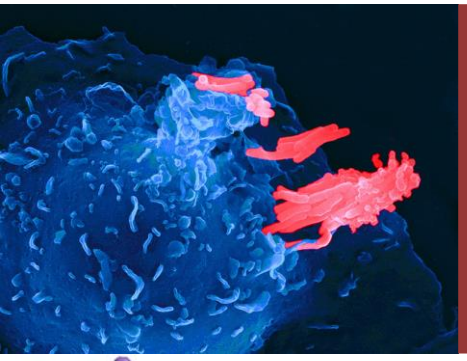
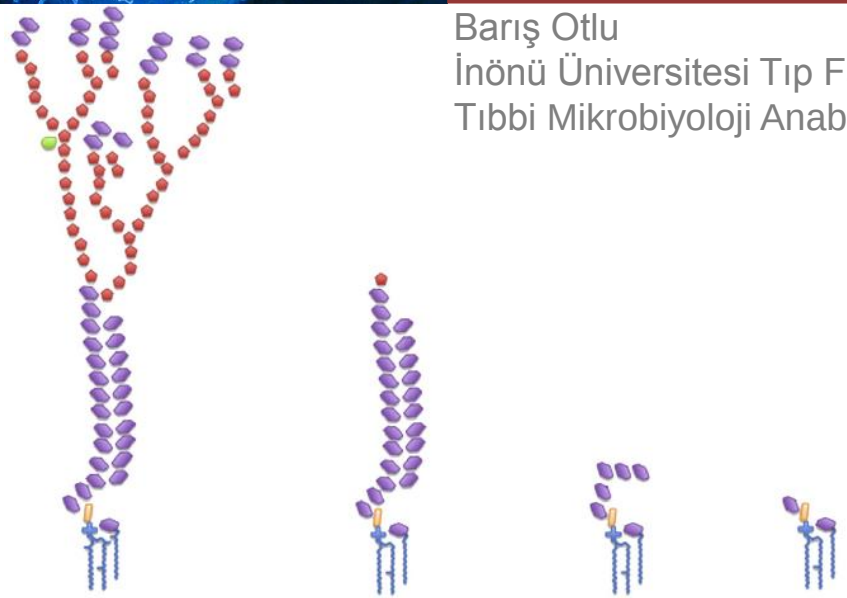


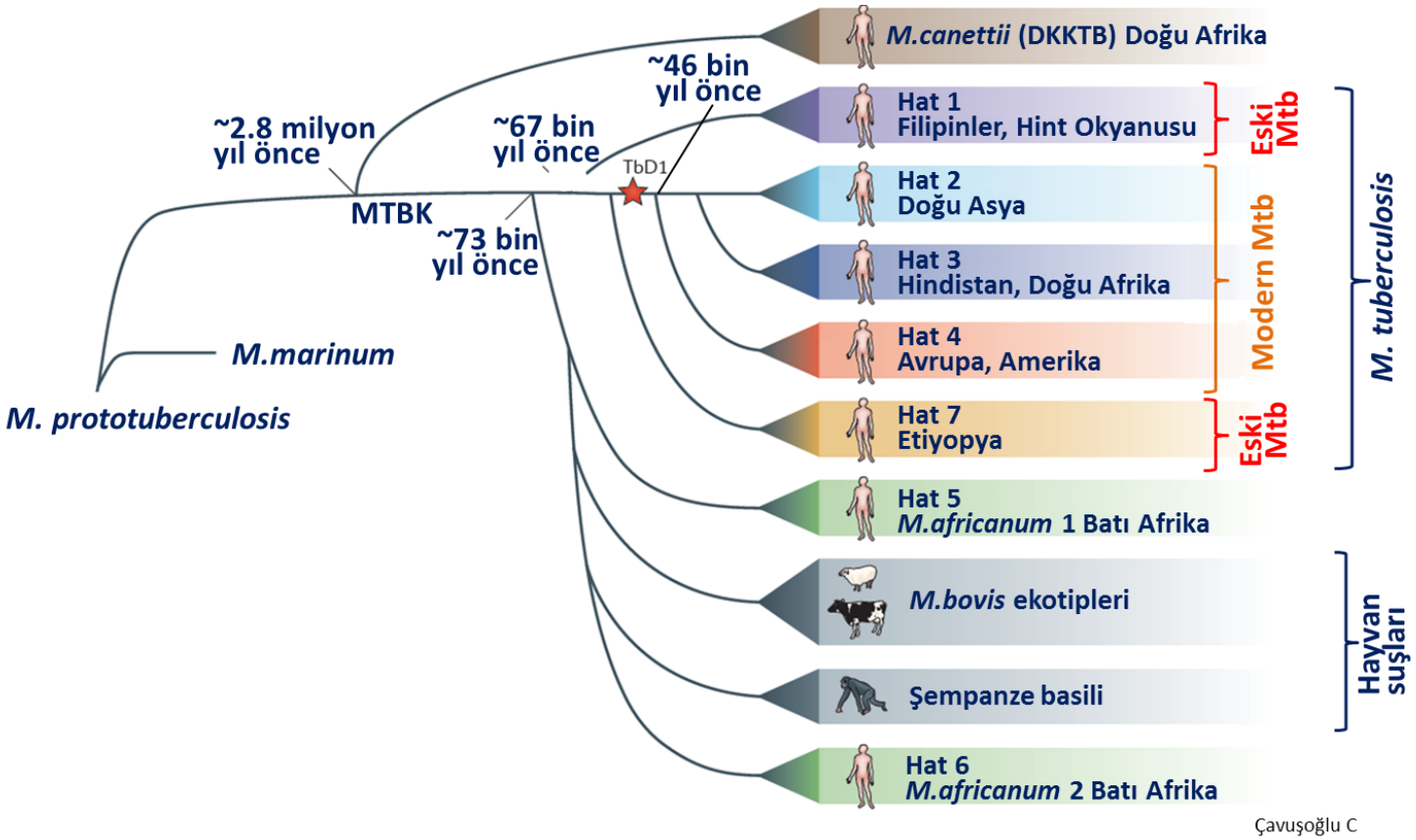
Mikobakteri infeksiyonlarının immünopatogenezi

Barış Otlu
İnönü Üniversitesi Tıp Fakültesi
Tıbbi Mikrobiyoloji Anabilim Dalı



Mycobacterium tuberculosis'in ortaya çıkışı

- *M.tuberculosis* kompleks türleri genetik olarak %99 benzerler.



Çavuşoğlu C

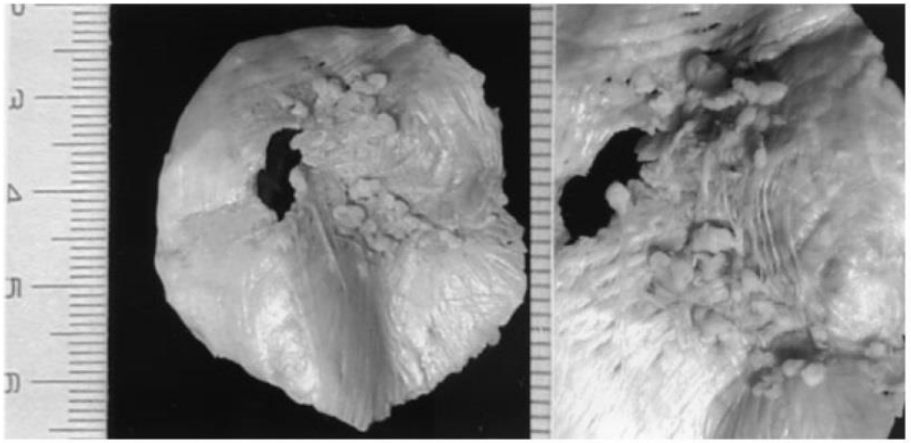
Mycobacterium tuberculosis'in ortaya çıkışı

Denizli'de 500 bin yıllık homo erectus

Denizli'de bulunan Türkiye'nin ilk homo erectus fosili, bilim dünyasında heyecan yarattı. Bir erkeğe ait 500 bin yaşındaki kafatası fosilinin, ilk insanların dünyaya dağılışları konusunda bilim dünyasına önemli ipuçları sağlaması bekleniyor.

AA
Güncelleme: 10:49 TSİ 12 Aralık 2007 Çarşamba

DENİZLİ - Dünyadaki bütün insanların Afrika kökenli olduğu ve diğer kıtalara buradan dağıldıkları, bu sırada Ortadoğu ve Anadolu'dan geçtikleri yönündeki tezleri desteklemesi açısından önem taşıyan fosil, "bilinen en eski tüberküloz vakası" olarak da tıp tarihine geçmeye hazırlanıyor.

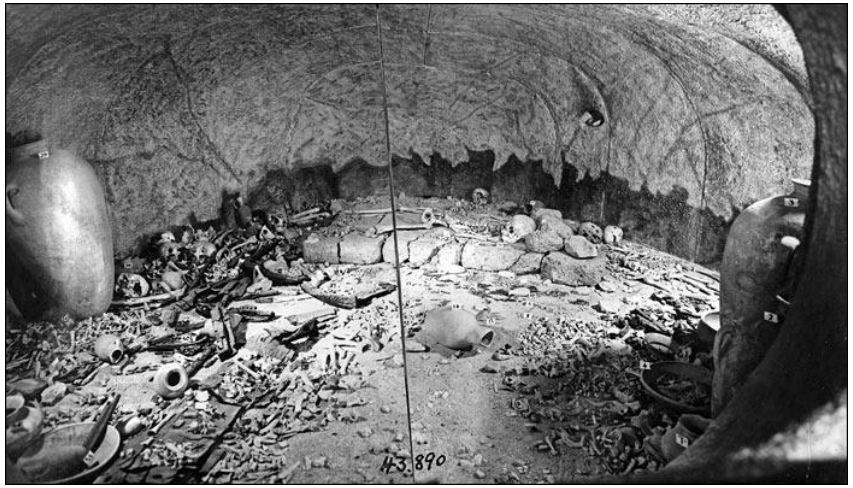


AMERICAN JOURNAL OF PHYSICAL ANTHROPOLOGY 139:442–444 (2009)

Letter to the Editor: Was Tuberculosis Present in *Homo erectus* in Turkey?

Mycobacterium tuberculosis'in ortaya çıkışı

- Mikobakteri ve insanoğlu birbirini iyi tanıyor.
- *Neden milyonlarca yıldır bu savaşın bir kazananı olmadı!!!*



The story today is about scientists examining 6000-year-old bones excavated from Jericho decades ago to trace the evolution of tuberculosis. The bones show extensive evidence of TB infection, and given Jericho's advanced age, some of them might yield clues to the early transmission of the disease.

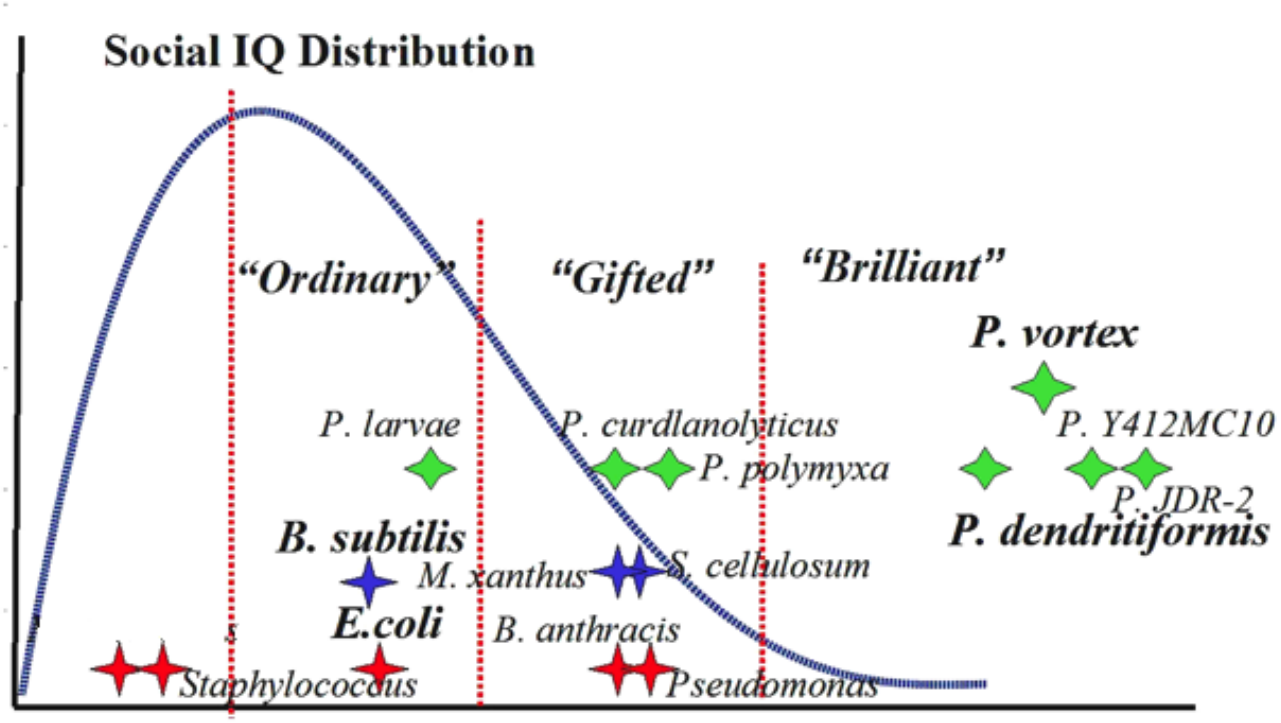
Çok mu zeki?

Research article

BMC Microbiology

A census of membrane-bound and intracellular signal transduction proteins in bacteria: Bacterial IQ, extroverts and introverts

Michael Y Galperin*



Mutasyon hızı mı yüksek?

RESEARCH Open Access

Evolution of extensively drug-resistant *Mycobacterium tuberculosis* from a susceptible ancestor in a single patient

Vegard Eldholm[1*], Gunnstein Norheim[1], Bent von der Lippe[2], Wibeke Kinander[1], Ulf R Dahle[1], Dominique A Caugant[1], Turid Mannsåker[1], Anne Torunn Mengshoel[1], Anne Ma Dyrhol-Riise[2,3] and Francois Balloux[4]

Abstract

Background: *Mycobacterium tuberculosis* is characterized by a low mutation rate and a lack of genetic recombination. Yet, the rise of extensively resistant strains paints a picture of a microbe with an impressive adaptive potential. Here we describe the first documented case of extensively drug-resistant tuberculosis evolved from a susceptible ancestor within a single patient.

Results: Genome sequences of nine serial *M. tuberculosis* isolates from the same patient uncovered a dramatic turnover of competing lineages driven by the emergence, and subsequent fixation or loss of single nucleotide polymorphisms. For most drugs, resistance arose through independent emergence of mutations in more than one clone, of which only one ultimately prevailed as the clone carrying it expanded, displacing the other clones in the process. The vast majority of mutations identified over 3.5 years were either involved in drug resistance or hitchhiking in the genetic background of these. Additionally, RNA-sequencing of isolates grown in the absence of drug challenge revealed that the efflux-associated *iniBAC* operon was up-regulated over time, whereas down-regulated genes include those involved in mycolic acid synthesis.

Conclusions: We observed both rapid acquisitions of resistance to antimicrobial compounds mediated by individual mutations as well as a gradual increase in fitness in the presence of antibiotics, likely driven by stable gene expression reprogramming. The rapid turnover of resistance mutations and hitchhiking neutral mutations has major implications for inferring tuberculosis transmission events in situations where drug resistance evolves within transmission chains.

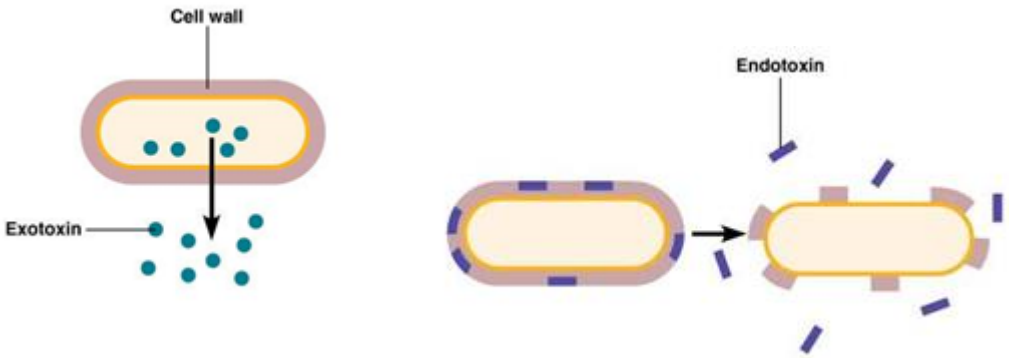
Mutation rates are inflated by drug-induced selection

In a recent study of longitudinal *M. tuberculosis* isolates, including all the major lineages, the substitution rate was estimated to 0.5 SNPs per genome per year (95% confidence interval (CI) 0.3 to 0.7) and the divergence was rarely found to be higher than five SNPs per three years [35]. In another study of transmission chains the substitution rate was found to be 0.4 mutations per genome per year [36]. After exclusion of transient mutations in the patient isolates, 4.3 mutations were acquired per year from SF1 to SF9, or 2.3 mutations per year when excluding resistance mutations.

Antibiotic-induced expansion of resistant clones could potentially distort mutation rate estimates as random SNPs in the genetic background of resistant clones sweep to fixation together with the resistance mutation. Our data set allowed us to directly test for this possibility, as a large number of resistance mutations emerged over time and as the frequency of all identified SNPs were known over nine time points. We plotted SNP frequencies over time, from which it became apparent that SNPs not involved in resistance were changing in frequency in concert with the resistance mutation. These SNPs are located in the genetic background of expanding and contracting drug-resistant clones and their frequency changes over time closely mirror those of the resistance SNP due to the absence of genetic recombination in *M. tuberculosis* (Figure 4C). We refer to such SNPs whose allele frequency change is driven solely by linkage to a resistance mutation under natural selection as hitchhiking SNPs.

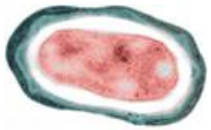
Virülans özellikleri?

- *Toksin yok*



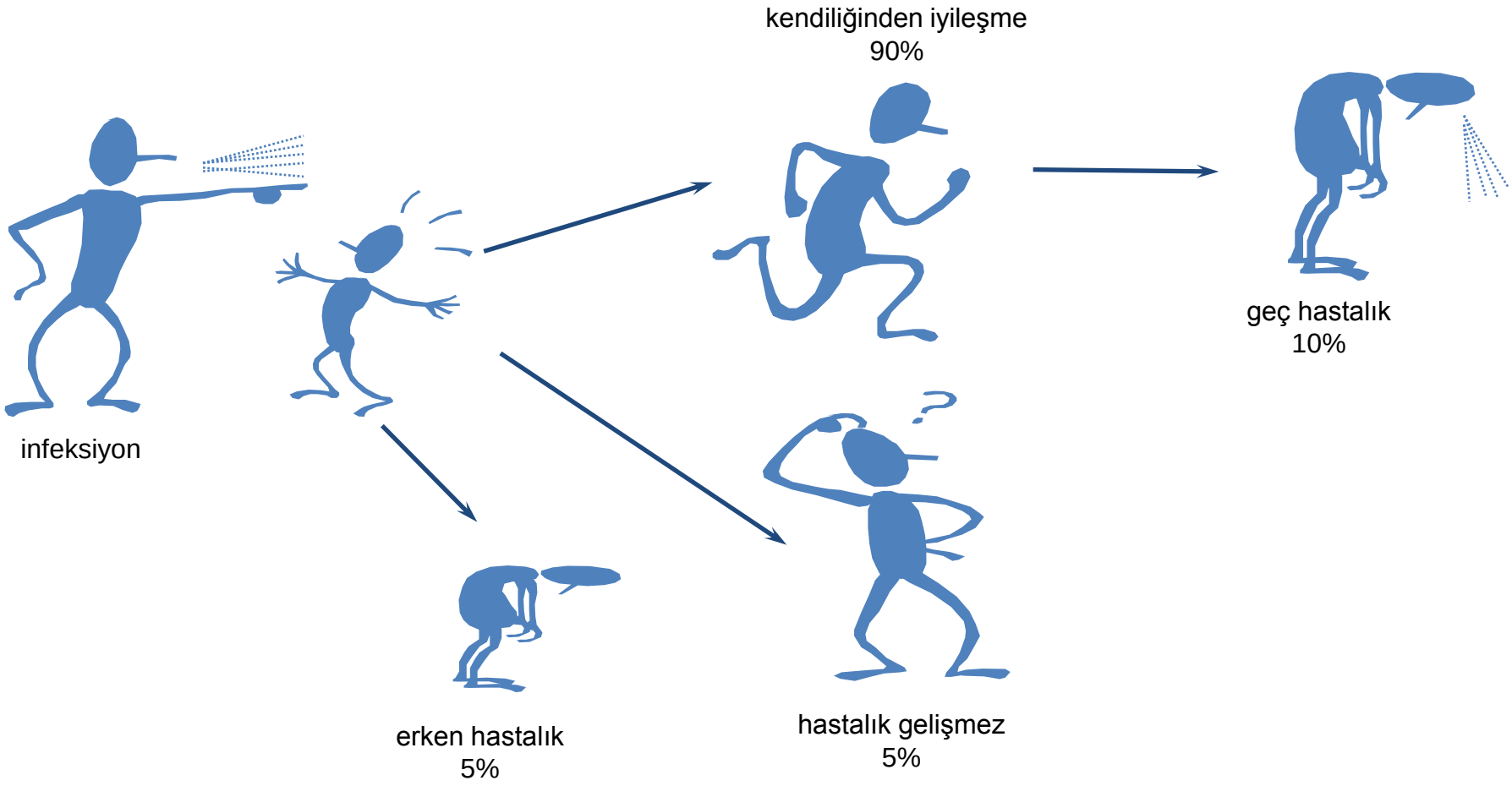
- *Kapsül yok*

- *Spor oluşumu yok*



Herkesi hasta mı yapıyor?

- *M.tuberculosis* ile infekte insanların sadece az (%5) bir kısmında tüberküloz ortaya çıkar.

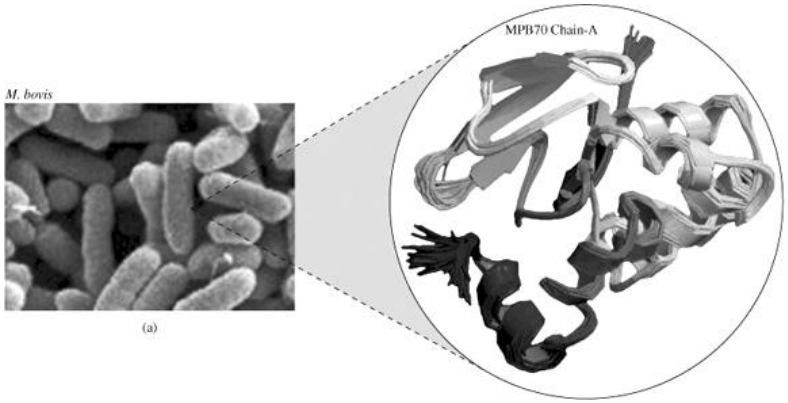


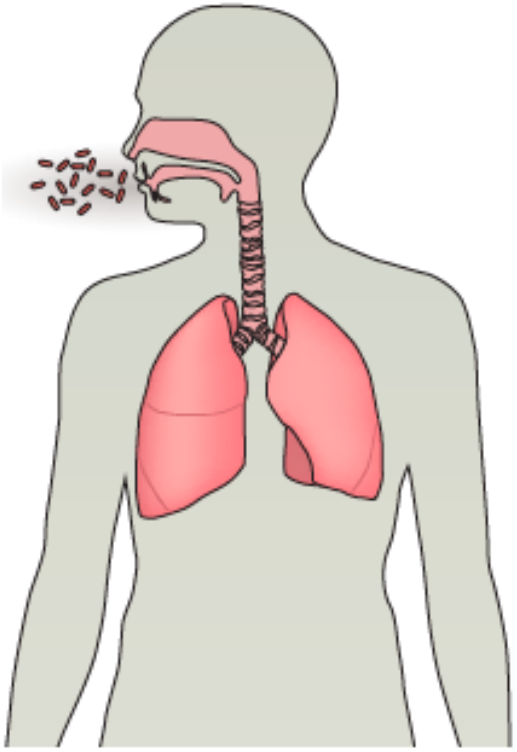
Peki bakteri neden başarılı?

- Tüberküloz patogenezinin anlaşılabilmesi için;

  konak ve patojen arasında gelişen moleküler etkileşimlerin açığa kavuşturularak gereklidir.

Basil ⟷ **Konak**

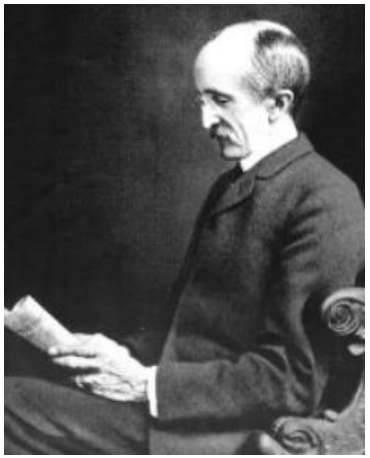




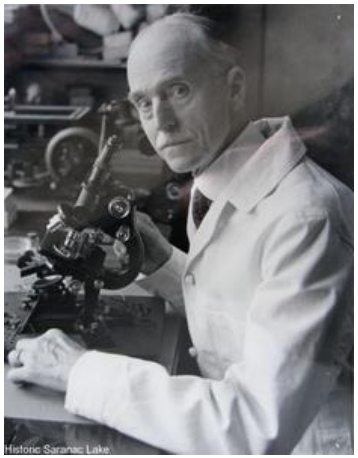
İlk Araştırmalar

- Çağın en önemli bilim adamları, etkeninin keşfinden hemen sonra tüberküloz patogenezinin anlaşılması ve aşı üretimi için araştırmalar yaptılar.

Louis Pasteur



Edward Trudeau



Edward Robinson Baldwin

Theobald Smith

İlk Araştırmalar-1923

X-RAY OBSERVATIONS OF THE PATHOGENESIS OF PULMONARY TUBERCULOSIS

By H. KENNON DUNHAM, M. D., JOHN H. SKAVLEM, M. D.

CINCINNATI, OHIO

The purpose of this paper is to outline the knowledge necessary to an understanding of the pathegenesis and progress of tuberculosis of which the x-ray chest plate is a record.

The ultimate aim of all medical research is benefit to the patient. Frequently the mass of detail of scientific study submerges this in the immediate problems to be solved. The test tube and the experimental animal are at our command and in them we are tempted to see end results. Our greatest knowledge of the pathogenesis and pathology of pulmonary tuberculosis has come from two sources; post-mortem studies and animal experimentation.

The most instructive study has been the artificial production of the disease in the animal. In our human patients we have been able to study the actual changes wrought in the lungs by the tubercle bacillus only by the indirect signs elicted by the clinical examination of the patient. We have realized our short comings and errors in translating physical signs into pathological changes within the lungs. Therefore we have seized upon animal experimentation to teach us more, since here we can control our material and make direct observations of the lungs at will.

In our zeal to find out more and more we have pushed our studies on the amimal to such a stage as to provoke the following remark from a learned scientific clinician, "It is almost as important to make observations on the human as it is to make them on experimental animals." We have learned and are learning much from the observation of animals; it behooves us as well to view each human patient as a source of scientific knowledge. Armed with the knowledge gained from experimental studies, the pathologist lays bare the dead lungs on the autopsy table and tells us what has happened. Armed with the same knowledge it is possible for the trained

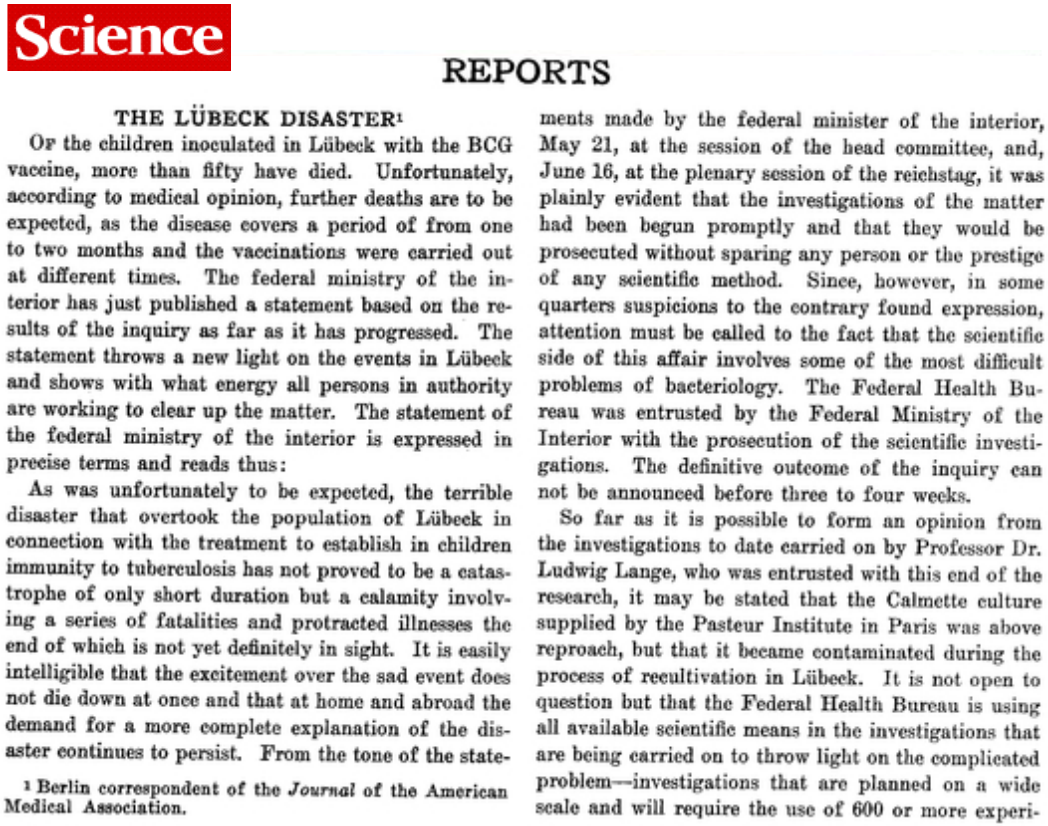
of lymphoid tissue are only filters for the lymph we naturally find lymph vessels in the walls of the bronchi out as far as we find lymphoid tissue. Lymphatic vessels are also associated with the arteries and veins. The pleura has an extremely rich supply of lymph vessels. The lymph flow and the lymphoid tissue within the parenchyma of the lung stand as strong barriers of defense to the invasion of inert foreign particles or living organisms. But beyond the end of the ductulus alveolaris there are no lymph vessels, there is no lymph flow, there is no lymphoid tissue. But the atria, air sacs and alveoli are not left without defense against invasion. Here the phagocyte plays the part of the scavenger in picking up dirt and bacteria, which have penetrated to these depths; carrying them over to the collections of lymphoid tissue where they are then within the realm of lymphatic defense. The role of the phagocyte has been shown to be peculiarly that of a passive barrier. The microscopic study of any lung showing anthracosis reveals these wandering cells engorged with pigment, apparently on their way to the depot of refuse in the lymphoid tissue. Just as pigment is handled so too the tubercle bacillus is disposed of. Excellent studies by Dr. Gerald Webb[20] and co-workers have indicated that while the phagocyte does engulf the tubercle bacillus, it is totally unable to combat or destroy it. Apparently the function of the phagocyte is only to seize and carry the bacillus over into the lymphoid tissue, which possesses the inherent ability to combat the invader. The normal lymph flow in the lung is from the parenchyma toward the hilum, except for a narrow strip of lung tissue immediately under the pleura which can drain into the pleura. The flow in the pleura is over the surface of the lung to the lymph nodes at the hilum. The direction of the flow is established and guarded by valves, which near the hilum open toward the hilum and near the junction of the septa and pleura, open toward the pleura. Pigment is not carried from the hilum into the lung, but vice versa; the tubercle bacillus is not carried from the hilum into the lung, but vice versa; disease does not progress from the hilum into the lung, but vice versa.

İlk Araştırmalar-1930

- Lubeck Felaketi;

252 yenidoğan BCG yerine canlı *Mycobacterium tuberculosis* ile oral yoldan aşılandı.

- 73 bebek ilk yıl içinde öldü
- 135 bebek enfekte oldu ancak iyileşti
- 44 bebeğe hiçbir şey olmadı



Science

REPORTS

THE LÜBECK DISASTER[1]

Of the children inoculated in Lübeck with the BCG vaccine, more than fifty have died. Unfortunately, according to medical opinion, further deaths are to be expected, as the disease covers a period of from one to two months and the vaccinations were carried out at different times. The federal ministry of the interior has just published a statement based on the results of the inquiry as far as it has progressed. The statement throws a new light on the events in Lübeck and shows with what energy all persons in authority are working to clear up the matter. The statement of the federal ministry of the interior is expressed in precise terms and reads thus:

As was unfortunately to be expected, the terrible disaster that overtook the population of Lübeck in connection with the treatment to establish in children immunity to tuberculosis has not proved to be a catastrophe of only short duration but a calamity involving a series of fatalities and protracted illnesses the end of which is not yet definitely in sight. It is easily intelligible that the excitement over the sad event does not die down at once and that at home and abroad the demand for a more complete explanation of the disaster continues to persist. From the tone of the statements made by the federal minister of the interior, May 21, at the session of the head committee, and, June 16, at the plenary session of the reichstag, it was plainly evident that the investigations of the matter had been begun promptly and that they would be prosecuted without sparing any person or the prestige of any scientific method. Since, however, in some quarters suspicions to the contrary found expression, attention must be called to the fact that the scientific side of this affair involves some of the most difficult problems of bacteriology. The Federal Health Bureau was entrusted by the Federal Ministry of the Interior with the prosecution of the scientific investigations. The definitive outcome of the inquiry can not be announced before three to four weeks.

So far as it is possible to form an opinion from the investigations to date carried on by Professor Dr. Ludwig Lange, who was entrusted with this end of the research, it may be stated that the Calmette culture supplied by the Pasteur Institute in Paris was above reproach, but that it became contaminated during the process of recultivation in Lübeck. It is not open to question but that the Federal Health Bureau is using all available scientific means in the investigations that are being carried on to throw light on the complicated problem—investigations that are planned on a wide scale and will require the use of 600 or more experi-

[1] Berlin correspondent of the *Journal* of the American Medical Association.

Mikobakterilerin antijenik komponentlerinin karakterizasyonu

- Mikobakterilerin antijenik komponentlerinin karakterizasyonu, mikobakterilere karşı gelişen immün cevabın ve patogenezin anlaşılmasında anahtar rol oynar.

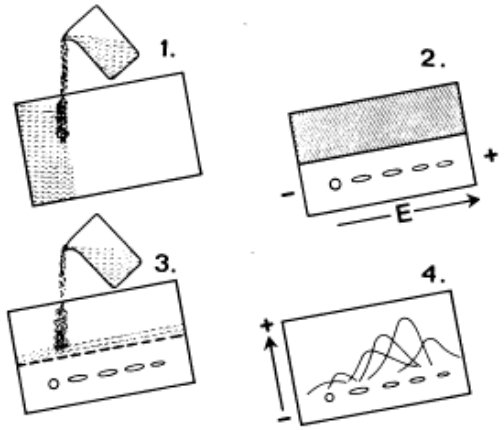


FIG. 1. *Diagrammatic illustration of the procedure for performing two-dimensional immunoelectrophoresis. 1. A hot (90 C) solution of 1% agarose in barbital buffer is poured onto an 8 by 10 cm glass slide. 2. Electrophoresis in the first direction is carried out at 12 ma per slide. The agarose in the region of the diagonal lines is then cut away. 3. A warm (50 C) mixture of equal parts 2% agarose in barbital buffer and antiserum is poured onto the slide to cover the region above the dashed line. 4. The second electrophoresis is then carried out at right angles to the first at 10 ma per slide for 20 hr.*

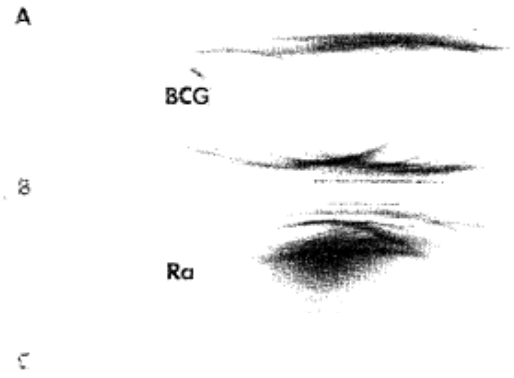


FIG. 3. *Conventional immunoelectrophoretic patterns of reactions of Mycobacterium bovis strain BCG (BCG) cell extract (CX) and M. tuberculosis strain H37Ra (Ra) CX with rabbit anti-BCG (troughs A and C) and rabbit anti-Ra (trough B).*

Mikobakterilerin antijenik komponentlerinin karakterizasyonu

- Mikobakteriyel antijenlerin ve bunlara karşı gelişen konak immün yanıtı ile ilişkili olarak ilk geniş çaplı araştırma 1978 yılında Daniel ve Janicki tarafından yapılmıştır.

MICROBIOLOGICAL REVIEWS, Mar., 1978, p. 84–113
0146-0749/78/0042-0084$02.00/0

Vol. 42, No. 1
Printed in U.S.A.

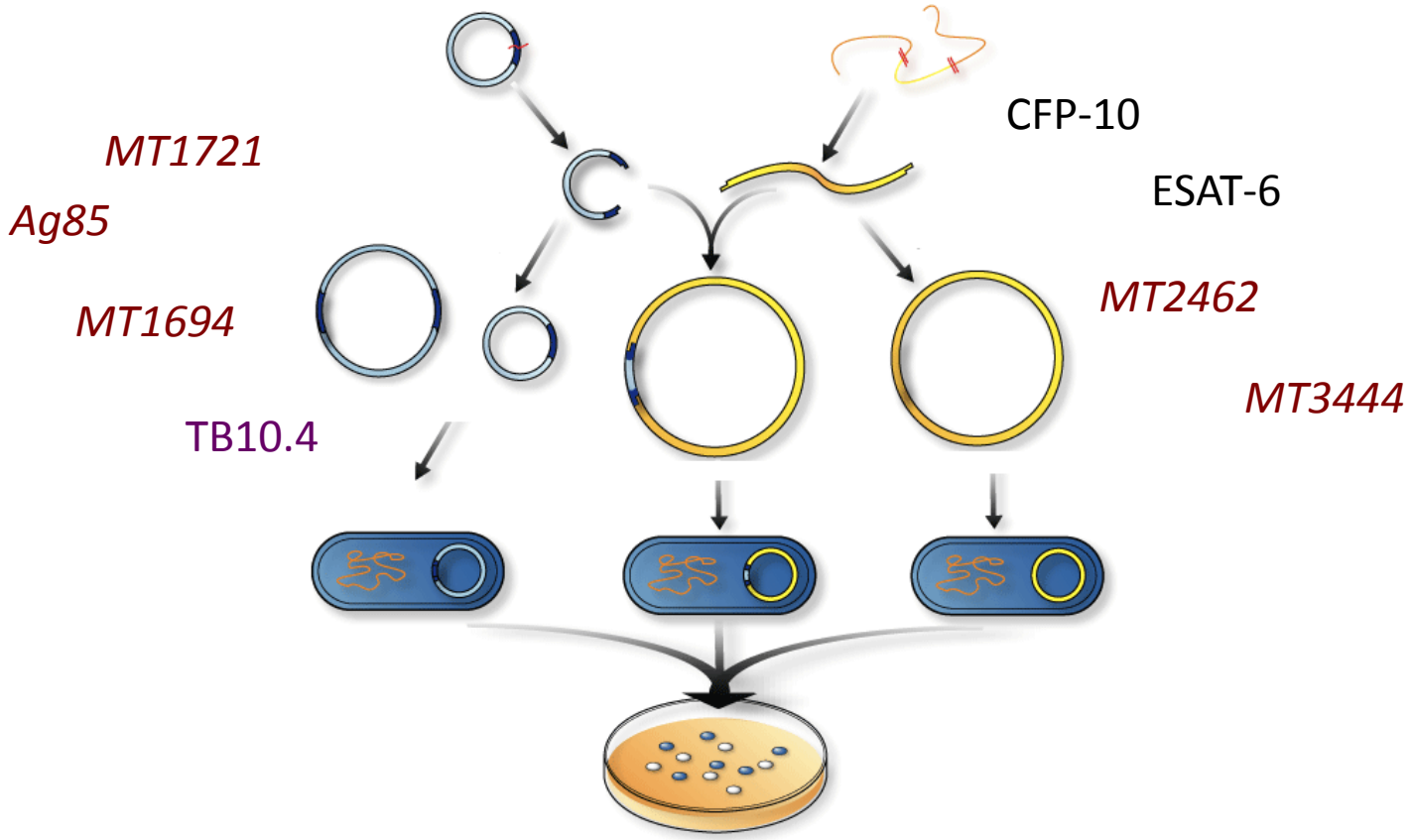
Mycobacterial Antigens: a Review of Their Isolation, Chemistry, and Immunological Properties

THOMAS M. DANIEL[1]* AND BERNARD W. JANICKI[2]

Department of Medicine, Case Western Reserve University and University Hospitals, Cleveland, Ohio 44106,[1] and National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014[2]

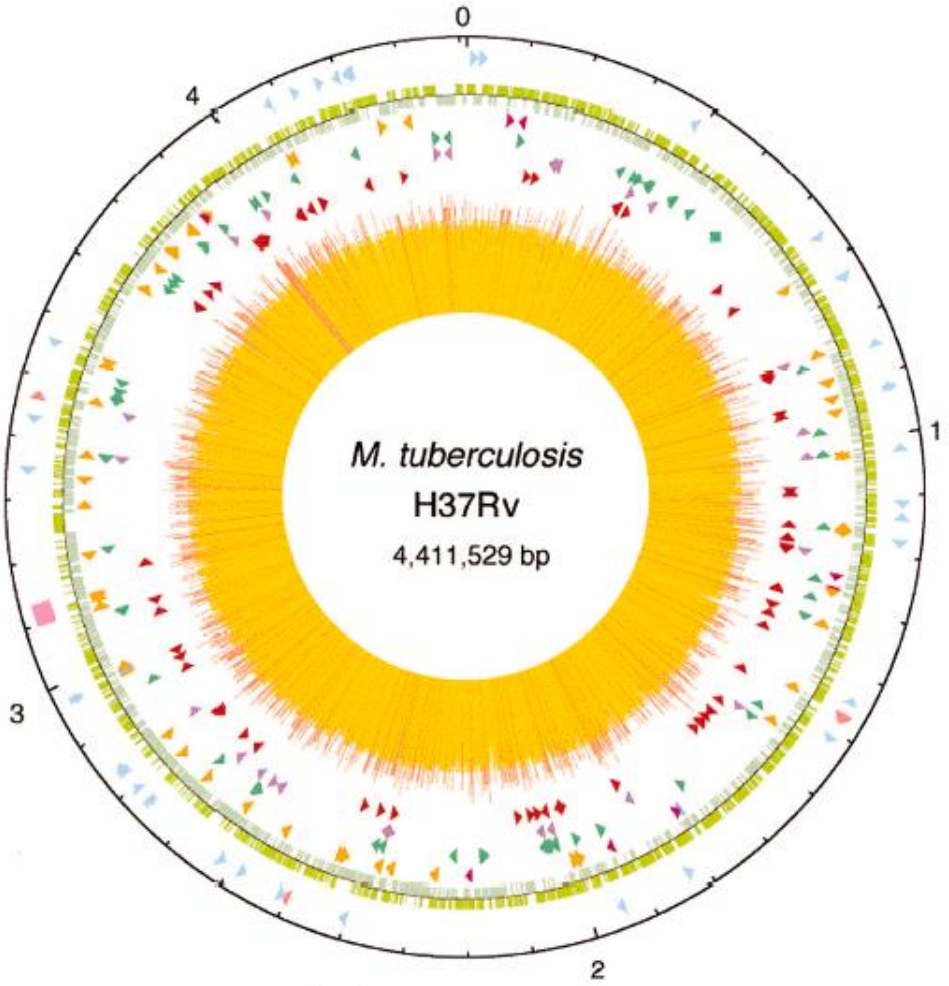
Mikobakterilerin antijenik komponentlerinin karakterizasyonu

- Bu tarihten sonra klonlama teknolojilerinin geliştirilmesi ile mikobakteriyel antijenlerin kompetan hücrelerde ekspresyonları ve antijenlerin saf olarak eldesi başarılmıştır.



MTB Tüm Genomunun Dizilenmesi

- Bu alana katkıda bulunan ikinci önemli gelişme ise dizi analizi yöntemlerindeki ilerlemelerdir.



Clinical Microbiology Reviews, July 2003, p. 463–496

MTB Genomu ve Biyoinformatik

- Gomez ve arkadaşları;

  mikobakteriyel antijenlerin araştırmak için Mtb genomunu farklı bilgisayar programları ile analiz etmişlerdir.

INFECTION AND IMMUNITY, Apr. 2000, p. 2323–2327 Vol. 68, No. 4
0019-9567/00/$04.00+0

NOTES

Identification of Secreted Proteins of *Mycobacterium tuberculosis* by a Bioinformatic Approach

MANUEL GOMEZ, SADIE JOHNSON, AND MARIA LAURA GENNARO*
Public Health Research Institute, New York, New York

Received 3 September 1999/Returned for modification 18 October 1999/Accepted 13 December 1999

Proteins secreted by *Mycobacterium tuberculosis* are usually targets of immune responses in the infected host. Here we describe a search for secreted proteins that combined the use of bioinformatics and *phoA′* fusion technology. The 3,924 proteins deduced from the *M. tuberculosis* genome were analyzed with several computer programs. We identified 52 proteins carrying an NH_2-terminal secretory signal peptide but lacking additional membrane-anchoring moieties. Of these 52 proteins—the TM1 subgroup—only 7 had been previously reported to be secreted proteins. Our predictions were confirmed in 9 of 10 TM1 genes that were fused to *Escherichia coli phoA′*, a marker of subcellular localization. These findings demonstrate that the systematic computer search described in this work identified secreted proteins of *M. tuberculosis* with high efficiency and 90% accuracy.

MTB Genomu ve Biyoinformatik

- Bu çalışmada,
  - Mtb genomunda 3924 adet protein kodlayabilecek gen bölgesi tespit edilmiştir.
  - Bunlardan 52'sinin salgısal protein olduğunu ve NH2-terminal sinyal peptidi taşıdığını belirlemişlerdir.

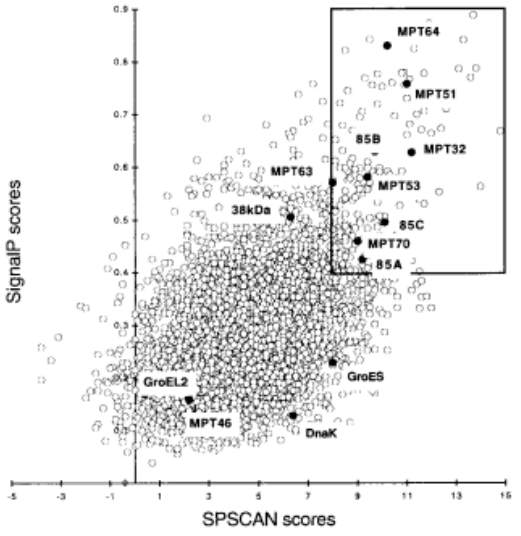


FIG. 3. Correlation between SignalP and SPScan scores. Each circle represents one of the 3,924 deduced proteins of *M. tuberculosis*. The position of the circle indicates the scores assigned by SignalP and SPScan to the signal peptide. For this study, the two computer programs were set in the mode for gram-positive bacteria. SPScan was used in the adjusted mode, which penalizes signal peptides longer than 45 amino acid residues (i.e., the maximal length for gram-positive bacteria). The boxed area contains the Top208 group of proteins that scored ≥0.4 with SignalP and ≥8 with SPScan. The solid circles within the boxed area represent nine known secreted proteins (Ag85A, Ag85B, Ag85C, MPT32, MPT51, MPT53, MPT63, MPT64, and MPB70) (34) that were used to set cutoff values for SignalP and SPScan scores. The solid circles outside of the boxed area represent four known proteins (MPT46, GroES, GroEL2, and DnaK) containing no signal peptide (34). Also outside of the boxed area is located the 38-kDa antigen, a secreted protein which exhibits an LPP type of signal peptide (14).

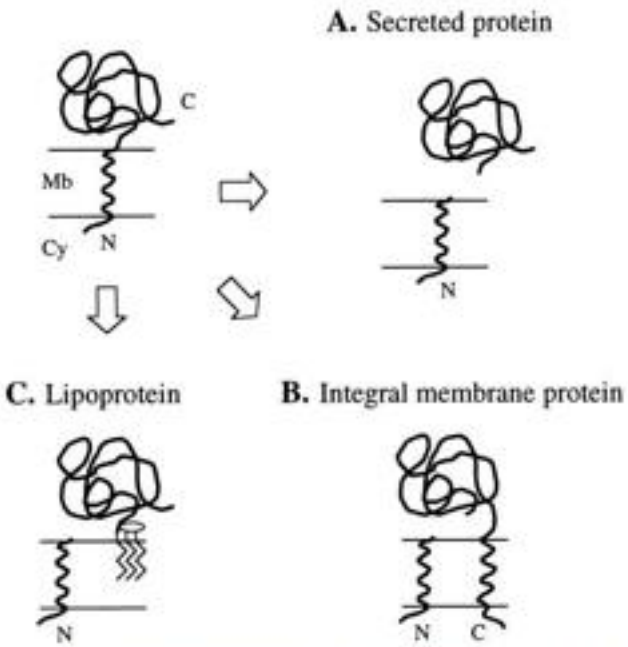
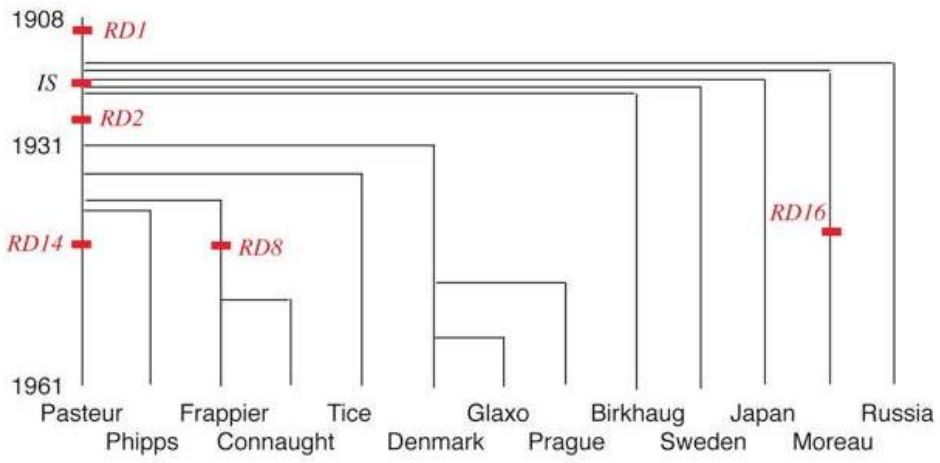
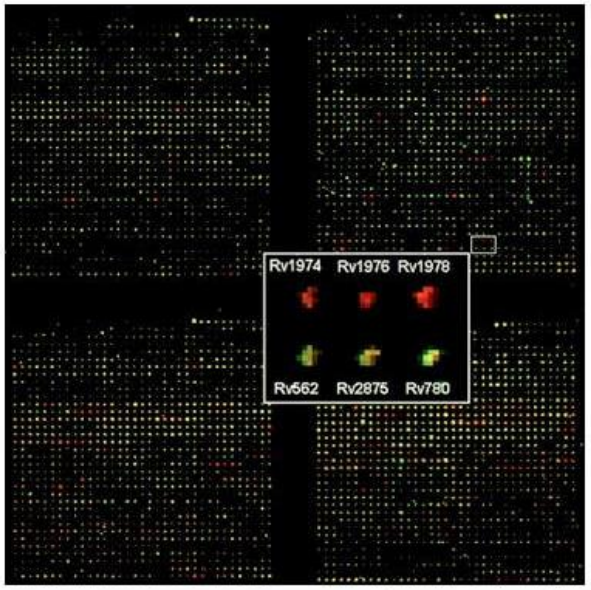


FIG. 1. Fates of proteins having an NH_2-terminal signal peptide. The NH_2-terminal signal peptide directs translocation of a protein across the cell membrane (top left panel). Processing of the preprotein by a type I signal peptidase releases the mature protein (A), providing that there are no additional transmembrane domains (B). Translocation of LPPs across the membrane is followed by modification with glycerol and fatty acids of the prolipoprotein and processing by a type II signal peptidase. The lipid moiety anchors the LPP to the membrane (C). Mb, cell membrane; Cy, cytoplasm; N, NH_2-terminal end; C, COOH-terminal end.

MTB Proteomik Araştırmalar

- Peptid kütüphanelerinin ve protein mikroarrayleri içeren yeni proteomik yaklaşımların geliştirilmesi, patogenezde rolü olan immün dominant antijenlerin araştırılmasını sağladı.



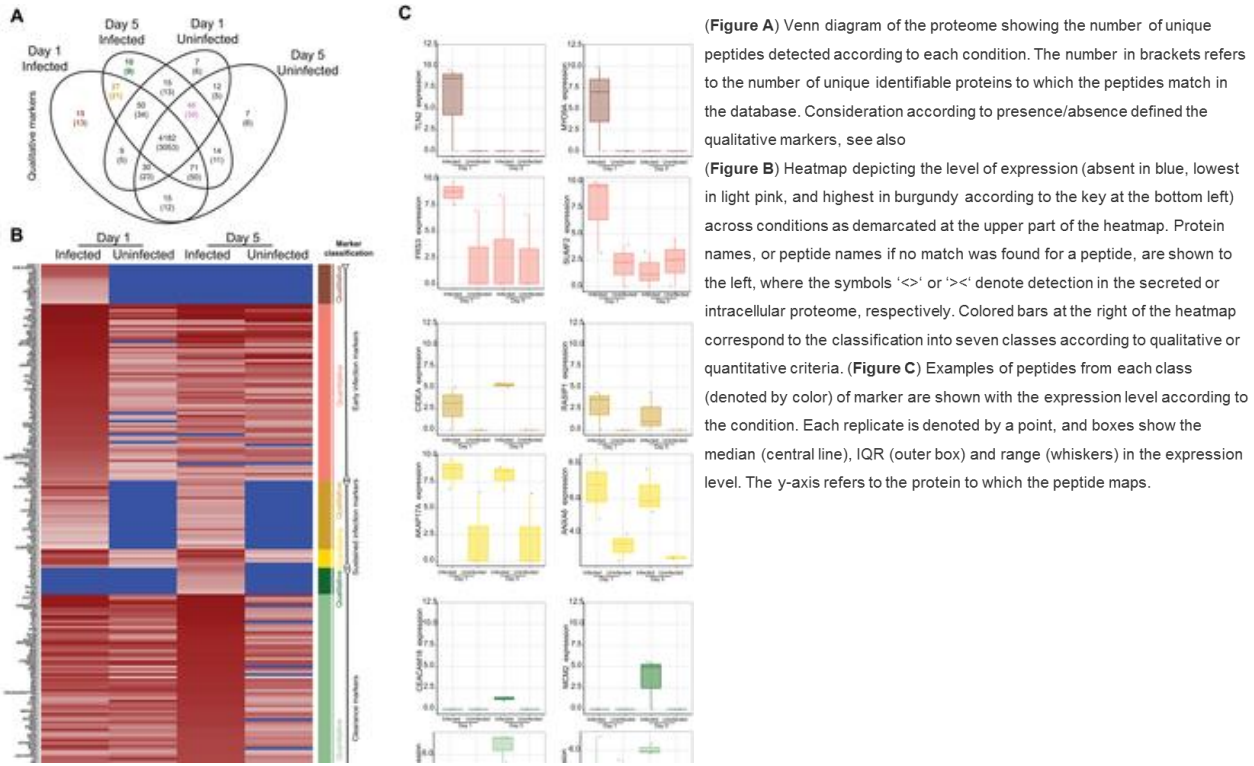


Behr MA et al., Science 284: 1520 (1999)

MTB Proteomik Araştırmalar

RESEARCH ARTICLE

Comparative Proteomics of Activated THP-1 Cells Infected with *Mycobacterium tuberculosis* Identifies Putative Clearance Biomarkers for Tuberculosis Treatment

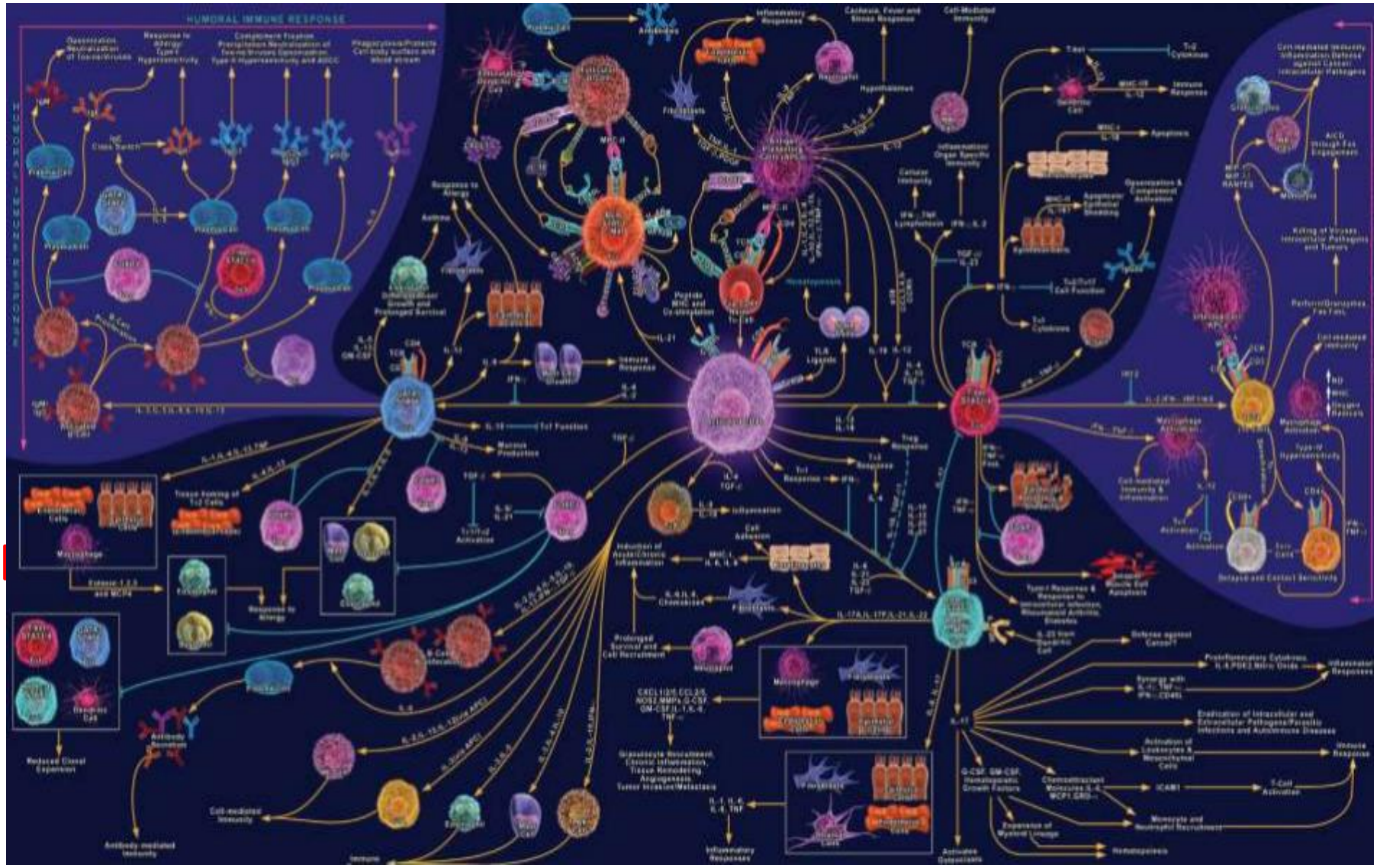


(**Figure A**) Venn diagram of the proteome showing the number of unique peptides detected according to each condition. The number in brackets refers to the number of unique identifiable proteins to which the peptides match in the database. Consideration according to presence/absence defined the qualitative markers, see also

(**Figure B**) Heatmap depicting the level of expression (absent in blue, lowest in light pink, and highest in burgundy according to the key at the bottom left) across conditions as demarcated at the upper part of the heatmap. Protein names, or peptide names if no match was found for a peptide, are shown to the left, where the symbols '<>' or '><' denote detection in the secreted or intracellular proteome, respectively. Colored bars at the right of the heatmap correspond to the classification into seven classes according to qualitative or quantitative criteria. (**Figure C**) Examples of peptides from each class (denoted by color) of marker are shown with the expression level according to the condition. Each replicate is denoted by a point, and boxes show the median (central line), IQR (outer box) and range (whiskers) in the expression level. The y-axis refers to the protein to which the peptide maps.

PLoS ONE 10(7): e0134168. doi:10.1371/journal.pone.0134168

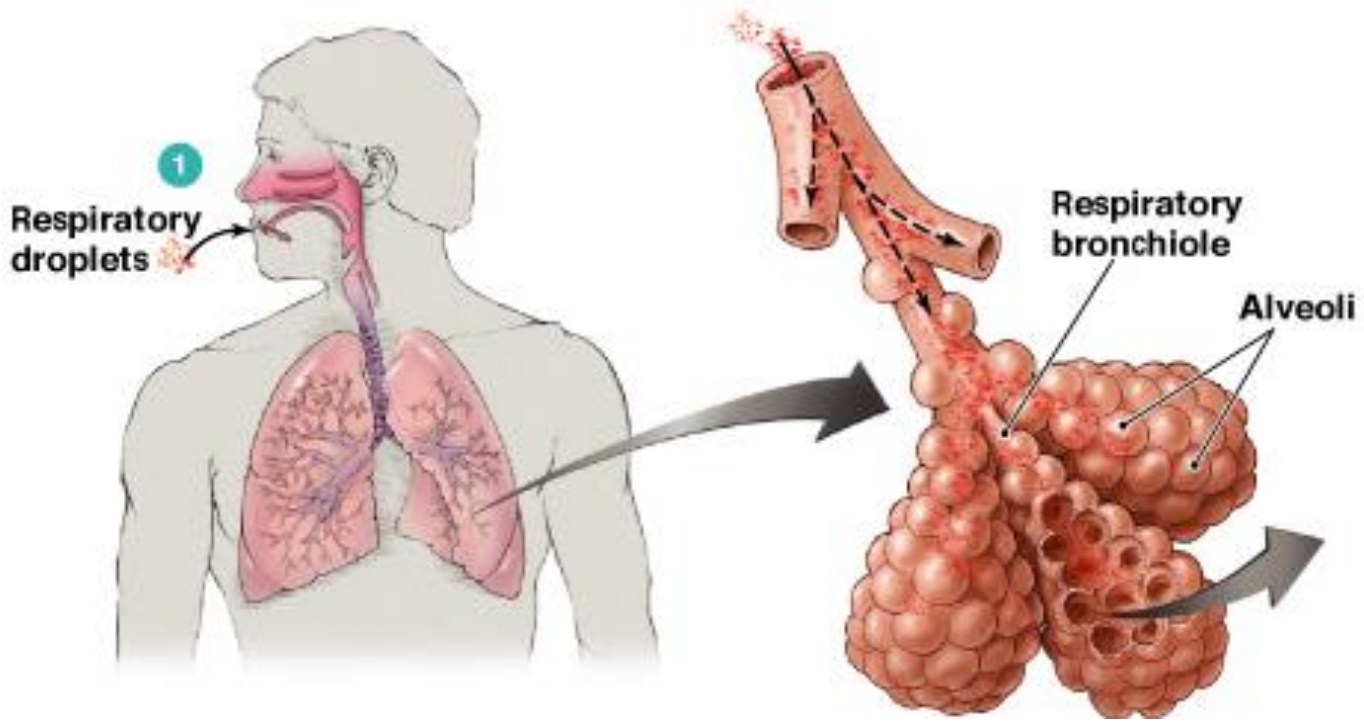
Çalışmaların Sonucu Neyi Gösterdi ?



Bay Verem Mikrobu - 1960

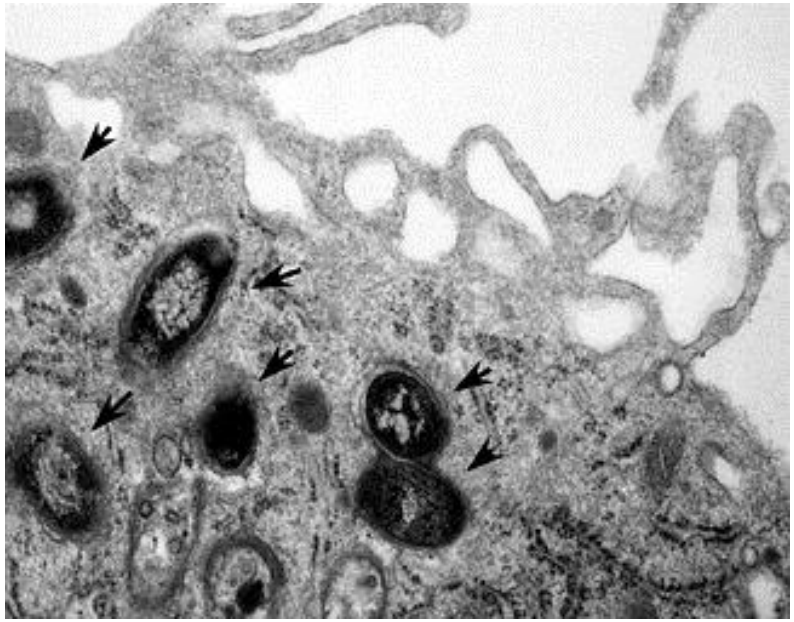
Alveollerde dört farklı olay gerçekleşebilir

- Damlacık çekirdeği ile alınan 1-3 bakterinin alveollere ulaşmasıyla tüberküloz infeksiyonu başlar.



Alveollerde dört farklı olay gerçekleşebilir

1- Basiller güçlü bir konakçı yanıtı ile herhangi bir lezyon oluşturmadan, alveoller makrofajlar tarafından yok edilebilir.

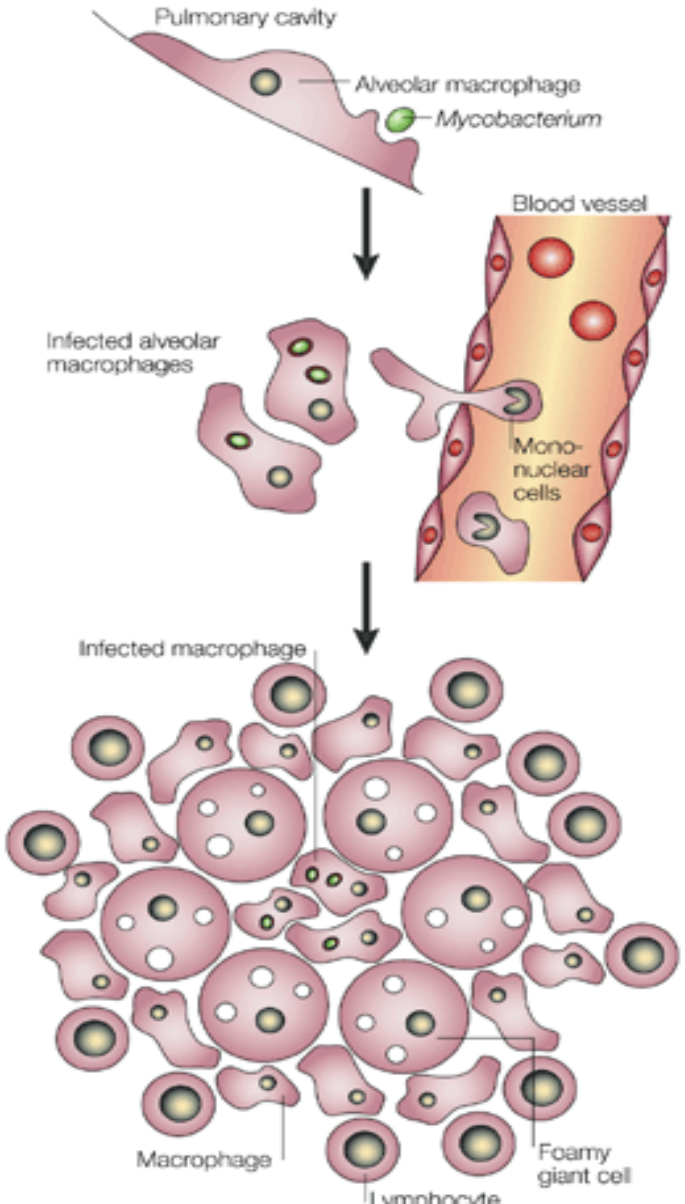


Dark ovals reveal tuberculosis bacteria encapsulated in vacuoles inside a macrophage cell.

Alveollerde dört farklı olay gerçekleşebilir

2- Basil başlangıçta çoğalabilir ancak immun yanıtla birkaç milimetre çapında küçük kazaöz lezyonlar oluşur ve koruyucu immünite gelişir.

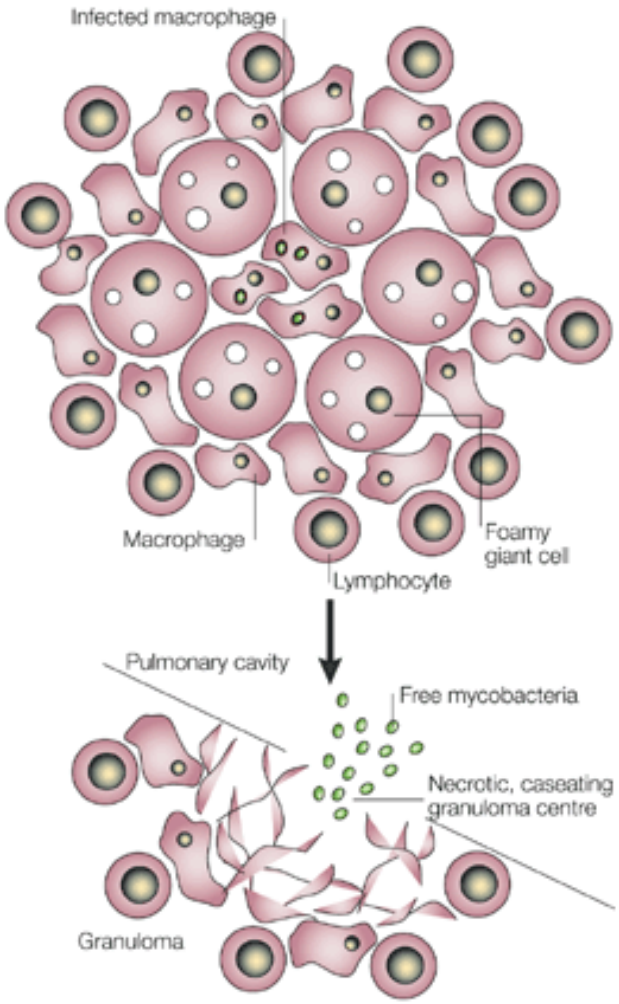
- Klinik rayolojik bulgu yok
- Tüberkülin deri testi pozitifleşerek primer infeksiyon oluşur
- Az sayıda basil dorman halde kalarak latent infeksiyon oluşturabilir.



Alveollerde dört farklı olay gerçekleşebilir

3- Basiller çoğalmaya devam eder, geniş kazeöz lezyonlar oluşur.

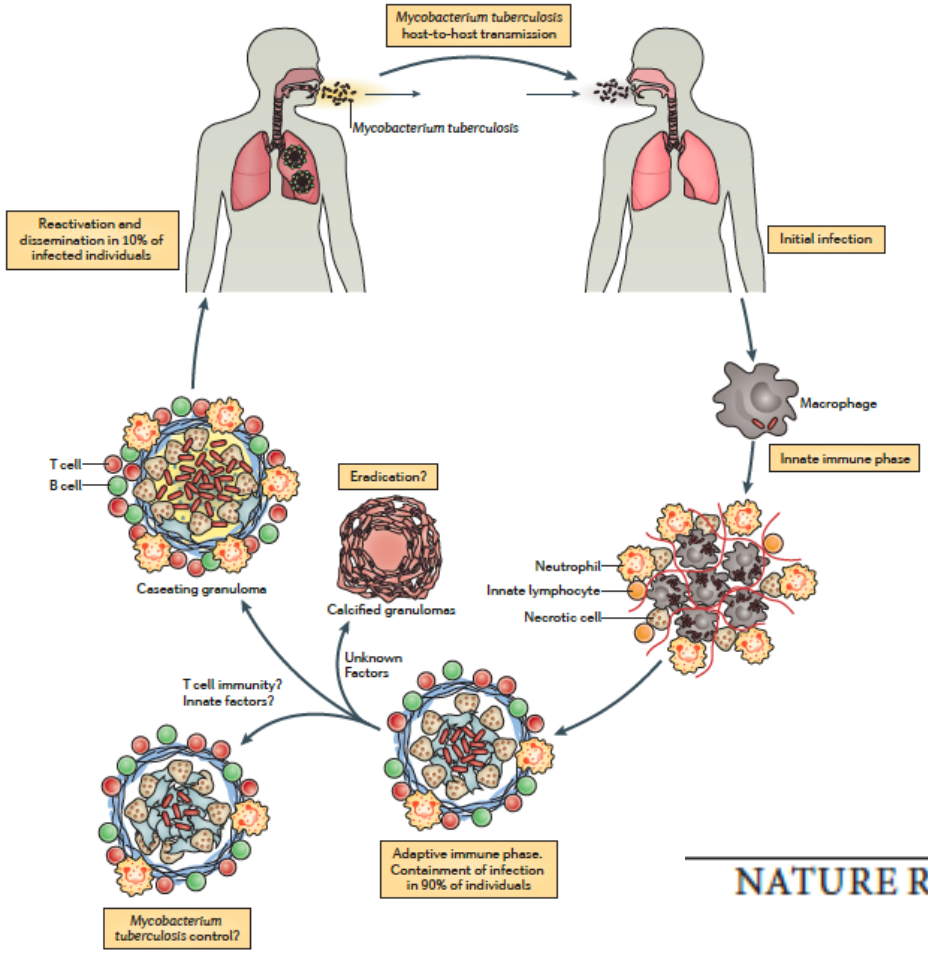
- Kan ve lenf damarları yoluyla basil özellikle akciğer , böbrek, beyin ve kemik dokusu başta olmak üzere tüm vücuda yayılabilir.
- Primer tüberküloz ya da erken hastalık olarak isimlendiren tablo ortaya çıkar



Nature Reviews | Molecular Cell Biology

Alveollerde dört farklı olay gerçekleşebilir

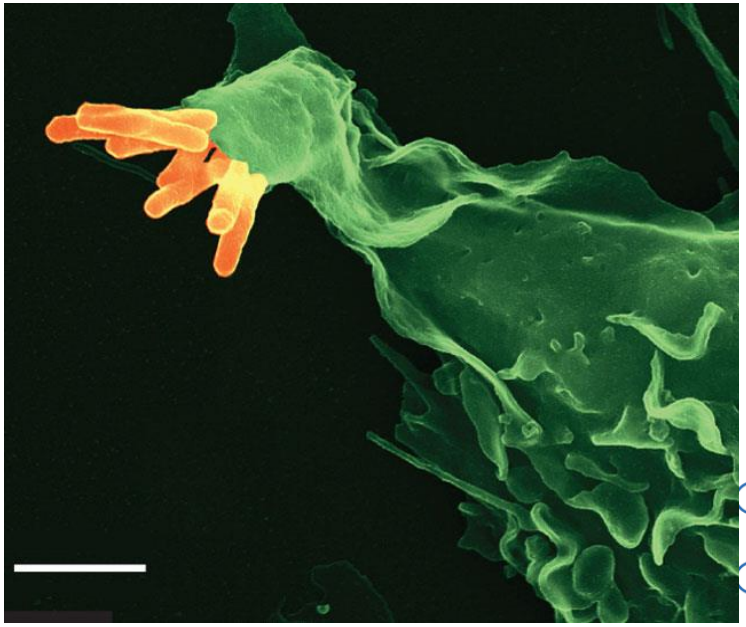
4- Primer infeksiyon sonrası dorman haldeki basillerin çoğalmaya başlaması ile geç reaktivasyon hastalığı (sekonder tüberküloz) gelişir.

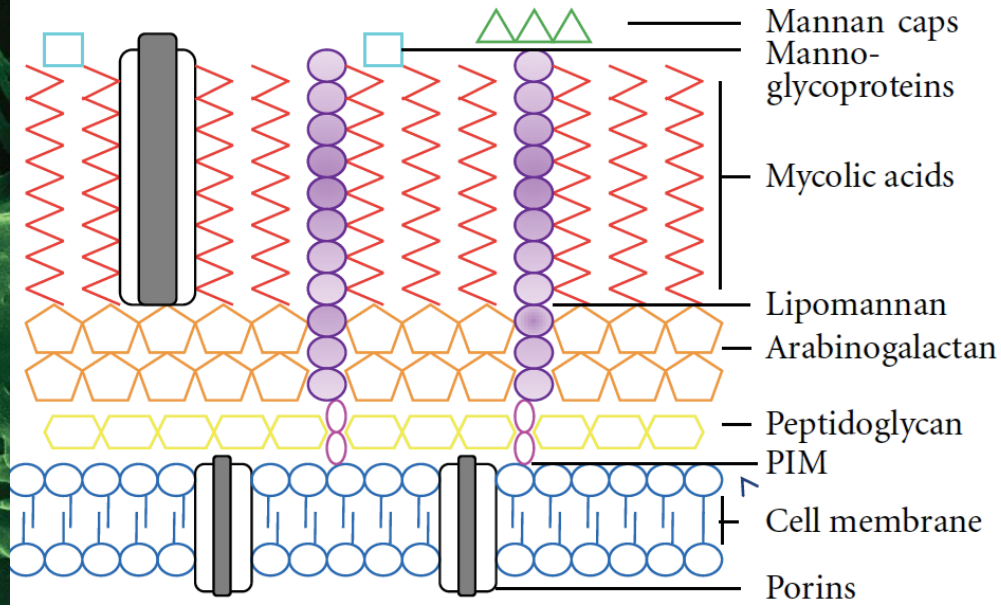


NATURE REVIEWS | MICROBIOLOGY

İlk Temas

- Alveolar makrofajlar; memeli hücrelerinde bulunmayan fakat mikrobiyal patojenlerde karakteristik olan yapıları tanır ve basil ile temas sağlanır.

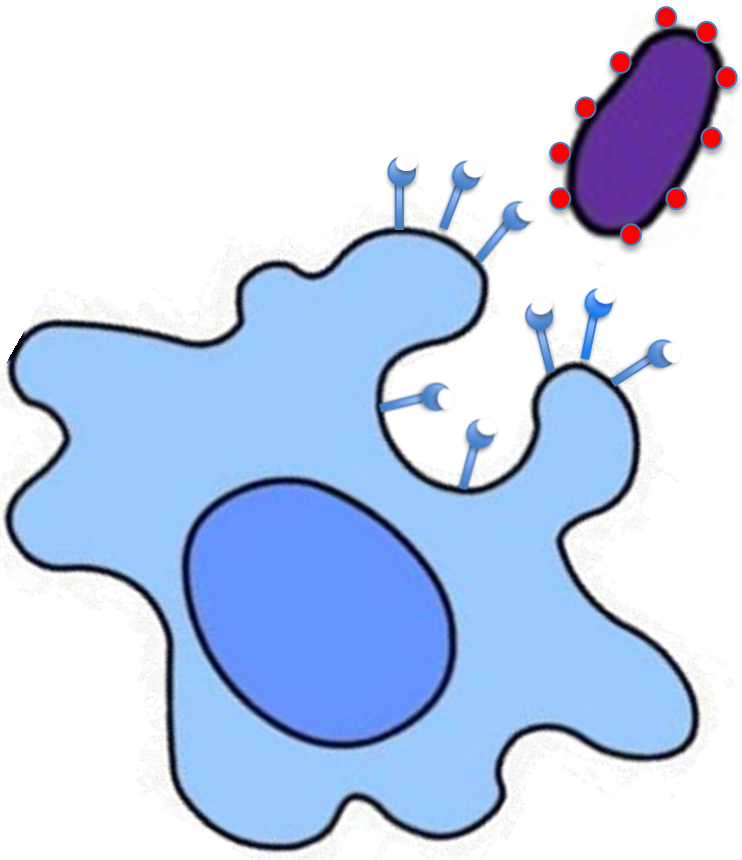




Nature 453, 295-296

İlk Temas ve Doğal Bağışıklık

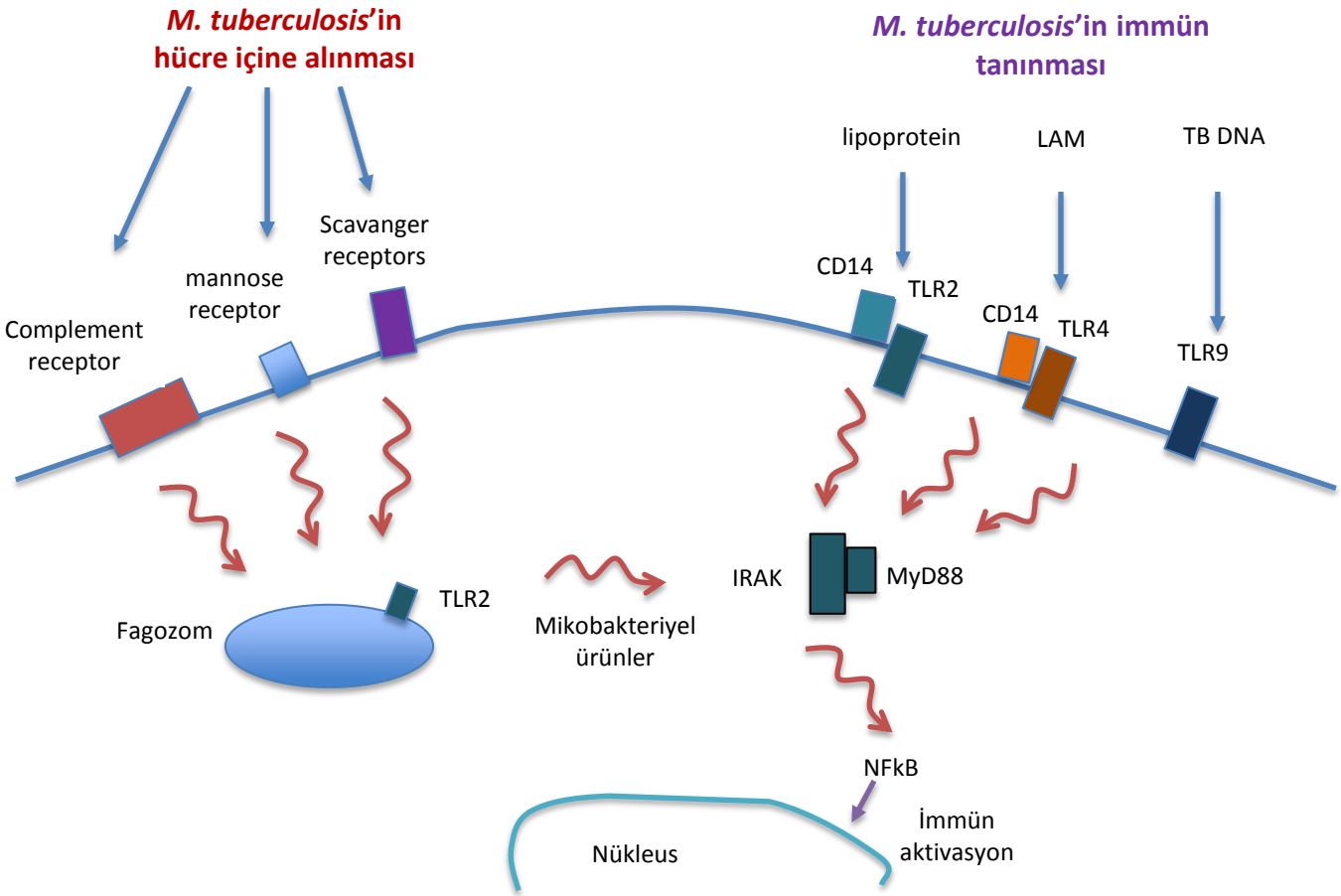
- Doğal bağışıklığın reseptörleri memeli hücrelerinde bulunmayan fakat mikrobiyal patojenlerde karakteristik olan yapıları tanır.



- Pathogen Associated Molecular Patterns-(PAMP)
  - Mikolik asit, Arabinomannan, Mannan, Mannoprotein
  - Lipomannan (LM) -Arabinogalaktan
  - Fosfalidil-myo-innositol mannozid (PIM)
  - Lipoarabinomannan (LAM) - ManLAM
- Pathogen Recognition Receptors-(PRR)
  - Toll-benzeri reseptörler (TLRs)
  - Nükleotid bağlayan oligomerizasyon boğumu (NOD) Benzeri reseptörler (NLRs)
  - Scavanger Reseptörler (SR)
  - Mannoz reseptörleri
  - Dendritic cell-specific intercellular adhesion molecule grabbing nonintegrin-(DC-SIGN) ve
  - Dectin-1 reseptörleri

İlk Temas ve Doğal Bağışıklık

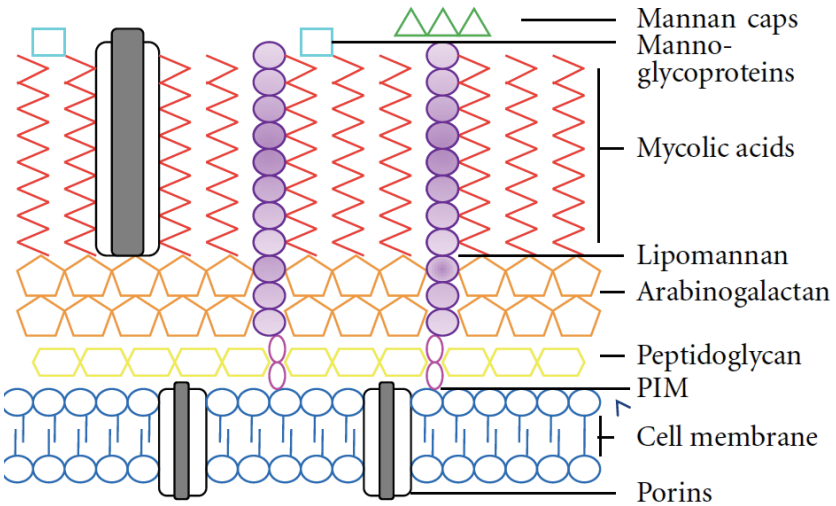
- Pathogen Recognition Receptors-(PRR)



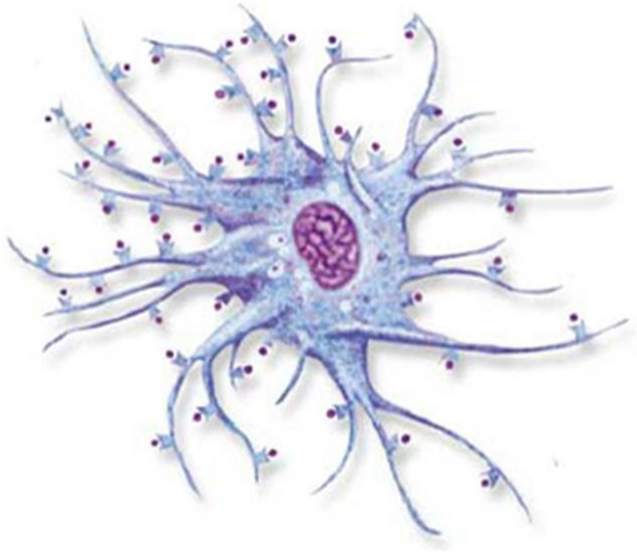
İlk Temas ve Doğal Bağışıklık

- *M. tuberculosis* e ait hangi moleküler patern, hangi reseptör tarafından tanınır.

Hangi PAMP ?



Hangi PRR ?

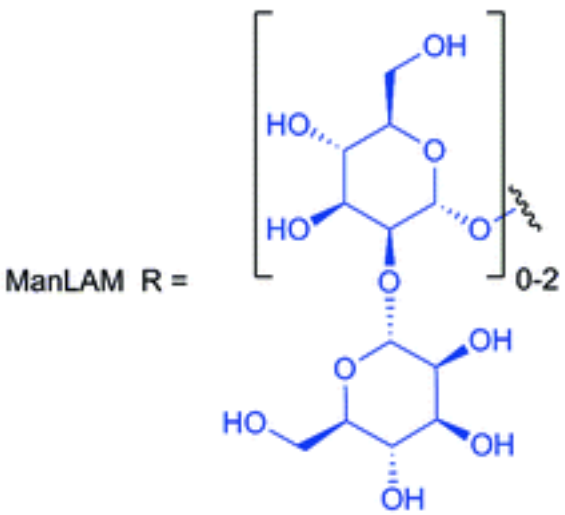


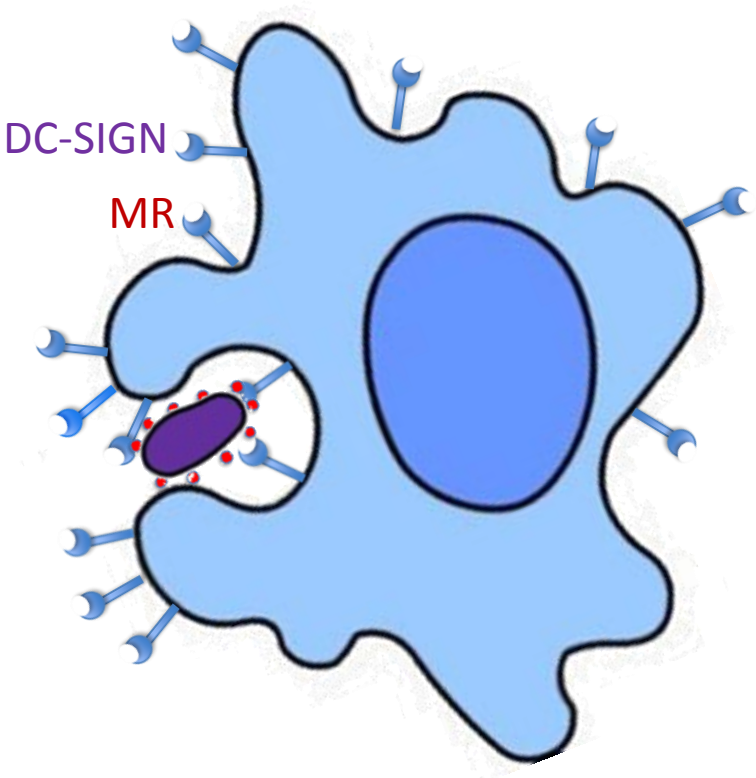
İlk Temas ve Doğal Bağışıklık

- ManLAM: Mannose-capped lipoarabinomannan

çok sayıda araştırma konusudur ve potansiyel virülans faktörüdür.

sadece patojen
mikobakterilerde var





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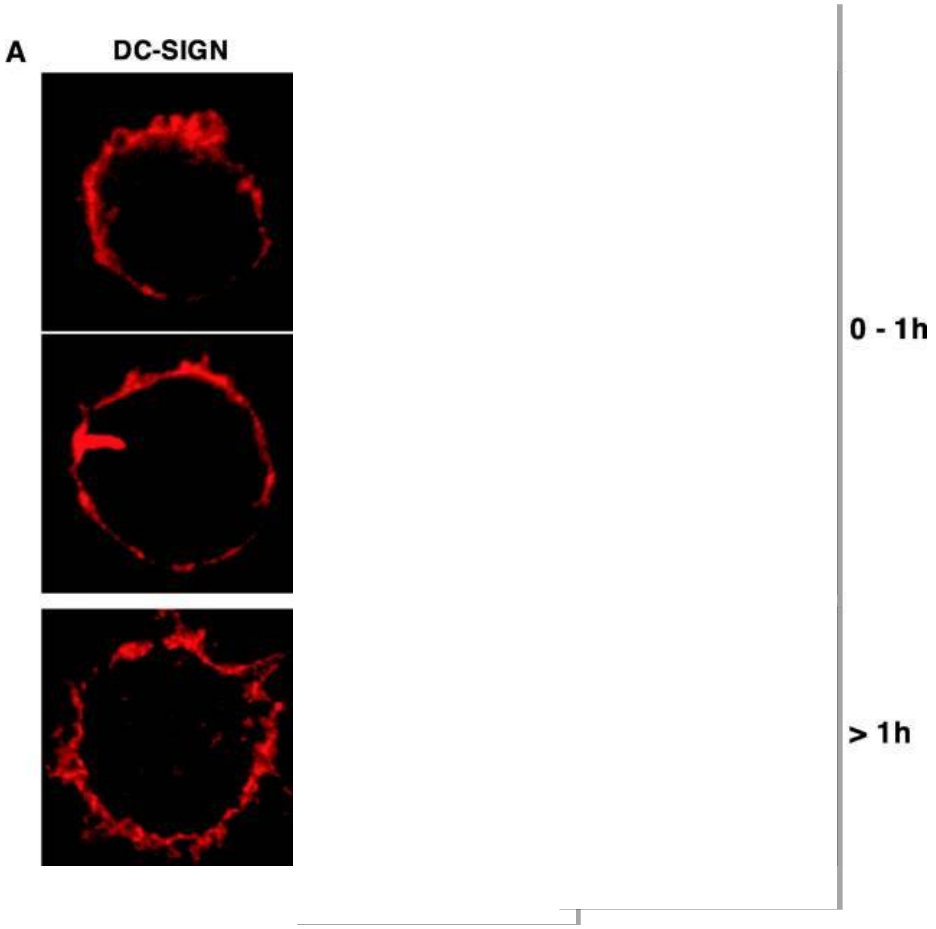


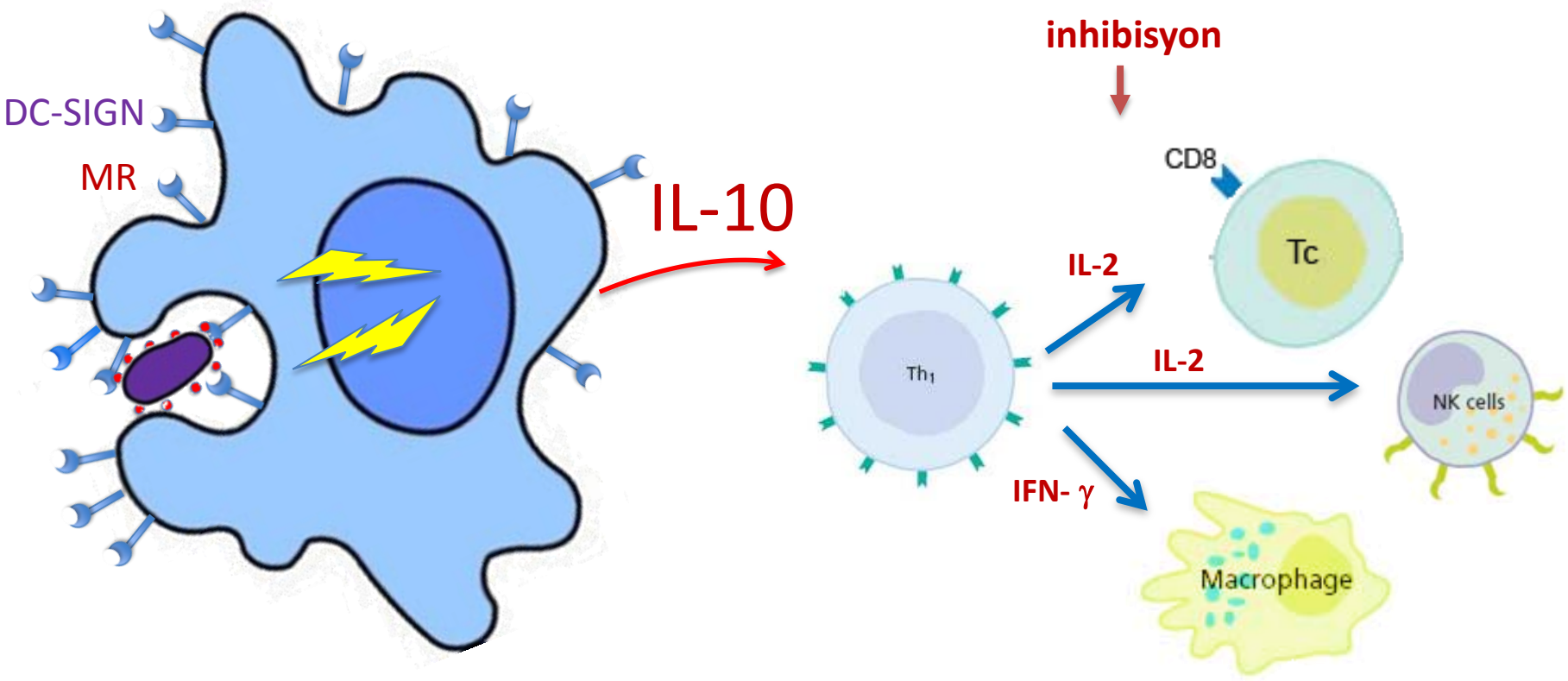
DC-SIGN is transiently present onto the *M. tuberculosis* phagosome. Cells were pulsed at 4°C for 3 h with GFP-*M. tuberculosis*, washed extensively in RPMI-1640, and chased at 37°C for the indicated periods of time. (A) The two top panels shows cells representative of early phagocytosis events; DC-SIGN was detected both at the cell surface and in intracellular vesicles, but due to the strong surface staining, the red signal had to be reduced. Each panel shows a representative cell.

J Exp Med. 2003 Jan 6; 197(1): 121–127.

İlk Temas ve Doğal Bağışıklık

- ManLAM: Mannose-capped lipoarabinomannan

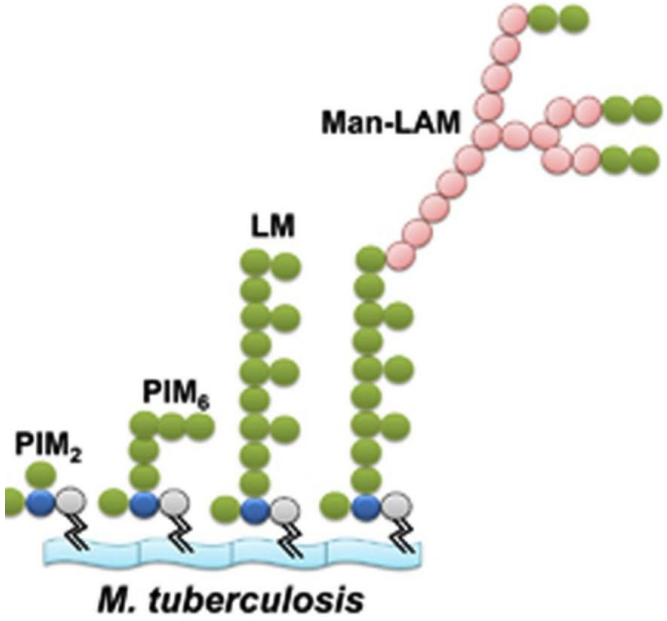
  DC-SIGN ve MR reseptörleri ile tanınma immün süpresyonla da sonuçlanır.



İlk Temas ve Doğal Bağışıklık

- ManLAM: Mannose-capped lipoarabinomannan

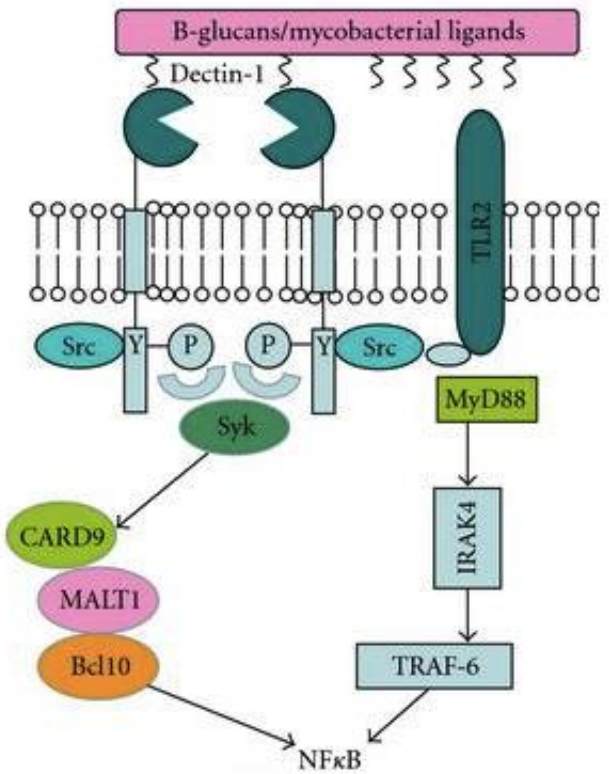
  taşımayan BCG ve *M. marinum* enfeksiyon yeteneğinden bir şey kaybetmiyor.



İlk Temas ve Doğal Bağışıklık

- Glikolipidyapılar:

  Dectin-1 reseptörü ile tanıyarak proinflamatuar sinyallerin oluşumunu başlatır

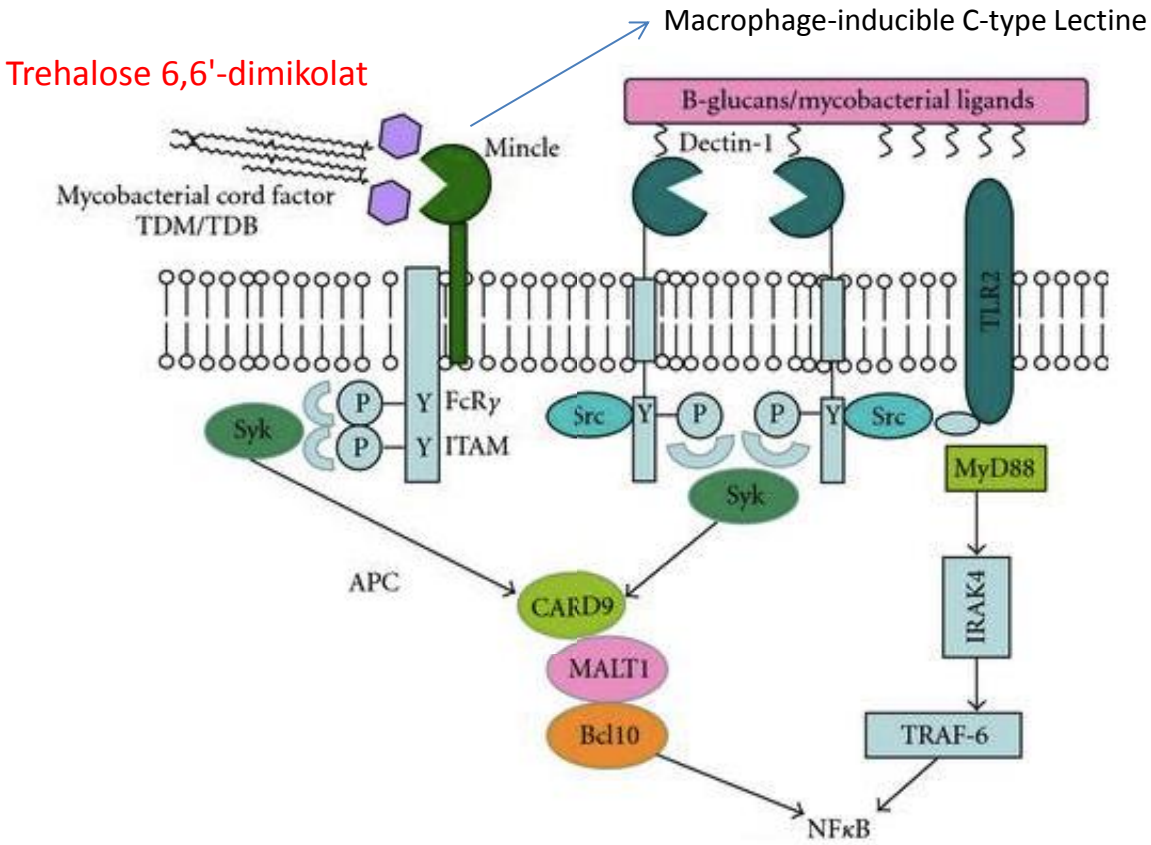


TNF-a, IL-6, IL-1b, IL-12, IL-23 ve IL-17A

İlk Temas ve Doğal Bağışıklık

- Kord Faktör (Trehalose dimycolate)

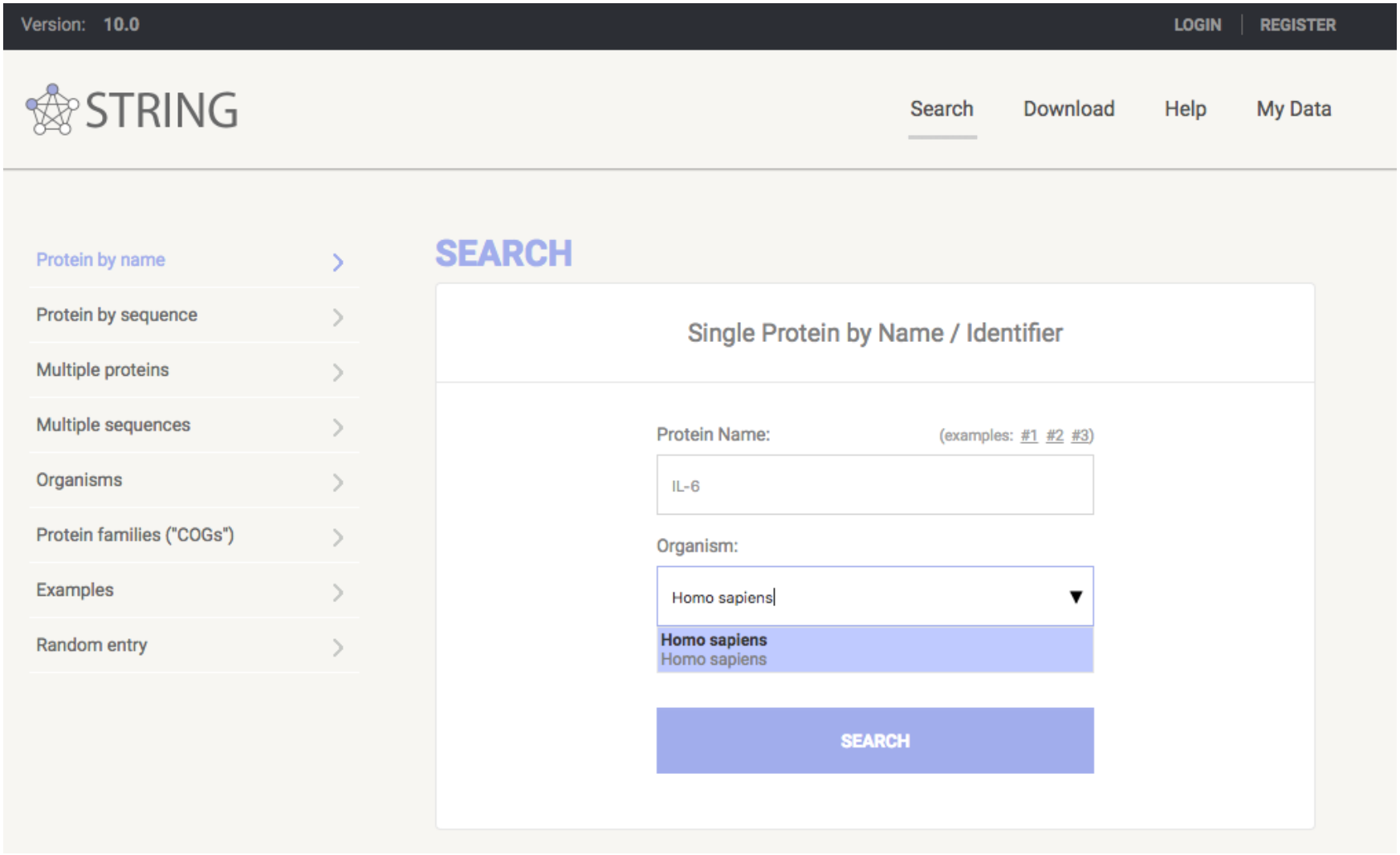
  Mincle (macrophage-inducible C-type lectin) reseptörleri ile tanınır.



TNF-a, IL-6, IL-1b, IL-12, IL-23 ve IL-17A

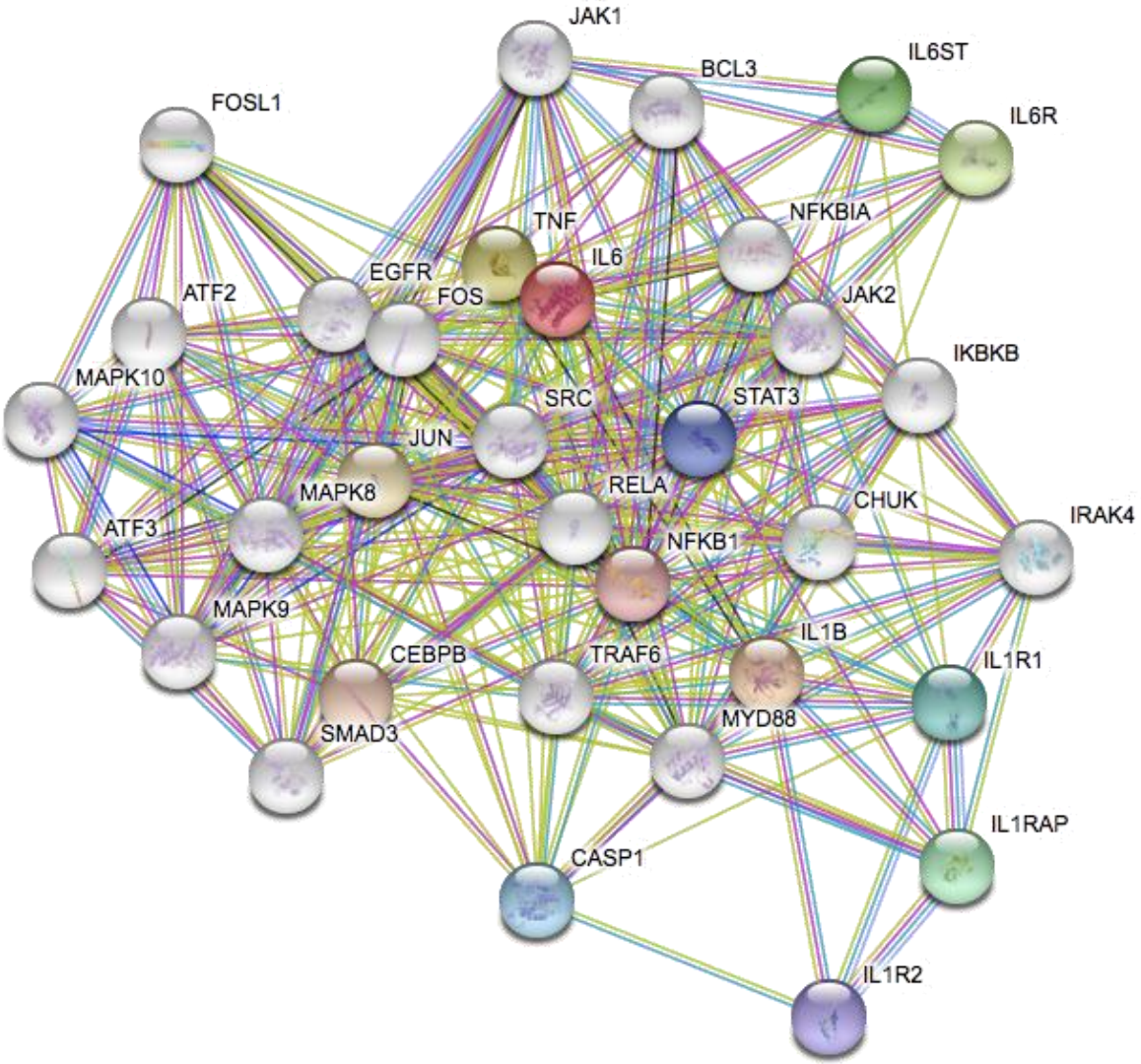
İlk Temas ve Doğal Bağışıklık

Sistem biyoloji veri tabanı; TNF-α, IL-6, IL-1b, IL-12, IL-23 ve IL-17A



İlk Temas ve Doğal Bağışıklık

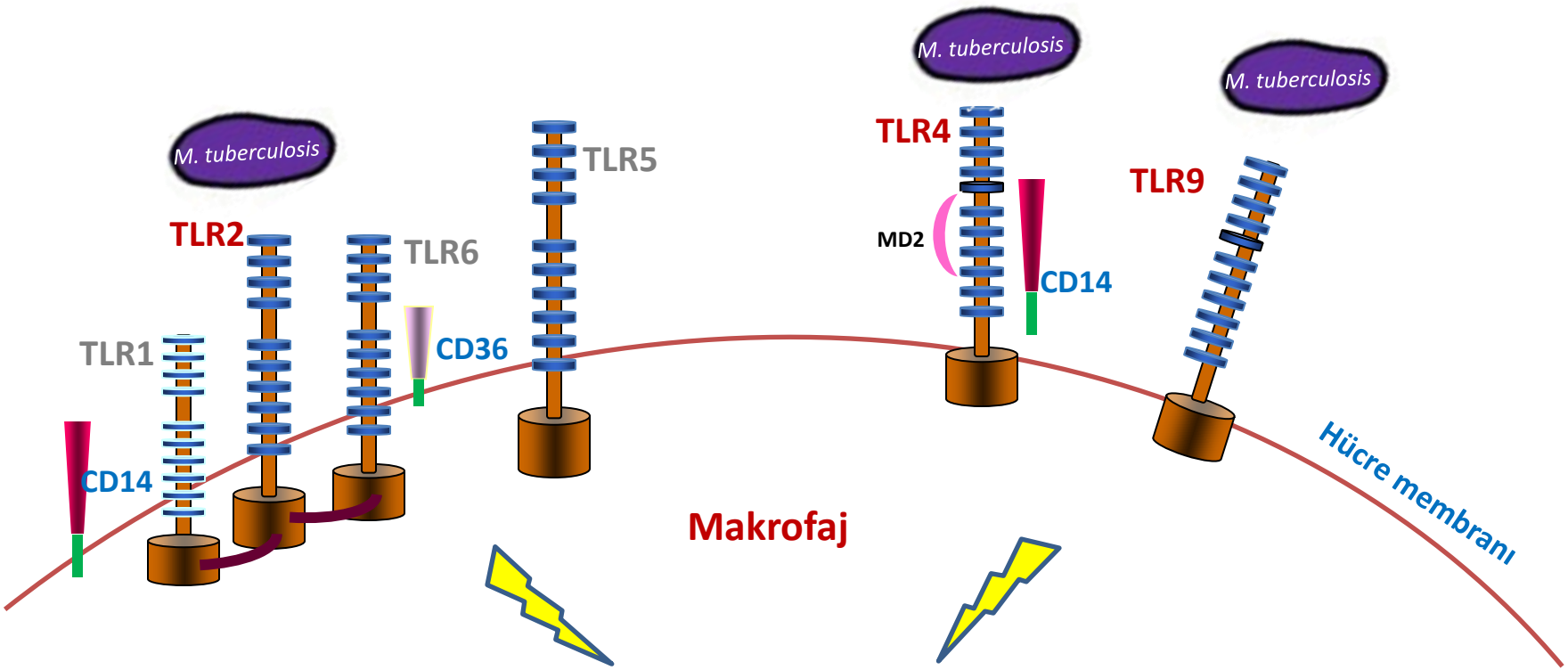
- Sistem biyoloji veri tabanı; TNF-α, IL-6, IL-1b, IL-12, IL-23 ve IL-17A



İlk Temas ve Doğal Bağışıklık

- *M.tuberculosis* TLR'ler ile ilişkisi;

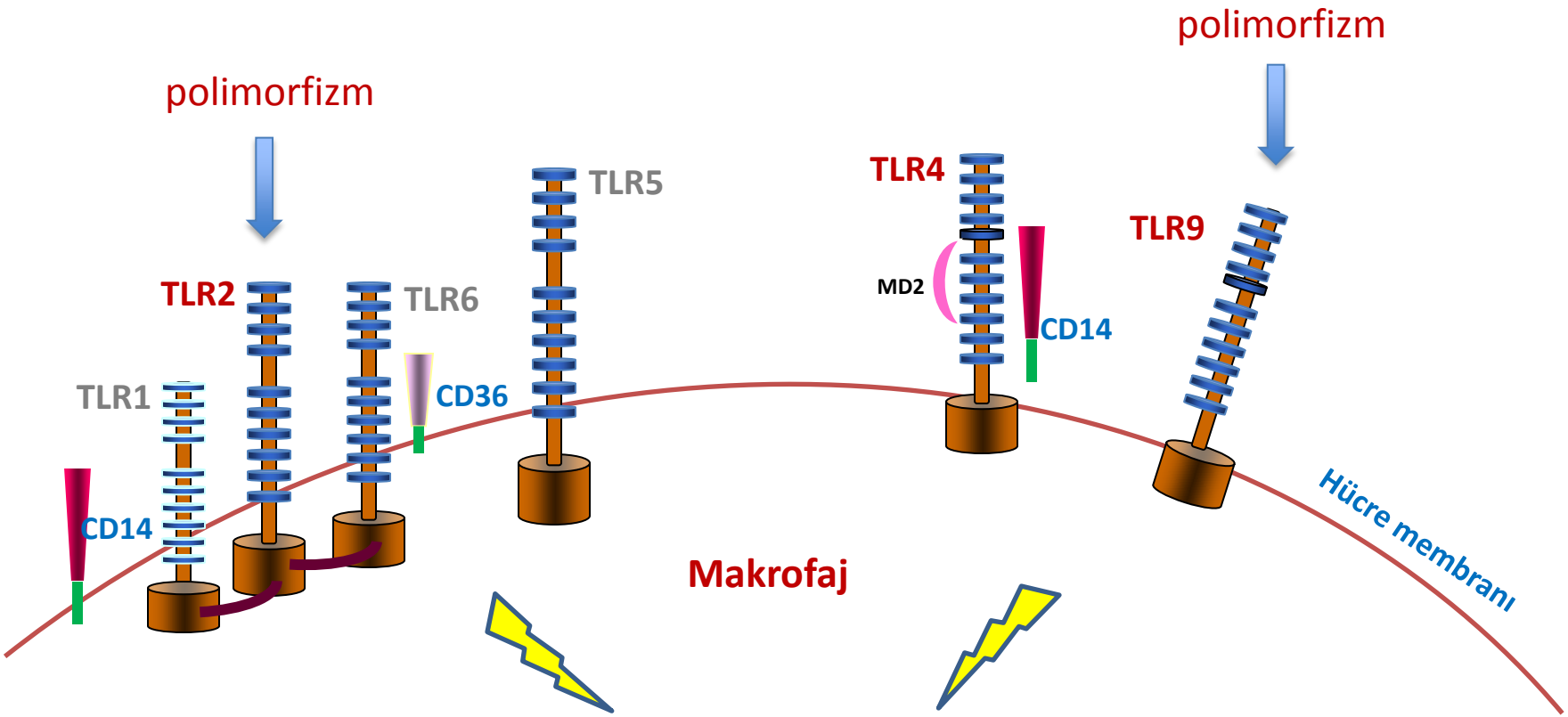
  konak için yararlı olan proinflamatuar yanıtı başlatan hücre içi sinyal yolaklarını harekete geçirir.



İlk Temas ve Doğal Bağışıklık

- TLR'lerdeki gen polimorfizmleri;

  mikobakteriyel lipopeptidlere karşı doğal immün yanıtı düzenler; bu da patojene karşı klinik duyarlılığın nedenlerinden bir tanesidir.



İlk Temas ve Doğal Bağışıklık

- Ülkemizden yapılan çalışmada TLR2 Arg753Gln tek nokta mutasyonun hastalık gelişme ihtimalini altı kata kadar arttırdığı belirtiliyor.

The Arg753Gln polymorphism of the human Toll-like receptor 2 gene in tuberculosis disease

A.C. Ogus*, B. Yoldas#, T. Ozdemir*, A. Uguz#, S. Olcen¶, I. Keser+, M. Coskun#, A. Cilli*, O. Yegin#

The Arg753Gln polymorphism of the human Toll-like receptor 2 gene in tuberculosis disease. A.C. Ogus, B. Yoldas, T. Ozdemir, A. Uguz, S. Olcen, I. Keser, M. Coskun, A. Cilli, O. Yegin. ©ERS Journals Ltd 2004.

ABSTRACT: Toll-like receptor 2 (TLR2), a member of the Toll-like receptor family, plays an important role in recognition of, and subsequent immune response activation against, mycobacteria. The genetic polymorphism of TLR2 (arginine to glutamine substitution at residue 753 (Arg753Gln)) has been associated with a negative influence on TLR2 function, which may, in turn, determine the innate host response to mycobacteria. The aim of the present study was to investigate the Arg753Gln single nucleotide polymorphism of the TLR2 gene in tuberculosis (TB) patients compared to healthy controls.

A retrospective case/control study was carried out. The Arg753Gln polymorphism of the TLR2 gene was studied in 151 TB patients compared to 116 ethnically and age-matched healthy control subjects.

The TLR2 polymorphism (adenine (A) allele) was observed in 17.9 and 7.7% of TB patients and controls, respectively. When the ratios of the three genotypes were compared between the two groups, the AA genotype was found to be more significantly associated with TB. Allele frequencies for guanine (G) and A were found to be 0.95 and 0.05 in the control group and 0.86 and 0.14 in the TB patient group, respectively. The risk of developing TB disease was increased 6.04- and 1.60-fold for carriers of the AA and GA genotypes, respectively.

In conclusion, the present data suggest that the arginine to glutamine substitution at residue 753 polymorphism of the Toll-like receptor 2 gene influences the risk of developing tuberculosis.

Eur Respir J 2004; 23: 219–223.

Depts of *Chest Medicine, #Paediatric Immunology, and +Medical Biology and Genetics, Akdeniz University Medical Faculty, and ¶State Tuberculosis Control Centre, Antalya, Turkey.

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polymorphism
Toll-like receptor
tuberculosis

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This study was supported by Akdeniz University Research Foundation, Akdeniz University, Antalya, Turkey (2002.01.0103.008).

İlk Temas ve Doğal Bağışıklık

- Diğer bir çalışmada ise;

  TLR2 T597C alellinin Beijing izolatlarında sık görüldüğü ve bunun da akciğer dışı tüberküloz riskini arttırdığı tespit edilmiş.

OPEN ACCESS Freely available online PLoS PATHOGENS

The Influence of Host and Bacterial Genotype on the Development of Disseminated Disease with *Mycobacterium tuberculosis*

Maxine Caws[1,2*], Guy Thwaites[3], Sarah Dunstan[1,2], Thomas R. Hawn[4], Nguyen Thi Ngoc Lan[5], Nguyen Thuy Thuong Thuong[1,6], Kasia Stepniewska[2], Mai Nguyet Thu Huyen[5], Nguyen Duc Bang[5], Tran Huu Loc[7], Sebastien Gagneux[5], Dick van Soolingen[8], Kristin Kremer[8], Marianne van der Sande[8], Peter Small[5,9], Phan Thi Hoang Anh[7], Nguyen Tran Chinh[6], Hoang Thi Quy[7], Nguyen Thi Hong Duyen[1], Dau Quang Tho[1], Nguyen T. Hieu[10], Estee Torok[1,2], Tran Tinh Hien[6], Nguyen Huy Dung[7], Nguyen Thi Quynh Nhu[1], Phan Minh Duy[1], Nguyen van Vinh Chau[6], Jeremy Farrar[1,2]

1 Oxford University Clinical Research Unit, Hospital for Tropical Diseases, District 5, Ho Chi Minh City, Vietnam, 2 Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Old Road, Headington, Oxford, United Kingdom, 3 Centre for Molecular Microbiology and Infection, Imperial College, London, United Kingdom, 4 University of Washington School of Medicine, Seattle, Washington, United States of America, 5 Institute for Systems Biology, Seattle, Washington, United States of America, 6 The Hospital for Tropical Diseases, District 5, Ho Chi Minh City, Vietnam, 7 Pham Ngoc Thach Hospital for Tuberculosis and Lung Diseases, District 5, Ho Chi Minh City, Vietnam, 8 Tuberculosis Reference Laboratory, National Institute for Public Health, Bilthoeven, The Netherlands, 9 Bill and Melinda Gates Foundation, Seattle, Washington, United States of America, 10 Hung Vuong Obstetric Hospital, Hung Vuong Street, Ho Chi Minh City, Vietnam

Abstract

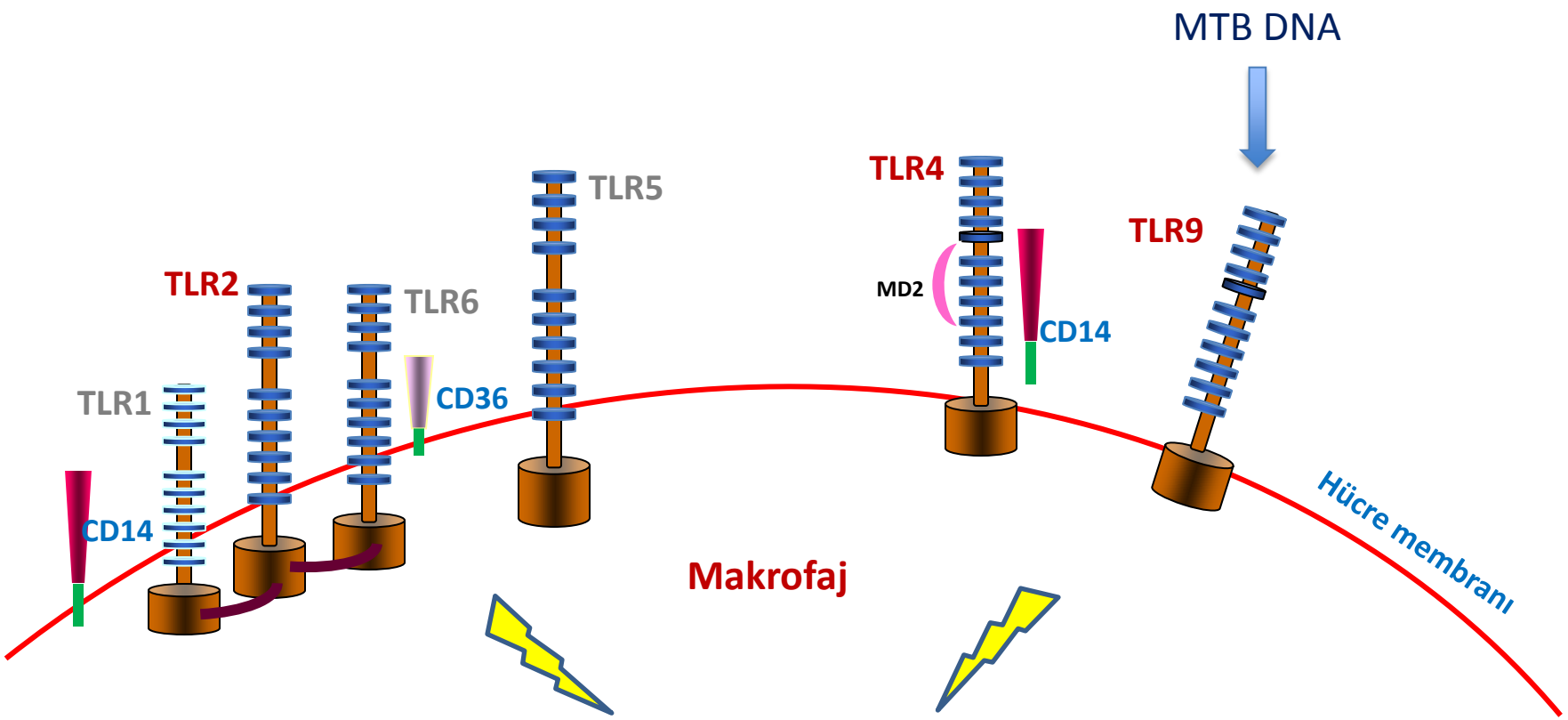
The factors that govern the development of tuberculosis disease are incompletely understood. We hypothesized that some strains of *Mycobacterium tuberculosis* (*M. tuberculosis*) are more capable of causing disseminated disease than others and may be associated with polymorphisms in host genes responsible for the innate immune response to infection. We compared the host and bacterial genotype in 187 Vietnamese adults with tuberculous meningitis (TBM) and 237 Vietnamese adults with uncomplicated pulmonary tuberculosis. The host genotype of tuberculosis cases was also compared with the genotype of 392 cord blood controls from the same population. Isolates of *M. tuberculosis* were genotyped by large sequence polymorphisms. The hosts were defined by polymorphisms in genes encoding Toll-interleukin 1 receptor domain containing adaptor protein (*TIRAP*) and Toll-like receptor-2 (*TLR*-2). We found a significant protective association between the Euro-American lineage of *M. tuberculosis* and pulmonary rather than meningeal tuberculosis (Odds ratio (OR) for causing TBM 0.395, 95% confidence intervals (C.I.) 0.193–0.806, P = 0.009), suggesting these strains are less capable of extra-pulmonary dissemination than others in the study population. We also found that individuals with the C allele of *TLR*-2 T597C allele were more likely to have tuberculosis caused by the East-Asian/Beijing genotype (OR = 1.57 [95% C.I. 1.15–2.15]) than other individuals. The study provides evidence that *M. tuberculosis* genotype influences clinical disease phenotype and demonstrates, for the first time, a significant interaction between host and bacterial genotypes and the development of tuberculosis.

İlk Temas ve Doğal Bağışıklık

- *M. tuberculosis'*in genomu da TLR9 ile bağlanmaya uygundur.

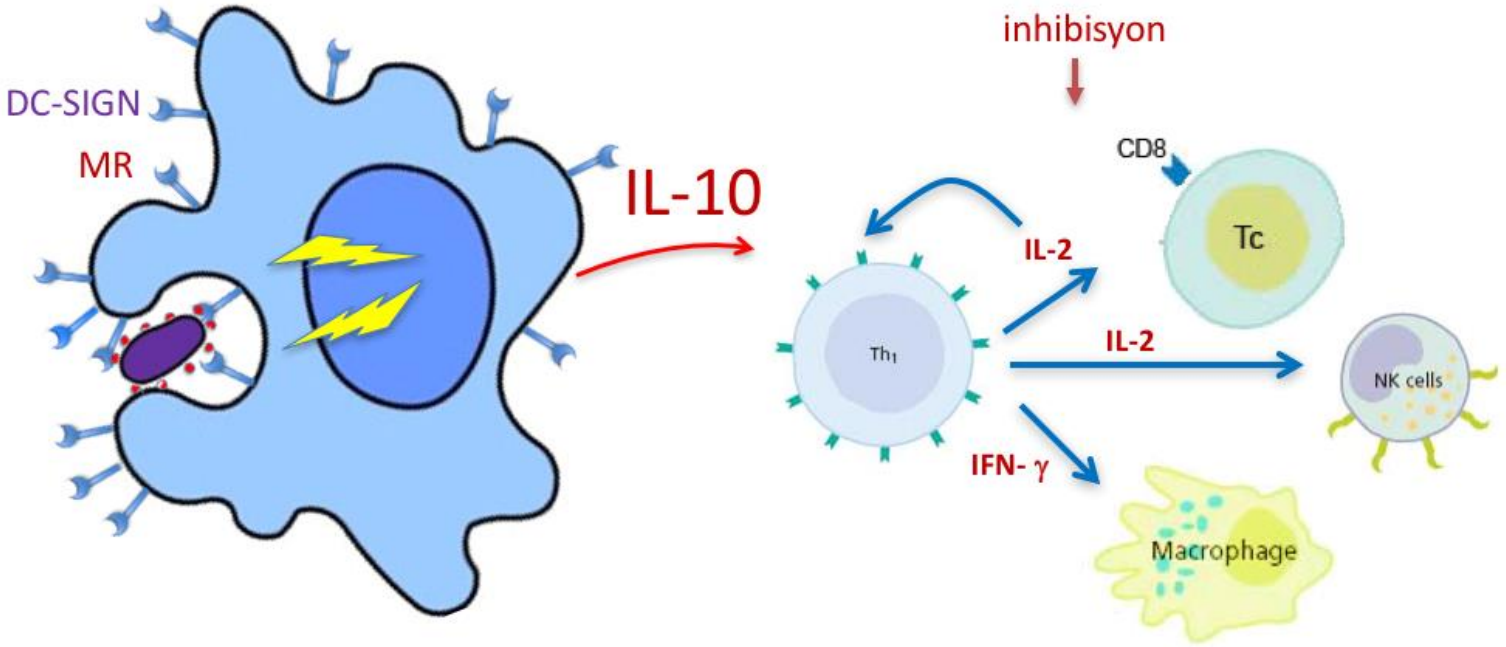
  Bu uyarım; granülom oluşumunu düzene sokmakta

  T lenfosit-1 (Th1) ve T lenfosit-2 (Th2) sitokin düzeylerini düzenlemektedir.



İlk Temas ve Doğal Bağışıklık

- Mikobakteriyel moleküler paternlerin tanındığı reseptöre göre immün sistem aktvasyonu değişir.



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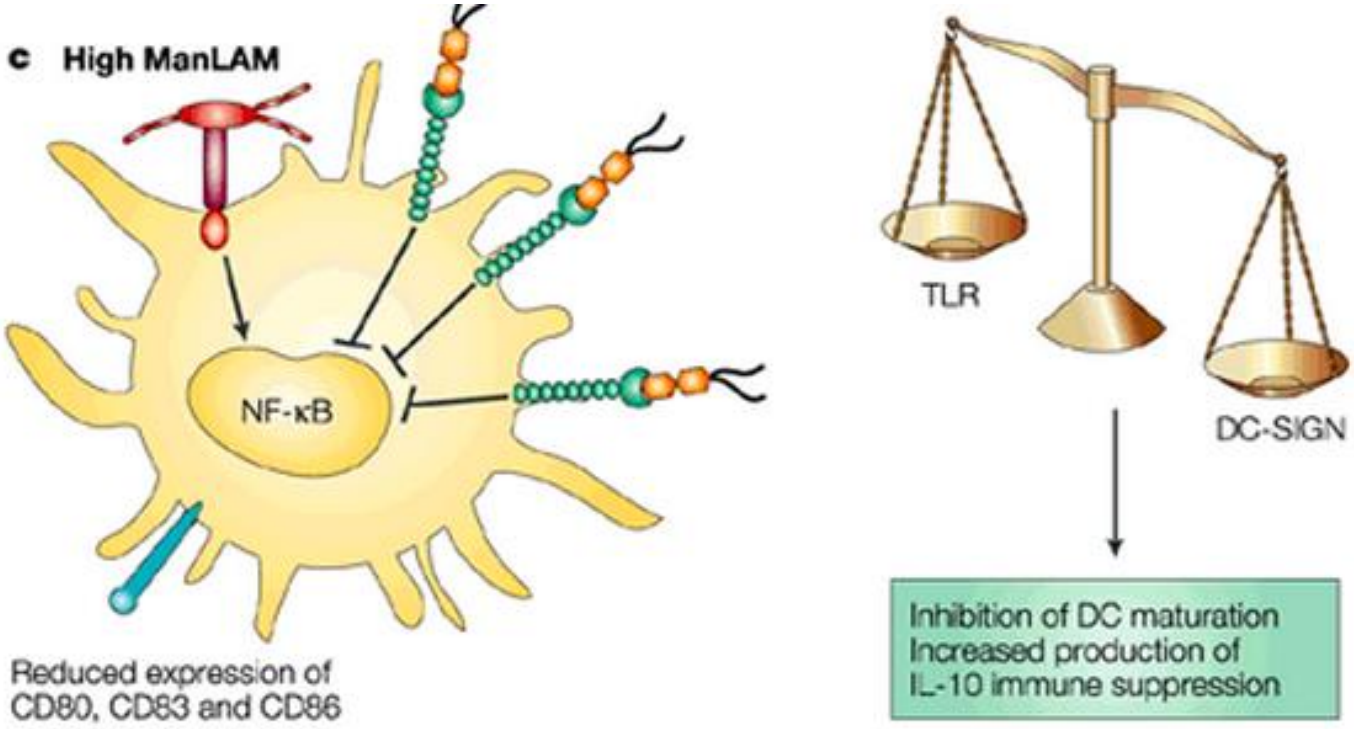


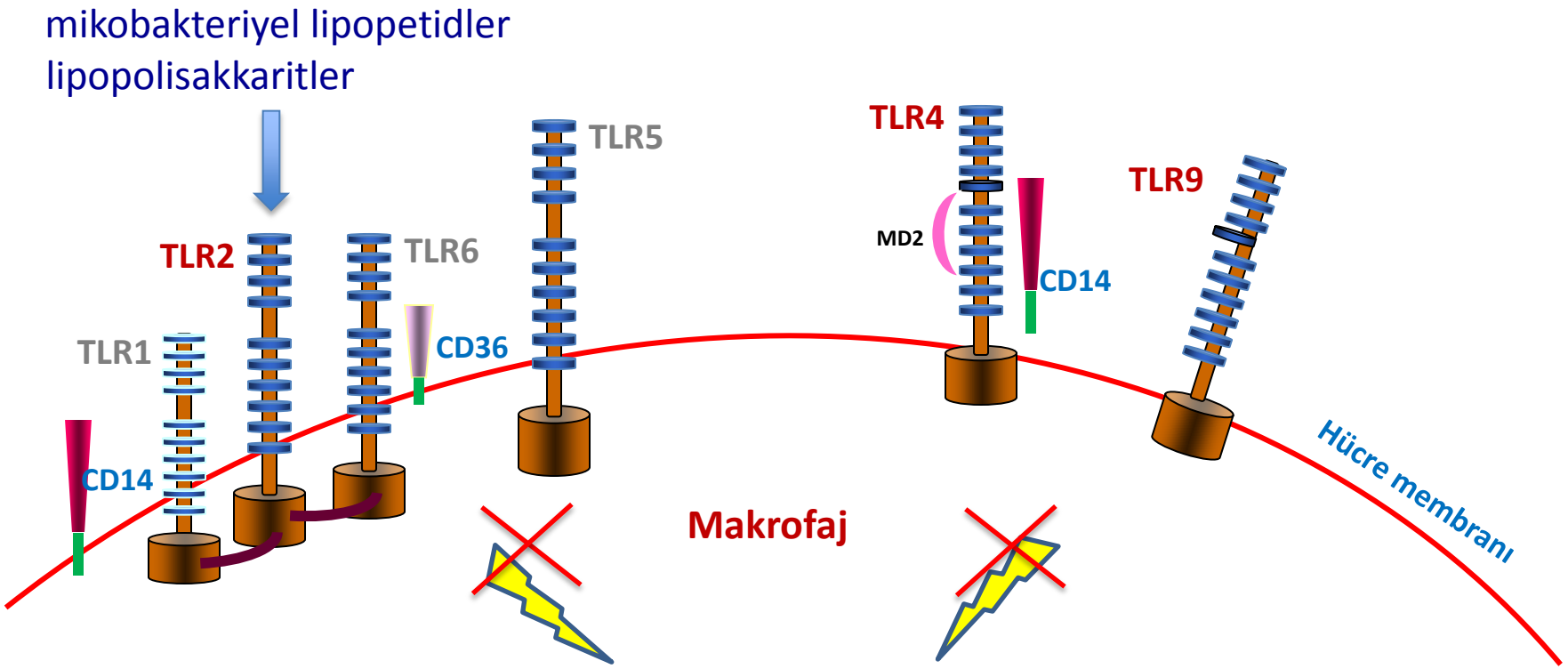
Nature Reviews Immunology **3**, 697-709

Nature Reviews | Immunology

İlk Temas ve Doğal Bağışıklık

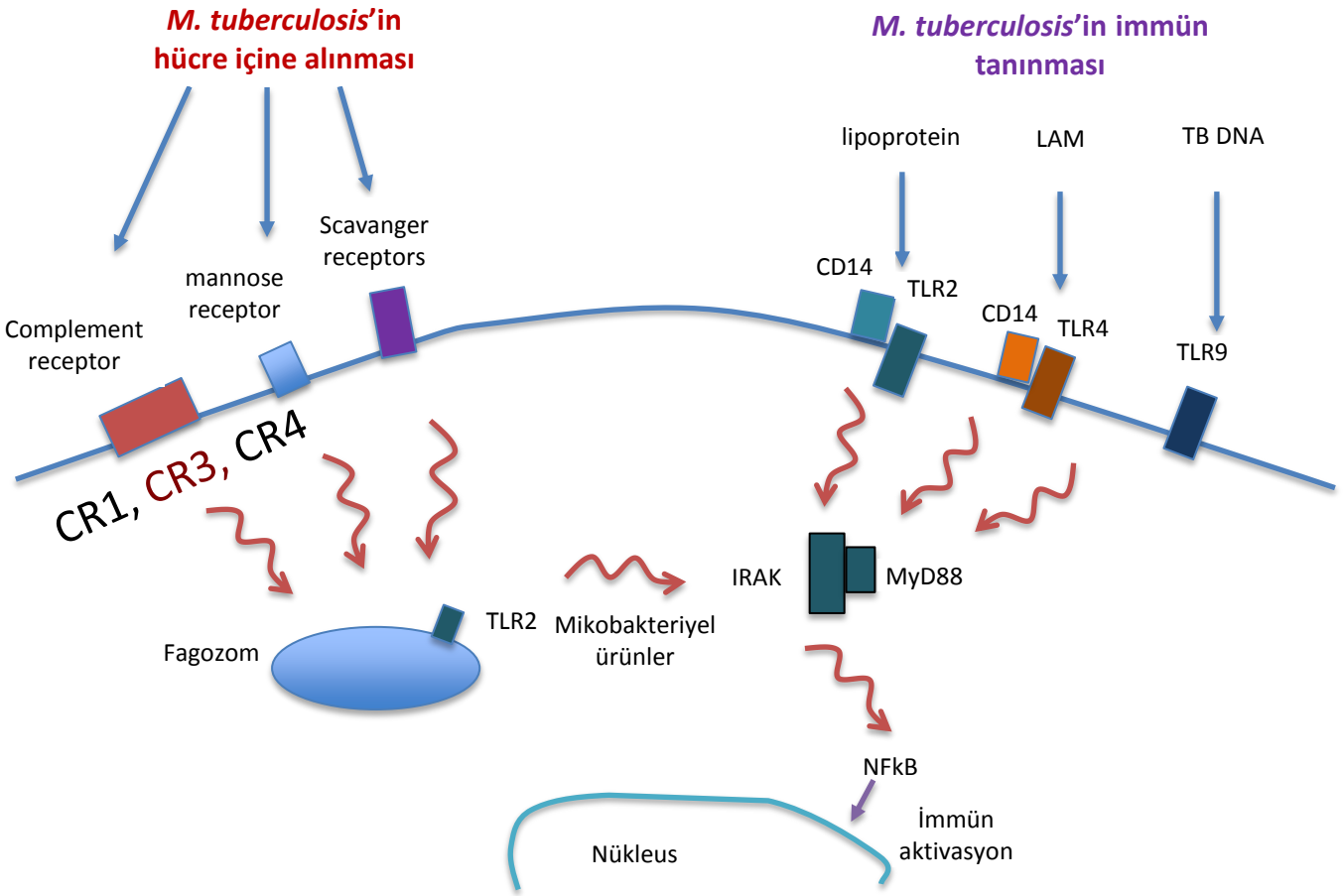
- TLR bu kadar önemli olduğu için mikobakteri de doğal immün yanıtı baskılayan veya düzenleyen sinyalleri harekete geçiren yöntemler geliştirmiştir.

  - sitokin sentezinin inhibisyonu
  - makrofajlarda MHC-sınıf II'nin ifade edilme düzeyini azalması



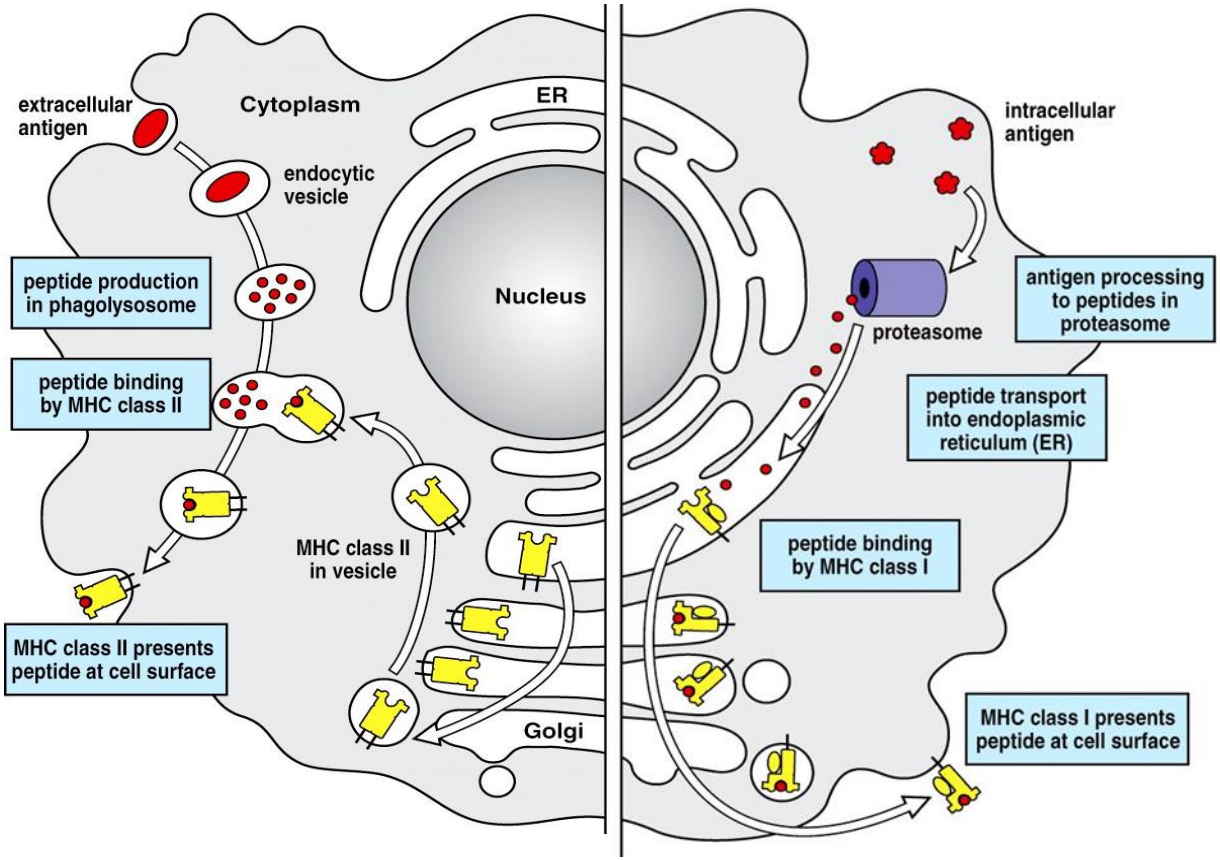
İlk Temas ve Doğal Bağışıklık

- Opsonizasyondan sonra CR1, CR3 ve CR4 aracılığıyla tutulup konak makrofajları tarafından alınabilir. CR3 yokluğunda makrofajları ve monositleri tarafından basil fagositozu %70-80 azalır



Kazanılmış Bağışıklık Mekanizmaları

Normalde olması gereken

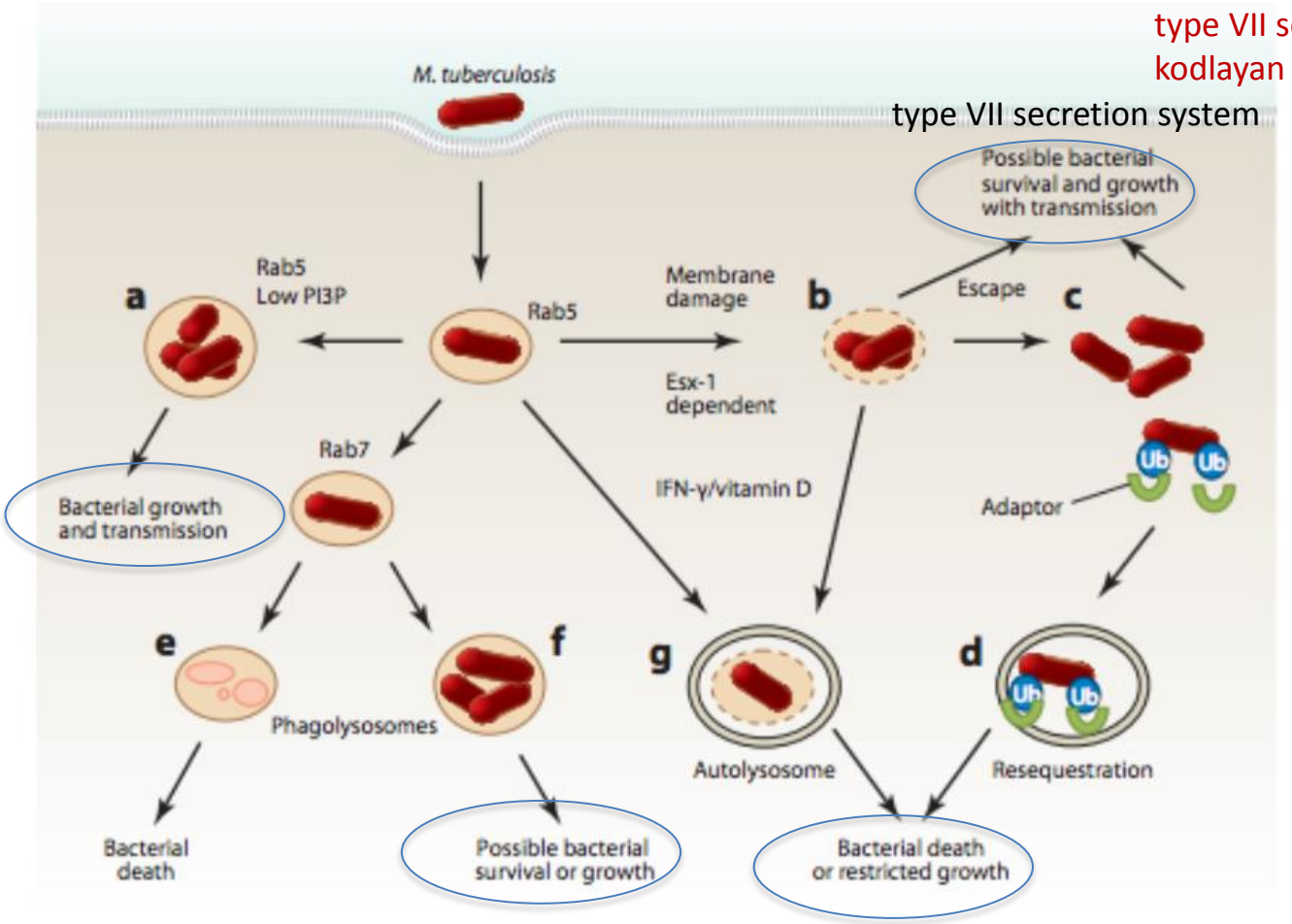


Kazanılmış Bağışıklık Mekanizmaları

Aslında olan

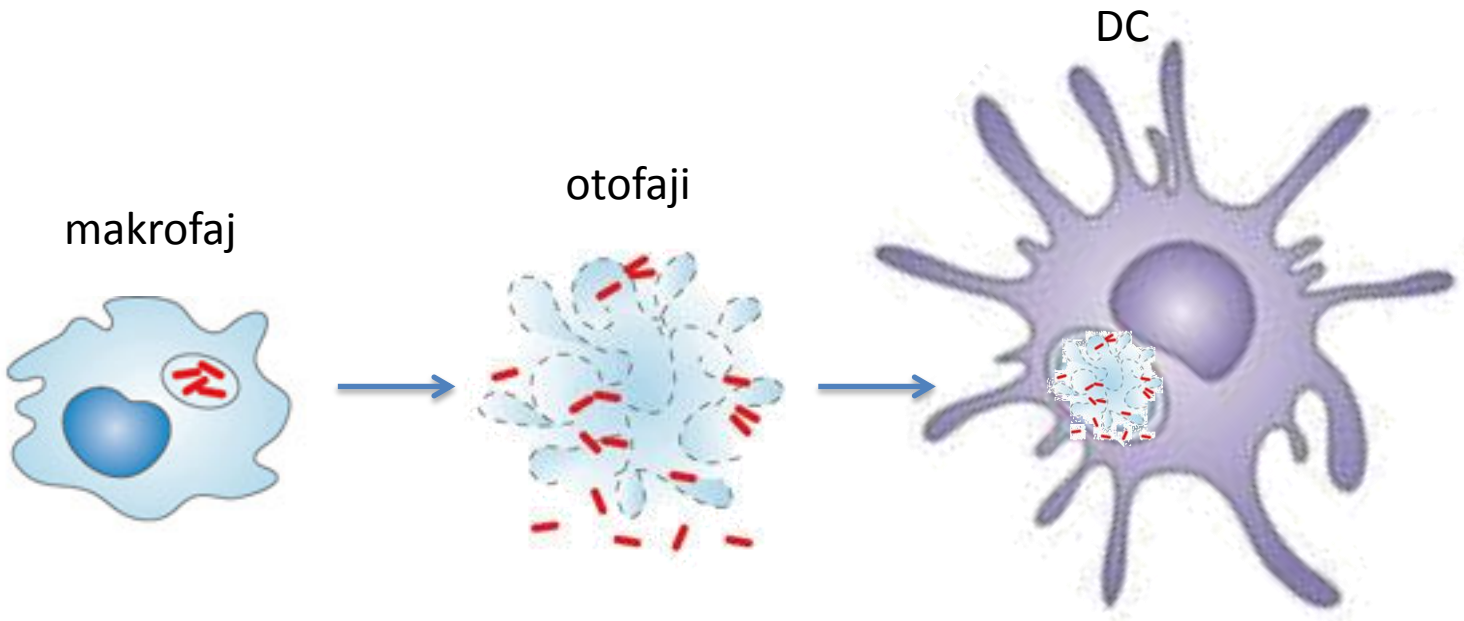
BCG'de
type VII sekresyon sistemini
kodlayan gen silinmiş

type VII secretion system



Konağın son çırpınışları-Otofaji

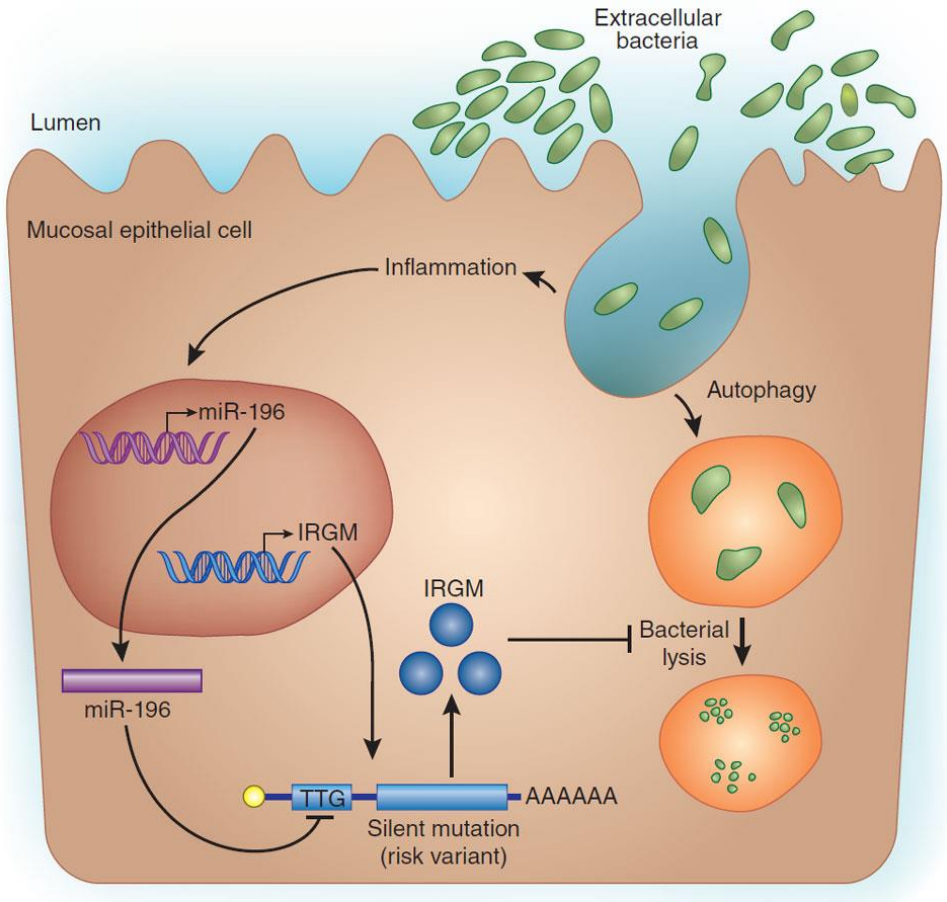
- Enfekte hücre bu koşullar altında hücreyi kaspaz bağımsız yolak üzerinden, apoptotik olmayan hücre ölümüyle, öldürebilmektedir.



Bakteriden bir karşı atak

- Mikobakterinin otofaji genini engelleyen geni var.

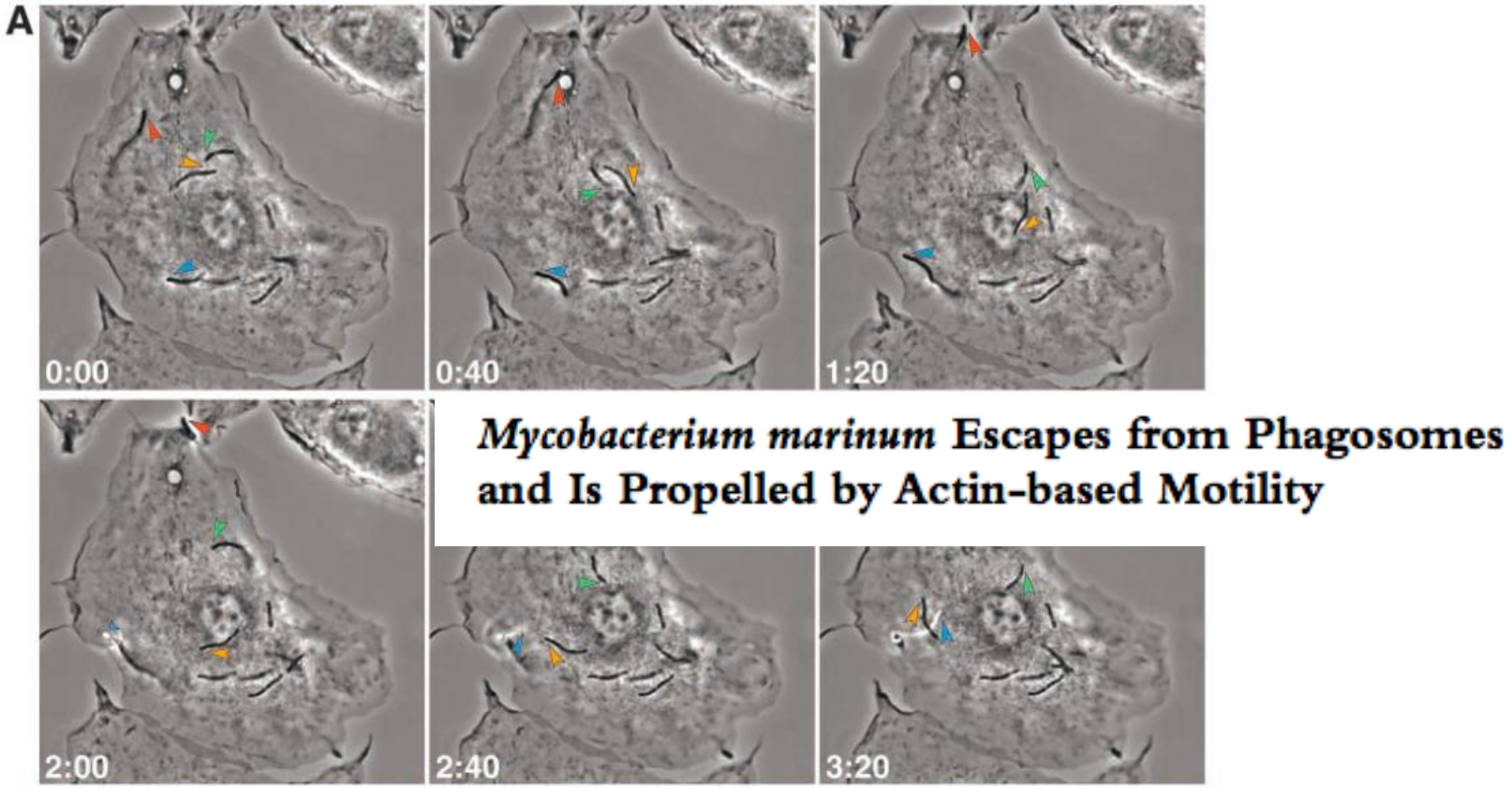
  IRGM geni (immunity-related GTPase family) ve otofaji mekanizmasını bloke edebilir.



Bakteriden bir karşı atak daha

- Actin-based Motility

  Şimdilik sadece *M. marinum'da*



T-regülatör hücreler -Treg

- T regülatör hücreler: *Mycobacterium tuberculosis* infeksiyonlarının

"aşil kemiği"

Immunol Res (2015) 62:386–398
DOI 10.1007/s12026-015-8654-0

INTERPRETIVE SYNTHESIS REVIEW ARTICLE

T regulatory cells: Achilles' heel of *Mycobacterium tuberculosis* infection?

Om Parkash[1] · Sonali Agrawal[1] · M. Madhan Kumar[2]

Published online: 7 May 2015

Abstract T regulatory cells (Treg) constitute a specialized subset of T cells that play a pivotal role in preventing the occurrence of autoimmune diseases by suppressing deleterious activities of immune cells. Contrarily, they can have adverse effect on immune response against infectious diseases where Treg weaken the host immunity leading to enhanced microbial load and thereby increase in severity of the disease. Here, we have attempted to review plethora of information documenting prevalence of Treg in tuberculosis (TB) and their involvement in progression and immunopathogenesis of the disease. Further, we have laid emphasis on the possible use of Treg as a biomarker for determining the TB treatment efficacy. Also, we have discussed the probable contribution of Treg in dampening the efficacy of BCG, the anti-TB vaccine. Finally, we have speculated some of the possible strategies which might be explored by exploiting Treg for enhancing the efficacy of TB management.

Introduction

Tuberculosis (TB) is a major health concern worldwide for mankind, from time immemorial. It is a pervasive, morbid disease and ranks second in leading cause of deaths among infectious diseases with a toll of about 1.5 million deaths and 9 million new cases as estimated in 2013 [1]. This aggravated burden is due to the emergence of multidrug-resistant (MDR) TB, extensively drug-resistant (XDR) TB and HIV coinfection [2–5]. *Mycobacterium tuberculosis* (MTB), the etiological agent of TB, is a highly successful intracellular pathogen which primarily infects lungs. Once infected, majority of the individuals develop latent TB due to persistence of MTB for years or decades and a relatively small proportion (5–10 %) of infected people will develop active TB disease [6]. The probability of developing active TB is much higher among people infected with HIV or in immunocompromised individuals. Despite the global ef-

T-regülatör hücreler -Treg

- Tüberkülozla ilişkili birçok farklı fenotipi tespit edilmiştir.

Table 1 Various Treg phenotypes reported in tuberculosis

Subsets	Phenotypes	References
$CD4^+$ Treg	$CD4^+CD25^{high}$, $CD4^+CD25^+FoxP3^+$, $CD4^+CD25^{high}FoxP3^+$	Guyot-Revol et al. [27], Pang et al. [28]
	$CD4^+CD25^+GITR^+$, $CD4^+CD25^+FoxP3^+CD223^+$, $CD4^+CD25^+FoxP3^+CD223^+IL\text{-}10^+$	Ordway et al. [29]
	$CD4^+FoxP3^+$, $CD4^+FoxP3^+ICOS^+$, $CD4^+FoxP3^+PD\text{-}1^+$	Scott-Browne et al. [30]
	$CD4^+CD25^{hi}CD39^+$,$CD4^+CD25^{hi}CD127^-$	Chiacchio et al. [31]
	$CD3^+CD4^+CD25^{high}CD127^{low}$, $CD4^+CD25^{high}CD127^{low}CD161^+$, $CD4^+CD25^{high}CD127^{low}CD39^+$, $CD4^+CD25^{high}CD147^{++}$	Feruglio et al. [32]
$CD8^+$ Treg	$CD8^+CD28^-$	He et al. [33]
	$CD8^+CD25^+$	Boer et al. [25]
	$CD8^+CD25^+FoxP3^+$	
	$CD8^+CD25^+FoxP3^+CD39^+$	
	$CD8^+CD25^+FoxP3^+CD39^+LAG\text{-}3^+CCL4^+$	

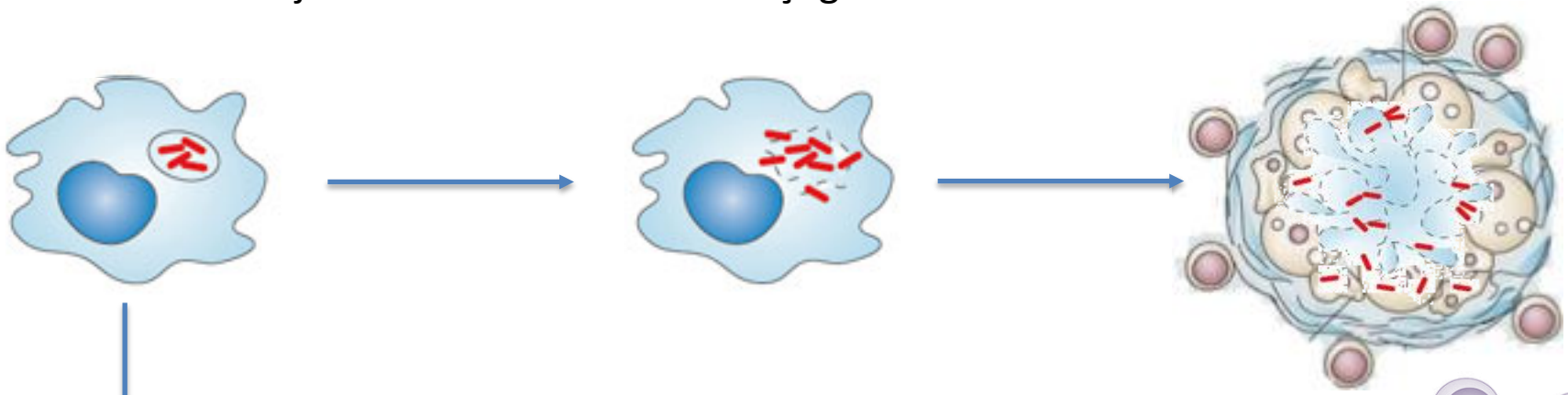
T-regülatör hücreler -Treg

- Tüberkülozla ilişkili birçok farklı fenotipi tespit edilmiştir.

alveoler mikarofaj

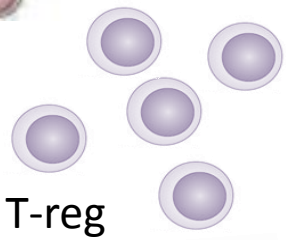
kontrolsüz çoğalma

hücre ölümü

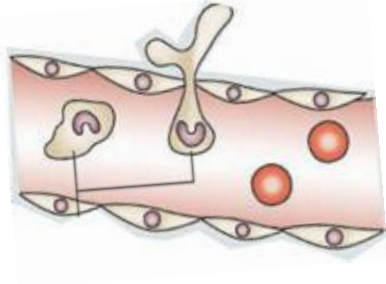


IL-12, IL-1, TNF-γ

manositler, makrofajlar
İmmün ve immün olmayan
hücreler olay yerine toplanırlar



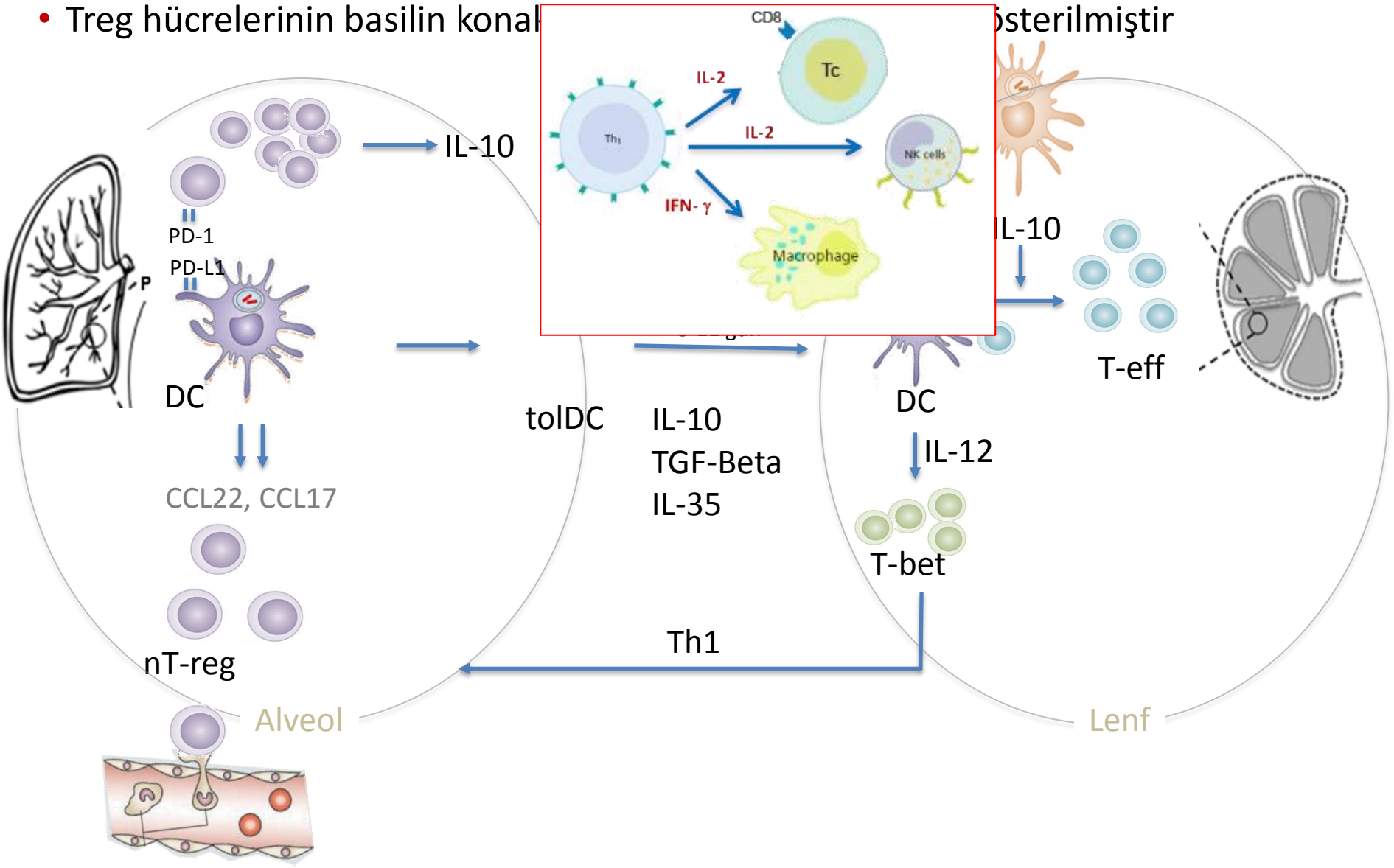
T-reg



Bu aşamada aşırı bir immün cevap oluşup-oluşmadığının saptanması için Treg hücreleri alana infiltre olur.

T-regülatör hücreler -Treg

- Treg hücrelerinin basilin konak[illegible]österilmiştir



T-regülatör hücreler -Treg

- Endemik alanlarda BCG ile aşılanmanın duyarlılaşmış aşırı Treg üretimine neden olduğu daha sonraki BCG uygulamalarının etkinliğini azaltacağı düşünülmektedir.

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Editorial

How to avoid the impact of environmental mycobacteria towards the efficacy of BCG vaccination against tuberculosis?

ARTICLE INFO

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Keywords:
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ABSTRACT

Bacillus Calmette–Guérin (BCG) remains the only widely used vaccine against tuberculosis (TB). Consistent efficacy has been proved in infants but not in adults from developing countries. Epidemiological and experimental studies have pointed out that, prior exposure to prevailing environmental mycobacteria could be responsible for the poor efficacy of BCG as an anti-TB vaccine in adults living in developing countries. Sensitization by environmental mycobacteria may down-modulate the immunologic behavior of BCG on the one hand and may mask its efficacy on the other hand. Some of the important deciding factors for poor efficacy of BCG, due to exposure of the subjects to prevailing environmental mycobacteria, are thought to be (i) Life stage: neonatus versus adolescence; (ii) shared antigens between prevailing environmental mycobacteria and BCG; and (iii) generation of cross-reactive T-regulatory cells against environmental mycobacteria and BCG. In this communication, some novel strategies have been discussed for countering the down modulating impact of environmental mycobacteria towards performance of BCG as an anti-TB vaccine.

T-regülatör hücreler -Treg

- CD4+Treg leri down-regüle eden bir subünit aşı ile kombine edilen BCG nin de daha koruyucu etki oluşturduğunu gösterilmiştir.

BASIC IMMUNOLOGY

doi: 10.1111/j.1365-3083.2011.02666.x

Subunit Vaccine Candidate AMM Down-Regulated the Regulatory T Cells and Enhanced the Protective Immunity of BCG on a Suitable Schedule

Y. Luo*[1], W. Jiang*†[1], Z. Da*, B. Wang‡, L. Hu‡, Y. Zhang§, R. An*, H. Yu*, H. Sun*, K. Tang*, Z. Tang¶, Y. Wang¶, T. Jing* & B. Zhu*

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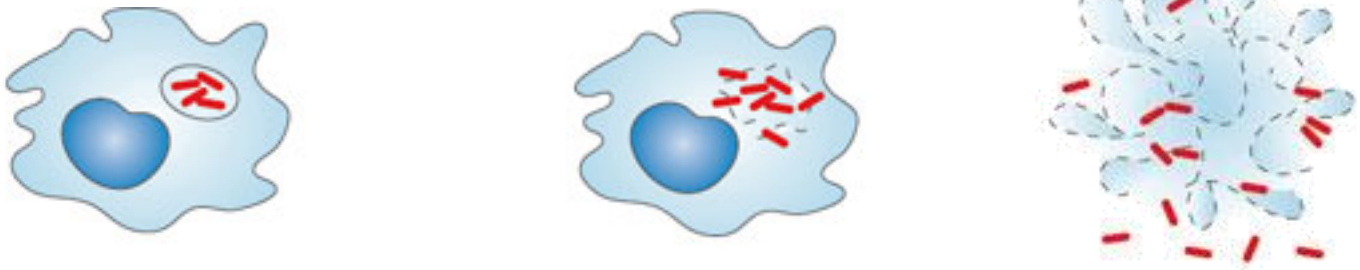
Abstract

Mycobacterium bovis bacillus Calmette-Guérin (BCG) priming and subunit vaccine boosting strategies are urgently needed to improve the protective efficacy of BCG in adult population. However, the schedule of subunit vaccine boosting is not well investigated, especially the optimal immune responses and vaccine immunization schedules are still not clear. We have constructed a novel subunit vaccine candidate consisting of fusion protein Ag85B-Mpt64 (190-198)-Mtb8.4 (AMM) in a complex adjuvant composed of dimo-thylidioctyl ammonium bromide (DDA) and BCG polysaccharide nucleic acid (BCG-PSN). In this study, we compared the effect of different boosting schedules of the subunit vaccine in the prime-boost strategies. C57BL/6 mice were primed with

Tüberküloz Patogenezi

- *M. tuberculosis'in patogenezdeki* başarısı,

  hücre içerisinde yaşayabilmesine ve bağışıklık sistemi hücrelerini kendi amacına göre kullanabilmesine bağlıdır.



Sonuç

- *M. tuberculosis patogenezde başarılı mı? Konak hücre yanıtı mı başarısız?*
- Tüberküloza karşı en iyi strateji yayılımını önlemek!