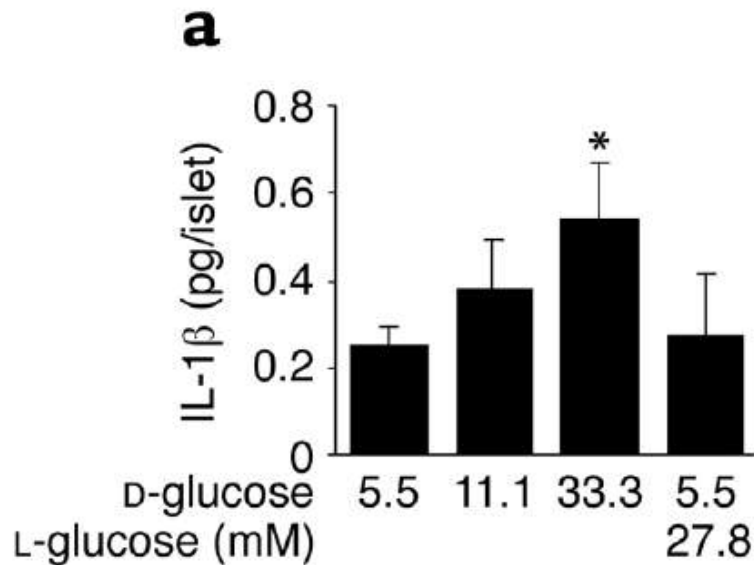
¹Division of Endocrinology and Diabetes, University Hospital, Zurich, Switzerland

²Louis-Jeantet Research Laboratories, University of Geneva Medical Center, Geneva, Switzerland

³Division of Surgical Research, Department of Surgery, University of Geneva Medical Center, Geneva, Switzerland

⁴Division of Clinical Immunology, University Hospital, Zurich, Switzerland

⁵University – Hadassah Medical Center, Jerusalem, Israel



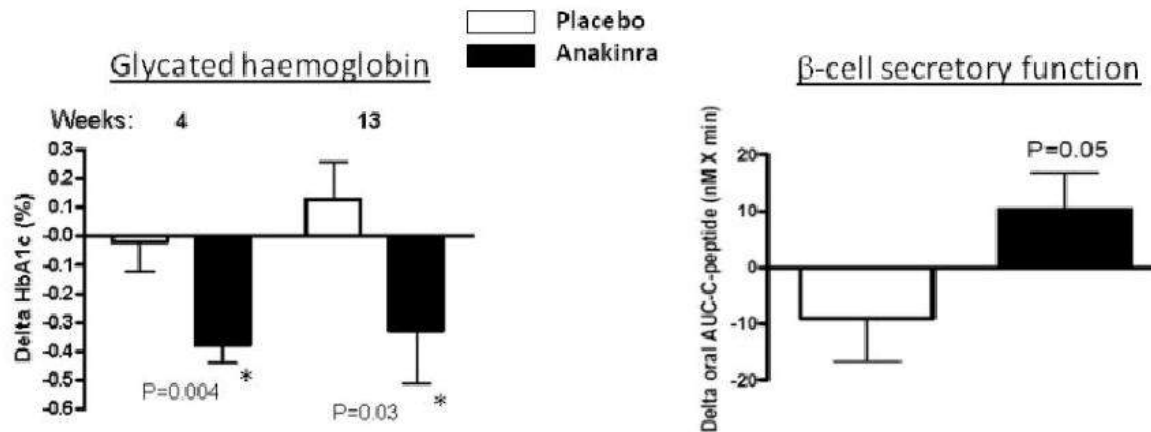
gested to be detrimental to pancreatic β cells, causing inflammation and promoting apoptosis in part. Recently, we have shown that increased glucose concentration promotes β cell apoptosis in human islets. The aim of the present study was to determine whether increased glucose concentration mediates the deleterious effects of high glucose on pancreatic islets. In diabetic organ donors, high glucose levels result in β cell apoptosis, which is followed by NF- κ B activation, Fas upregulation, DNA damage, and apoptosis. The IL-1 receptor antagonist protected cultured human islets from apoptosis. These findings suggest that IL-1 itself was identified as the islet cellular source of IL-1. In type 2 diabetes, β cells were observed in pancreatic sections of type 2 diabetic subjects. Similarly, IL-1 β was induced in β cells of type 2 diabetic subjects. Treatment of the animals with phloretin protected β cell expression of IL-1 β . These findings implicate IL-1 in the pathogenesis of glucotoxicity in type 2 diabetes and identify the β cell as the source of IL-1 β in this condition.

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

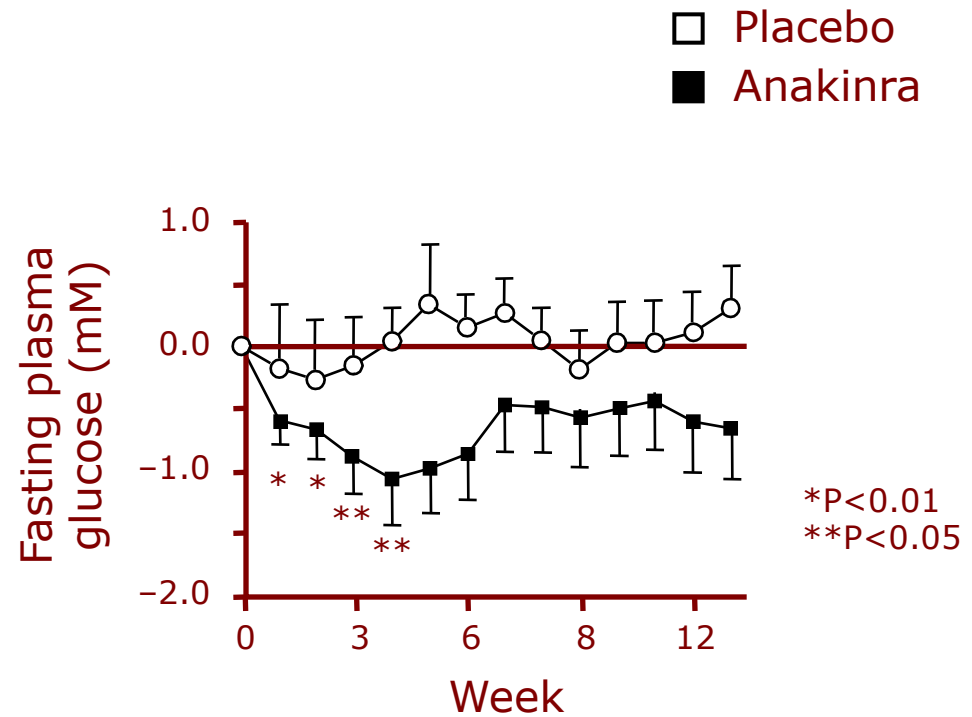
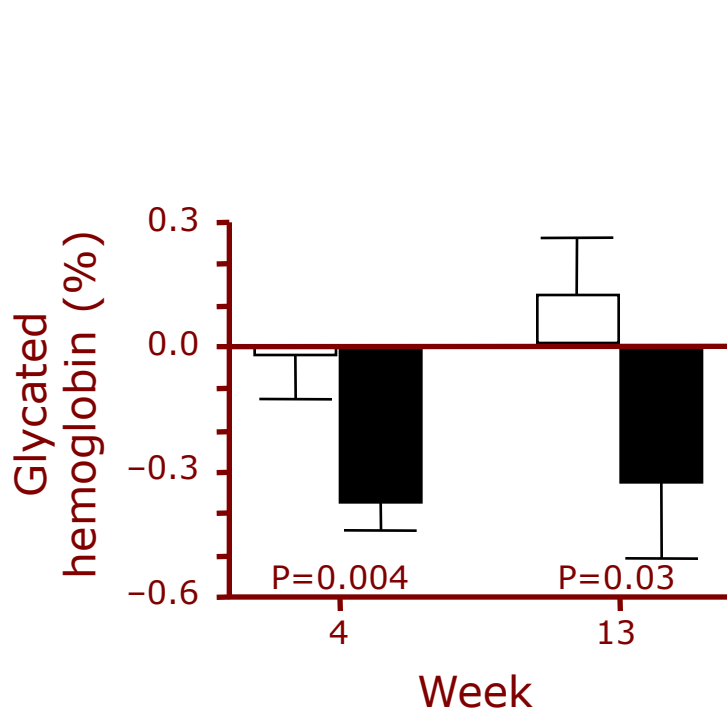
ORIGINAL ARTICLE

Interleukin-1-Receptor Antagonist in Type 2 Diabetes Mellitus

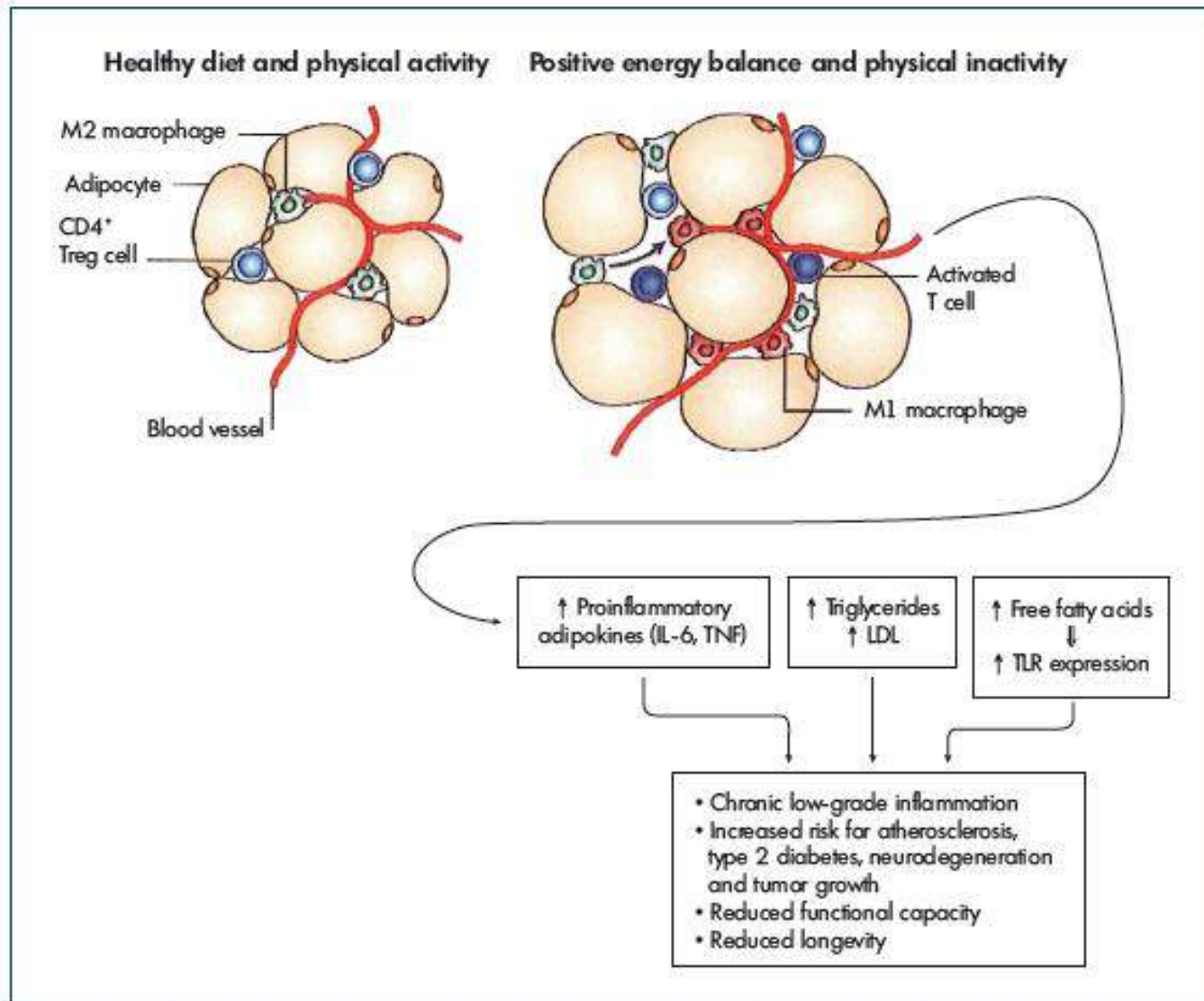
Claus M. Larsen, M.D., Mirjam Faulenbach, M.D., Allan Vaag, M.D., Ph.D.,
Aage Volund, M.Sc., Jan A. Ehses, Ph.D., Burkhardt Seifert, Ph.D.,
Thomas Mandrup-Poulsen, M.D., Ph.D., and Marc Y. Donath, M.D.



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



Diyet ve fiziksel aktivitenin inflamasyon ve hastalık üzerine etkisi



EGZERSİZ

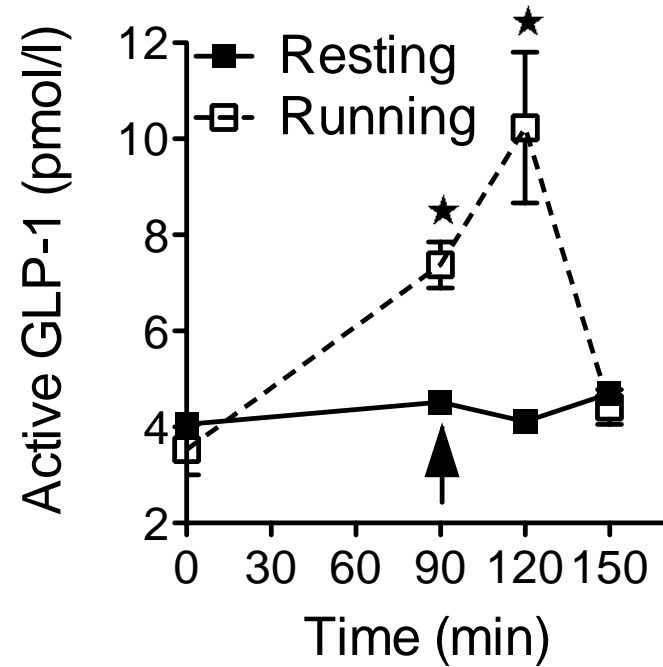
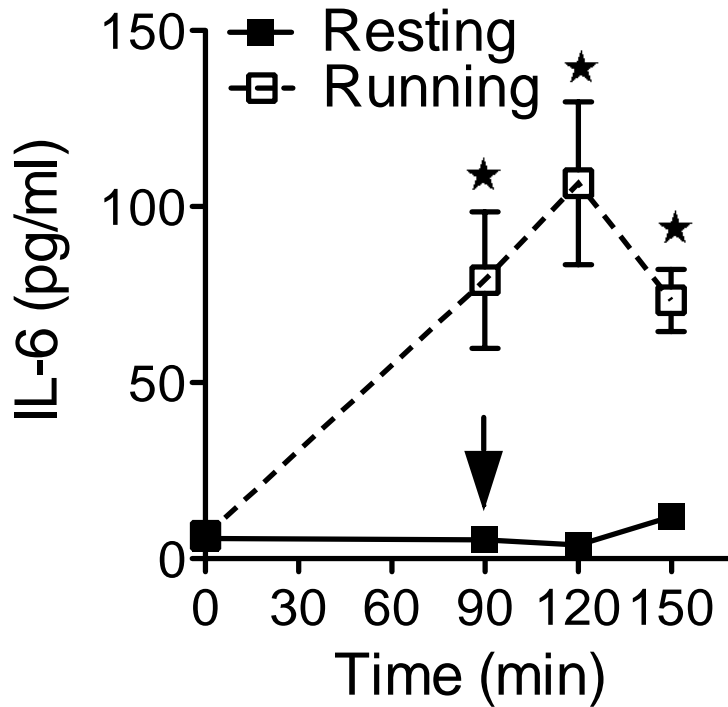


OBEZİTE



IL-6

Egzersizin indüklediği GLP-1 IL-6 bağımlıdır.



Proglukagon işlenmesi...

Proglukagon



L hücresi

α hücresi

Prohormoneconvertase 1/3 (PC1/3)

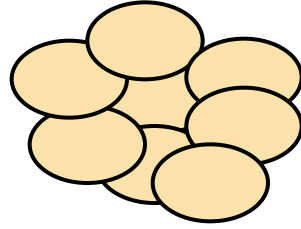


Prohormoneconvertase 2 (PC2)



ADIPOZ DOKU

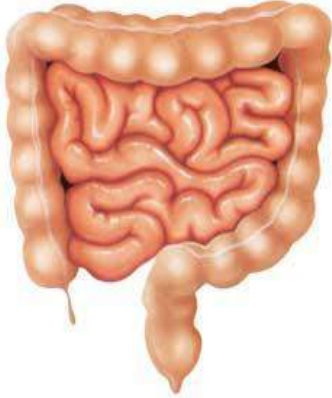
İSKELET KASI



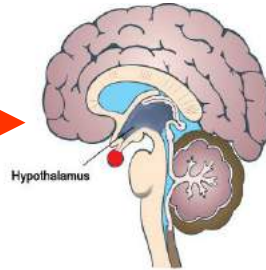
IL-6

İNTESTİN

PANKREATİK ADACIK



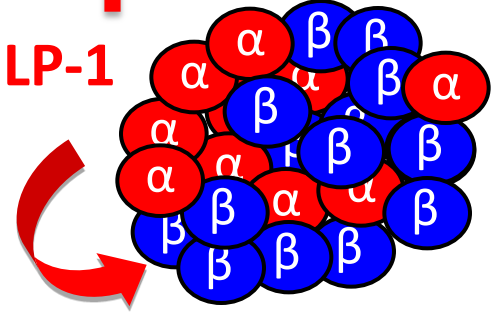
↑ GLP-1



DOYGUNLUK

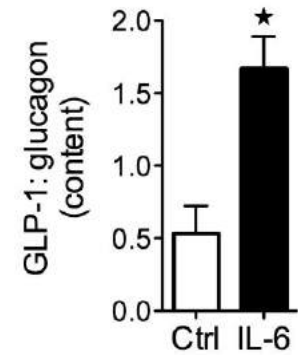
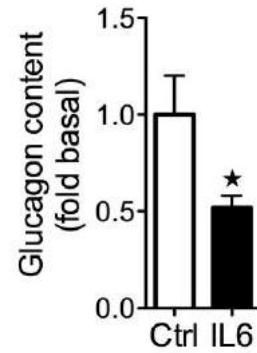
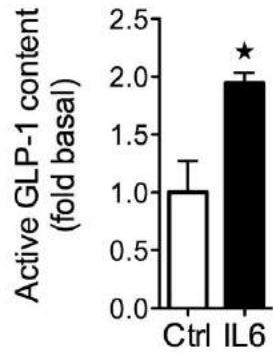
↑ PC1/3

↑ GLP-1



↑ β fonksiyonu ve survi

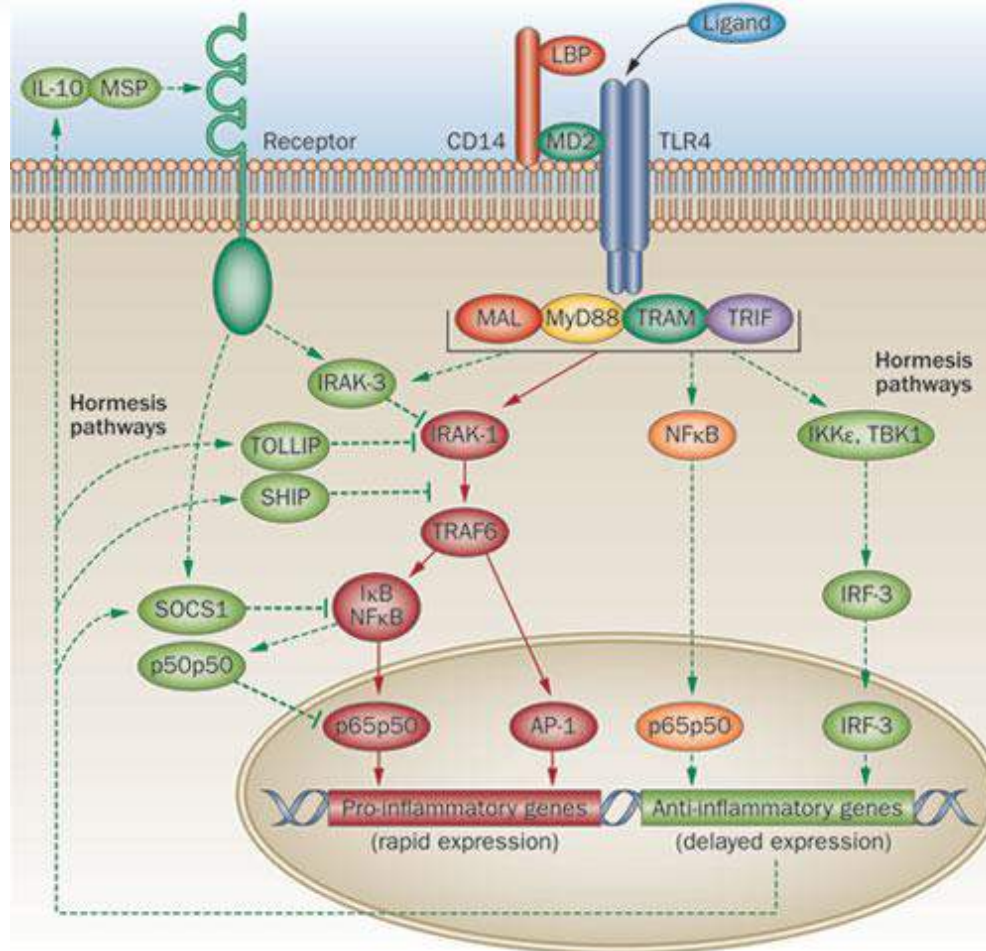
IL-6 insan α hücrelerinde GLP-1 i arttırır.



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) inflammasom'u Tip2 DM de adacık inflamasyonunu tetiklerler ve bu tetikleyicilerin makrofajları aktive etmesi adacık hücrelerinin disfonksiyonuna aracılık eder.
- Bu reseptörleri hedef alan terapötik yaklaşımlar hiperglisemiye düzeltebilir ve beta hücrelerini koruyabilir.

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

NLRP3

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

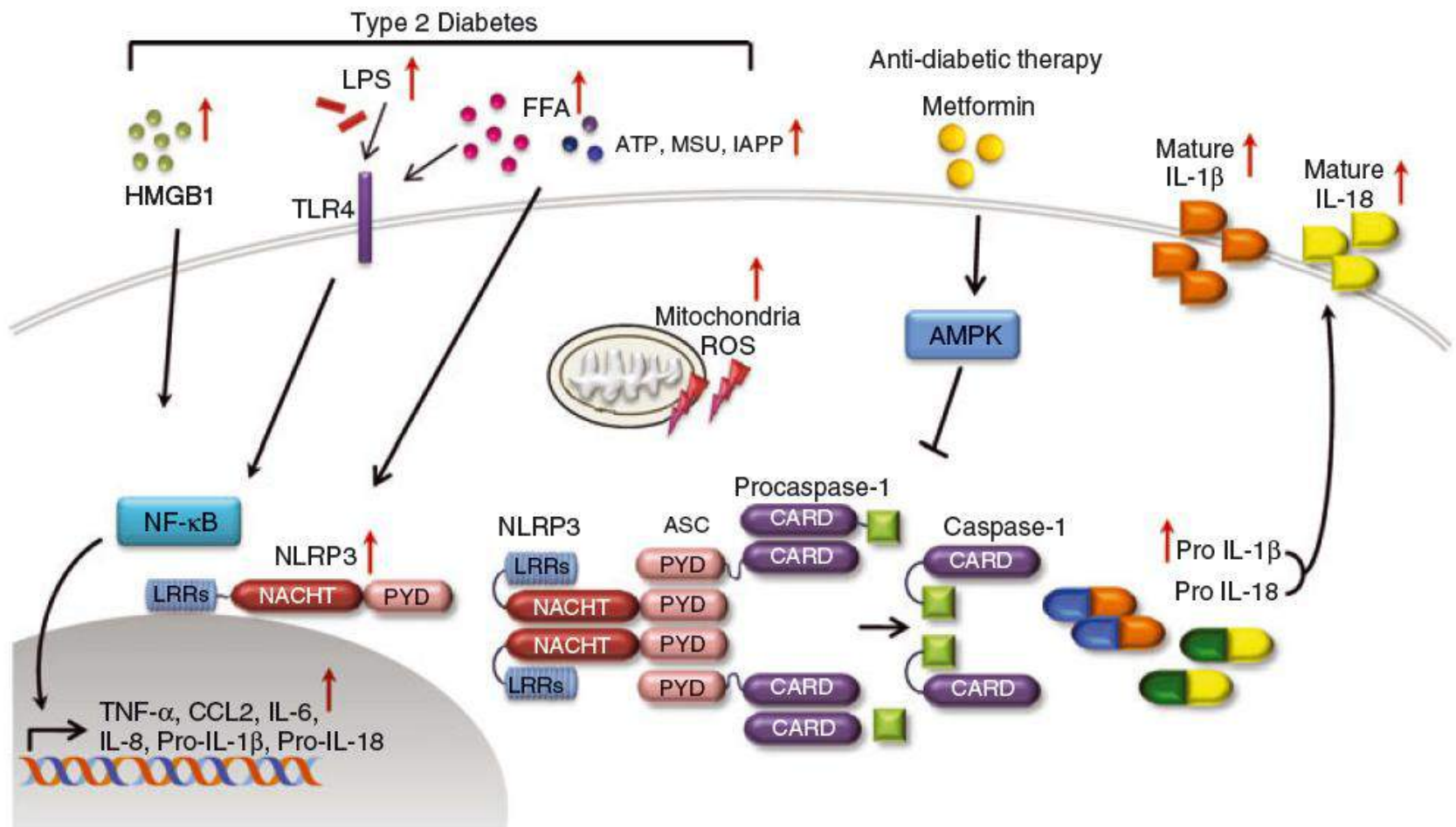


Figure 2. Enhanced activation of NLRP3 inflammasomes in type 2 diabetes (T2D) myeloid cells. In drug-naïve T2D, NLRP3 inflammasomes are activated by diverse obesity-associated alarm molecules. In monocyte-derived *Mφs*, basal NLRP3 and ASC protein levels, as well as proinflammatory cytokines, are elevated when compared with those of controls. In addition, caspase-1 cleavage and interleukin (IL)-1 β 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-1 β . The activation of the AMPK pathway by metformin may modulate NLRP3 inflammasome activation through unknown mechanisms.

Protection from diabetes development by single-chain antibody-mediated delivery of a NF- κ B 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 Schirmmacher,³ and Stephan Schneider^{1,4}

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

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Ueberberg S, Deutschbein T, Klein HH, Dietrich JW, Akinturk S, Prochnow N, Schirmmacher R, Schneider S. Protection from diabetes (2).

β -CELL PROTECTION BY SCA-NBD FUSION PROTEIN

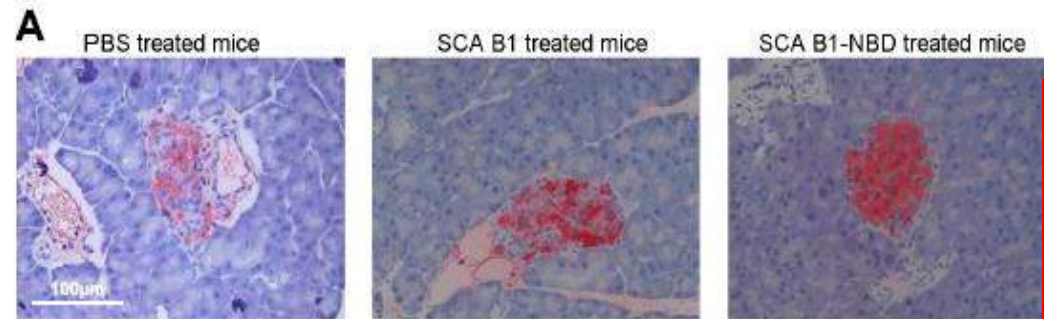
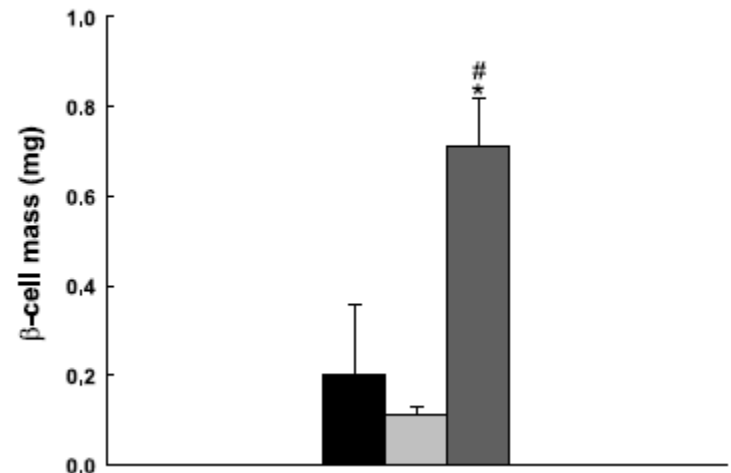
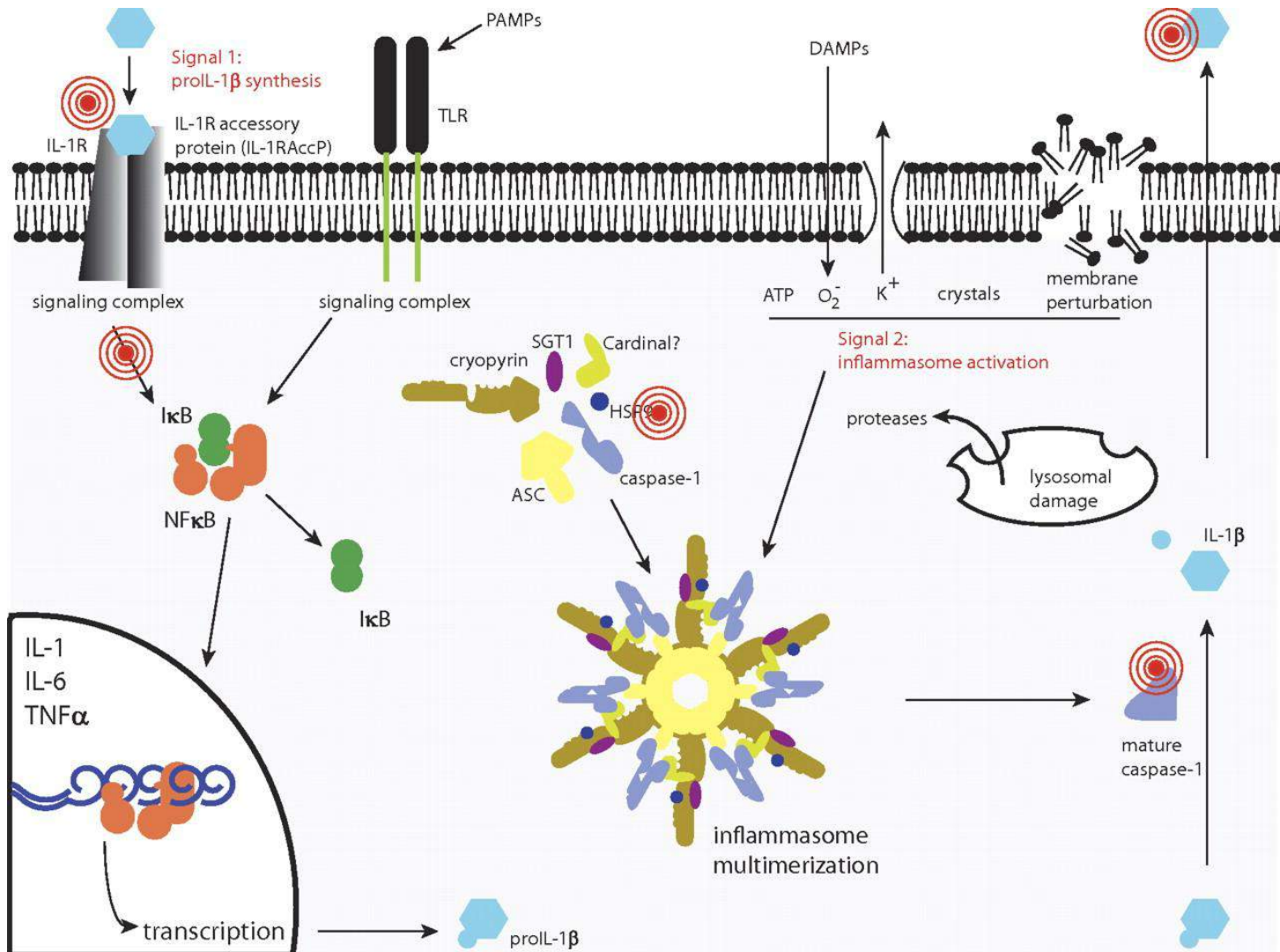


Fig. 6. **A**: histological sections of the pancreas in a PBS-, SCA B1-, or SCA B1 NBD-treated mouse 28 days after the last injection of STZ stained for insulin (red). **B**: pancreatic β -cell mass of CD mice treated with PBS (black bars; $n = 10$), SCA B1 (gray bars; $n = 10$), or SCA B1-NBD (dark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

of the NF- κ B complex is bound to two (κ B β), and the cytoplasmic regulatory modifier (NEMO) prevents the NF- κ B translocation to the nucleus as well as its

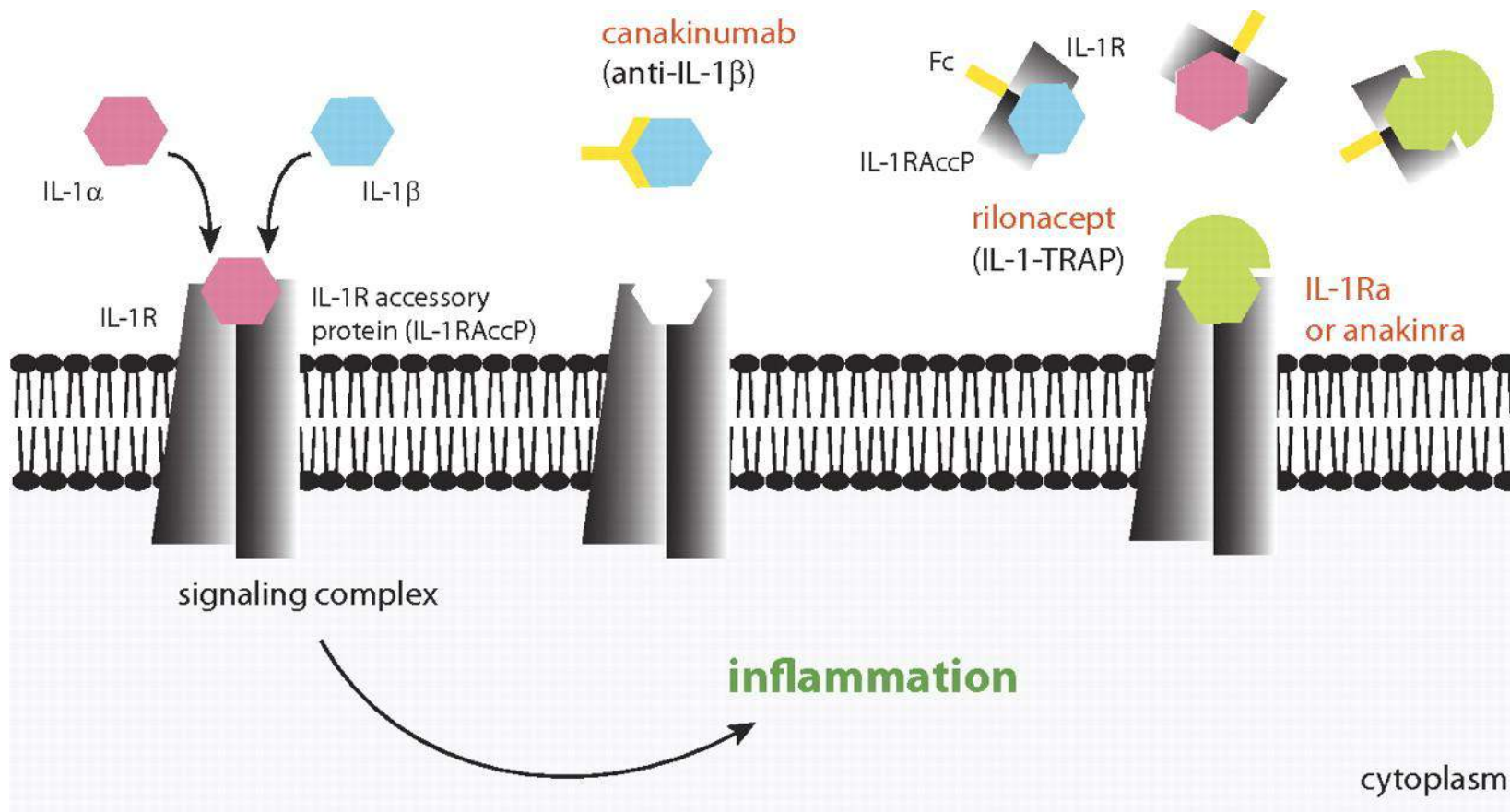


TİP 2 DM TEDAVİSİNDE ANTI-İNFLAMATUVAR YAKLAŞIM



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

Current mechanisms of IL-1-targeted therapy.



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

TİP 2 DM TEDAVİSİNDE ANTI-İNFLAMMATUVAR 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 antagonism	single dose of anti-IL-1β antibody (gevokizumab)	13 weeks	HbA1c ↓; CRP ↓; insulin secretion ↑	–	Cavelti-Weder et al., 2012
IL-1β antagonism	anti-IL-1β antibody (canakinumab)	4 weeks	insulin secretion ↑; CRP ↓	short duration	Rissanen et al., 2012
IL-1β antagonism	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 antagonism	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- κ B inhibition	salsalate	4 weeks	FBG \downarrow ; CRP \downarrow ; insulin sensitivity \uparrow ; adiponectin \uparrow	short duration	Fleischman et al., 2008
IKK- β -NF- κ B inhibition	salsalate	2–4 weeks	FBG \downarrow ; CRP \downarrow ; adiponectin \uparrow	short duration	Goldfine et al., 2008
IKK- β -NF- κ B inhibition	salsalate	1 week	FBG \downarrow ; insulin \uparrow ; CRP \downarrow	short duration	Koska et al., 2009
IKK- β -NF- κ B inhibition	salsalate	12 weeks	HbA1c \downarrow ; FBG \downarrow ; triglyceride \downarrow ; Adiponectin \uparrow	–	Goldfine et al., 2010
IKK- β -NF- κ B inhibition	salsalate	12 weeks	HbA1c \downarrow ; FBG \downarrow ; insulin secretion \uparrow ; triglyceride \downarrow	drug-naive patient; strong effects on glycemia	Faqhihimani et al., 2011
IKK- β -NF- κ B inhibition	salsalate	12 weeks	FBG \downarrow ; adiponectin \uparrow	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 \downarrow ; insulin secretion \uparrow ; 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 \downarrow , adiponectine \uparrow ; LDL \downarrow ; no effect on insulin sensitivity	short duration	Bernstein et al., 2006
Decrease of TNF- α and IL-1 β by an unknown mechanism of action	diacerein	8.5 weeks	HbA1c \downarrow ; FBG \downarrow ; insulin secretion \uparrow	drug-naive patient; strong effects on glycemia	Ramos-Zavala et al., 2011