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Editör
Doğan YÜCEL
ORCID iD: 0000-0001-5487-2857

Yayın Koordinatörü
Yasin DİLMEN

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Akademisyen Kitabevi A.Ş.

Halk Sokak 5 / A Yenişehir / Ankara
Tel: 0312 431 16 33
siparis@akademisyen.com

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Akademisyen Yayınevi A.Ş.

İÇİNDEKİLER

YAZARLAR

Dr. Öğr. Üyesi Yasemin ATICI
Lokman Hekim Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya AD.

Arş. Gör. Hatice Tuğçe BERBEROĞLU
KTO Karatay Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü

B. Eda GÖÇMEN
Tıp Fakültesi Dönem VI Öğrencisi, Lokman Hekim Üniversitesi, Tıp Fakültesi

Doç. Dr. Aysun HACIŞEVKİ
Gazi Üniversitesi, Eczacılık Fakültesi, Biyokimya AD.

Dr. Öğr. Üyesi Hatibe KARA
Bursa Uludağ Üniversitesi, Veteriner Fakültesi, Biyokimya AD.

Cemal NAS
Tıbbi Biyokimya Uzmanı, MD

Ahsenur SEVİM
YL Öğrencisi, Bursa Uludağ Üniversitesi Sağlık Bilimleri Enstitüsü Veteriner Biyokimya AD.

Abdullah Kaan YAĞIZ
Tıp Fakültesi Dönem VI Öğrencisi, Lokman Hekim Üniversitesi, Tıp Fakültesi

Uzm. Dr. Arzu YÜKSEL
Başakşehir Çam ve Sakura Şehir Hastanesi

Zeynep ÖKTEN
Tıp Fakültesi Dönem VI Öğrencisi, Lokman Hekim Üniversitesi, Tıp Fakültesi

BÖLÜM 1

HÜCRE ÖLÜM YOLAKLARI

Yasemin ATICI [1]
Abdullah Kaan YAĞIZ [2]

GİRİŞ

Hücre ölümü, organizmanın gelişimi ve homeostazının sürdürülmesi için kritik bir mekanizmadır. Programlanmış hücre ölümü olarak adlandırılan süreç, hücrelerin kontrollü bir şekilde yok olmasına olanak tanır ve genellikle apoptoz, otofaji, nekroz ve ferroptoz gibi farklı yollarla gerçekleştirilir. Apoptoz, hücrenin kendi kendini yok etme süreci olup, genetik materyalin ve hücresel yapıların parçalanmasıyla sonlanır. Diğer yandan, otofaji, hücrenin bozulmuş veya hasar görmüş bileşenlerini lizozomal bir yolla sindirdiği bir süreçtir ve hücresel homeostazın korunmasında önemli bir rol oynar. Nekroz ise, çoğunlukla hücre hasarı sonucunda gerçekleşen düzensiz bir hücre ölümü şeklidir, ancak son yıllarda nekroptoz adı verilen programlanmış bir nekroz tipi keşfedilmiştir. Ferroptoz, demir bağımlı lipid peroksidasyonu ile gerçekleşen yeni bir hücre ölüm yolu olarak öne çıkmaktadır. Bu farklı hücre ölüm yolakları, organizmada hayatta kalmayı sağlayan ve aynı zamanda hastalıkların gelişimine yol açan karmaşık biyolojik süreçleri temsil eder. Apoptoz ve otofaji, genellikle fizyolojik durumlarla ilişkilendirilse de kanser gibi patolojik durumlar bu süreçlerin kontrolsüz işlemesi ile karakterizedir. Nekrozun da çeşitli hastalıkların etiyolojisinde rol oynadığı, özellikle enflamasyonla ilişkilendirildiği bilinmektedir. Ayrıca, ferroptoz gibi atipik hücre ölüm yollarının keşfi, bu süreçlerin daha iyi anlaşılmasını ve tedavi stratejilerinin geliştirilmesini sağlamaktadır. Bu bağlamda, hücre ölümü mekanizmalarının derinlemesine incelenmesi, yeni terapötik yaklaşımlar için temel oluşturmaktadır.

[1] Dr. Öğr. Üyesi, Lokman Hekim Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya AD., yasemin.atici@lokmanhekim.edu.tr, ORCID iD: 0000-0003-1833-7595
[2] Tıp Fakültesi Dönem VI Öğrencisi, Lokman Hekim Üniversitesi, Tıp Fakültesi, 211110216@lhu.edu.tr, ORCID iD: 0009-0003-3804-9328

lerin serbest bırakılması, hücre ölümünden bağımsız bir mekanizma ile gerçekleşir (112).

Klasik yolakta inflammazomlar, kaspaz-1 aktivasyonu için bir platform görevi görür (113). Kaspaz-1, pro-IL-1β ve IL-18'i olgun sitokinlere çevirir, GSDMD'yi keserek plazma membranında porlar oluşturur ve lizise neden olur (114).

Klasik olmayan yolakta kaspaz-11, hücre içi LPS'ye yanıt vererek doğrudan GSDMD'yi hedefler (104). İnsanlarda kaspaz-4 ve kaspaz-5, kaspaz-1 olmadan GSDMD'yi keserek piroptozu tetikler (115, 116). Bu kaspazlar LPS'yi doğrudan bağlayarak reseptör görevi görür (117).

LPS'nin kaspaz-4 ve kaspaz-11 tarafından algılanması, guanilat bağlı proteinler (GBP) aracılığıyla gerçekleşir (118). GBP1, LPS'ye bağlanarak kaspaz-4 aktivasyonunu sağlar (119).

Kaspaz-4 ve kaspaz-11, IL-1β ve IL-18'in olgunlaşmasını sağlamaz, ancak K+ iyonu çıkışını tetikleyerek NLRP3 aktivasyonuna katkıda bulunur (120).

SONUÇ

Hücre ölümü, organizmanın sağlıklı bir şekilde işleyebilmesi için gerekli olan bir süreçtir ve apoptoz, otofaji, nekroz ve ferroptoz gibi farklı yollarla gerçekleştirilir. Bu hücre ölüm yolakları hem fizyolojik hem de patolojik durumlarla ilişkilidir. Apoptoz ve otofaji, hücrelerin hasar gördüğünde ya da yaşlandığında kontrollü bir şekilde ölmesini sağlayarak organizmanın homeostazını korur. Ancak nekroz ve ferroptoz gibi süreçler, genellikle hücresel hasar veya dış uyarılar sonucu meydana gelir ve hastalıkların gelişiminde rol oynar.

Bu bağlamda, hücre ölüm yollarının daha ayrıntılı bir şekilde anlaşılması, yeni tedavi stratejilerinin geliştirilmesinde önemli bir adım olacaktır. Özellikle kanser ve enflamasyon gibi hastalıkların tedavisinde, hücre ölüm süreçlerinin düzenlenmesi, potansiyel terapötik yaklaşımlar sunmaktadır. Ferroptoz gibi yeni keşfedilen hücre ölüm yolları, bu alandaki araştırmaları derinleştirerek, daha etkili tedavi yöntemlerinin bulunmasına olanak sağlayabilir. Sonuç olarak, hücre ölümünün biyolojik rolü ve mekanizmaları, hastalıkların tedavisi açısından büyük önem taşımaktadır.

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BÖLÜM 2

HASTALIKLARIN PATOJENEZİNDE S100 PROTEİNLERİNİN ROLÜ

Hatice Tuğçe BERBEROĞLU [1]
Aysun HACIŞEVKİ [2]

GİRİŞ

S100 proteinleri ilk kez 1965 yılında Moore ve ark.'ları tarafından sığır beyninden izole edilmiş (1), doymuş amonyum sülfat çözeltisinde %100 oranında çözündüğünden "S100" olarak isimlendirilmiştir (2). Bugüne kadar bu aileye ait 25 üye tanımlanmıştır (3). S100 proteinleri belirli bir dizilim ve yapısal benzerliğe sahip olmakla birlikte her protein, protein eksprese eden hücrelerde ve biyolojik işlevlerde belirgin farklılıklara sahip spesifik bir gen tarafından kodlanmaktadır (4). S100 proteinleri yalnızca omurgalılarda eksprese edilmekte ve doku/hücreye spesifik dağılım sergilemektedir. Örneğin, S100B esas olarak glial hücrelerde olmak üzere belirli nöronal popülasyonlar, melanositler, lenfositler, kondrositler veya adipositlerden; S100A1 nöronlar, iskelet ve kalp kası hücreleri, böbrek hücrelerinden; S100A3 saç kökü ve astrositom hücrelerinden; S100A6 fibroblastlar, epitelyal hücreler, nöronlar ve glial hücrelerden; S100A8 ve S100A9 makrofajlar ve endotelyal hücrelerden; S100A12 ise nötrofiller, makrofajlar ve düz kas hücrelerinden eksprese edilmektedir (5).

S100 proteinleri; moleküler ağırlığı 10-12 kDa olan, asidik yapıda ve kalsiyum bağlayan proteinlerdir (6). Bu protein ailesinin çoğu üyesi homodimerler halinde bulunurken, birkaçı ise heterodimer, trimer ve tetramer halinde bulunmaktadır (7). S100 proteinleri C ve N terminal bağlanma bölgesinden oluşmaktadır (8). C terminal bağlanma bölgesi, N terminal bağlanma bölgesine göre Ca^{+2} için daha yüksek affiniteye sahiptir. Ca^{+2} bağlandıktan sonra S100 proteinlerinde konfor-

[1] Arş. Gör., KTO Karatay Üniversitesi, Sağlık Bilimleri Fakültesi, Beslenme ve Diyetetik Bölümü, hatice.tugce.aca@karatay.edu.tr, ORCID iD: 0000-0002-7098-7344
[2] Doç. Dr., Gazi Üniversitesi, Eczacılık Fakültesi, Biyokimya AD., abozkir@gazi.edu.tr, ORCID iD: 0000-0002-3844-5772

talıkların patofizyolojisindeki etki mekanizmalarının aydınlatılmasının, yeni ve daha etkili terapötik yaklaşımların geliştirilmesi ve uygulanmasına katkıda bulunabileceği düşünülmektedir. Bu nedenle gelecekteki araştırmalar, S100 proteinlerinin erken hastalık tespiti ve prognozunda biyobelirteç olarak doğrulanmasına ve S100 karşıtı tedavilere dayalı yeni stratejilerin geliştirilmesine odaklanmalıdır.

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BÖLÜM 3

MİDE KANSERİNDE KULLANILAN BİYOBELİRTEÇLER VE CA 72-4

Arzu YÜKSEL [1]

GİRİŞ

Mide kanseri (GC), Dünya çapında beşinci en yaygın tümör ve üçüncü en ölümcül kanserdir (1). Helicobacter pylori (Hp) enfeksiyonu, cinsiyet, yeme alışkanlıkları ve sigara kullanımı dahil olmak üzere çeşitli risk faktörleri GC insidansını etkilemektedir (2). Hp enfeksiyonu, gastrite yol açan GC ile yakından ilişkili olup bunu gastrik atrofi ve gastrik intestinal metaplazi izlemektedir (3). Hp'nin eradikasyon tedavisi GC insidansını azaltabilir (4). Dahası, genetik ve epigenetik değişiklikler de hastaların GC'ye olan duyarlılığını artırabilir (5).

GC'li hastaların sağ kalım oranı nispeten düşüktür. Bunun nedeni vakaların geç tanı alması, cerrahi ve kemoterapi gibi tedavilerin yetersiz kalmasıdır. Serum tümör belirteçleri tanı, sağ kalım oranlarını tahmin etmek ve ameliyat sonrası nüksü izlemek için faydalıdır (6). Karsinoembriyonik antijen (CEA), karbonhidrat antijeni 19-9 (CA 19-9) ve CA72-4 en sık kullanılan klinik belirteçlerdir. GC'nin tanı, tedavi ve prognozunda yararlı oldukları gösterilmiştir (6).

CEA ilk olarak Gold ve Freedman tarafından 1965'te tanımlanmış, immünoglobulin süper ailesine ait bir glikoproteindir (7). CEA ağırlıklı olarak kolorektal karsinomun yönetimi için kullanılır ve serum seviyeleri mide, akciğer, pankreas ve meme karsinomunda da artabilir (6). Önceki çalışmalar, serum karsinoembriyonik antijenin (CEA) hem önemli bir prognostik faktör hem de rektal kanserli hastalarda terapötik etkinin ve nüksün bir göstergesi olduğunu göstermiştir (8). Kolorektal kanser ameliyatından sonra CEA seviyelerinin kalıcı olarak yükselmesi, eksik rezeksiyonu veya gizli metastatik hastalığı düşündürür ve nüks için prognostik bir özellik gösterir (9).

[1] Uzm. Dr., Başakşehir Çam ve Sakura Şehir Hastanesi,arzusekerciyuksel@gmail.com, ORCID iD: 0000-0001-6210-5033

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BÖLÜM 4

mikroRNA'LAR VE DÜZENLEYİCİ ROLLERİ[1]

Ahsenur SEVİM [1]
Hatibe KARA[2]

GİRİŞ

DNA'nın genetik materyal olarak keşfinden bu yana, genlerin çalışma mekanizmalarını düzenleyen süreçler, bilim dünyasının önemli araştırma alanlarından biri olmuştur. Gen ifadesinin düzenlenmesi, organizmaların çevresel değişimlere uyum sağlamasından hücresel işlevlerin kontrolüne ve gelişimsel süreçlerin yönetimine kadar birçok kritik biyolojik olayı yönlendirir. Bu düzenleme süreci oldukça karmaşıktır ve transkripsiyondan translasyona kadar farklı aşamalarda gerçekleşir. mikroRNA (miRNA)'lar transkripsiyon sonrası aşamadaki düzenlemelerde rol alan elemanlardan biridir. miRNA'lar, küçük, kodlamayan RNA molekülleridir ve mRNA'ya bağlanarak hedef genlerin translasyonunu durdurabilir veya mRNA'nın yıkımını gerçekleştirebilir. Kodlama yapmayan RNA'lar grubunda yer alan miRNA'ların farklı hastalıklar ve metabolik süreçlerdeki fonksiyonlarına ilişkin araştırmalar her geçen gün artmaktadır. Bu bölümde miRNA'lar tanıtılarak gen düzenleyici özellikleri üzerinde durulacak ve ilişkili oldukları metabolik süreçler hakkında bilgi verilecektir.

A. MİRNA'LAR

1. Tanımı ve Özellikleri

miRNA'lar, 18 ila 25 nükleotid uzunluğunda, tek iplikçikli ve kodlama yapmayan kısa RNA moleküllerdir. Hedef genlerin ekspresyonunu transkripsiyon sonrası seviyede düzenleyerek gen ifadesini kontrol ederler. Bunu, hedef mRNA'nın trans-

[1] YL Öğrencisi, Bursa Uludağ Üniversitesi Sağlık Bilimleri Enstitüsü Veteriner Biyokimya AD., ahsenursevim@gmail.com, ORCID iD: 0009-0003-4919-8644
[2] Dr. Öğr. Üyesi, Bursa Uludağ Üniversitesi, Veteriner Fakültesi, Biyokimya AD., hatibekara@uludag.edu.tr, hatbertuk@yahoo.com, ORCID iD: 0000-0002-7037-3940

tırmalar gerekmektedir. Gelecekte, miRNA'ların hedeflenmesine yönelik geliştirilecek yeni biyoteknolojik yaklaşımlar, hastalıkların erken teşhisi ve kişiye özel tedavi stratejilerinin oluşturulmasında önemli fırsatlar sunacaktır.

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BÖLÜM 5

ALZHEIMER HASTALIĞINDA miRNA VE ETKİLERİ

Yasemin ATICI [1]
Zeynep ÖKTEN [2]
B. Eda GÖÇMEN [3]

GİRİŞ

Alzheimer Hastalığı (AH), yaşlanma ile birlikte en yaygın görülen nörodejeneratif hastalıklardan biridir ve demansın en sık nedeni olarak kabul edilmektedir. AH, bilişsel işlevlerin ilerleyici kaybı, hafıza bozuklukları ve davranışsal değişikliklerle karakterizedir. Günümüzde kesin bir tedavisi bulunmamakla birlikte, hastalığın altında yatan moleküler mekanizmaların anlaşılması, etkili tedavi stratejilerinin geliştirilmesi açısından büyük önem taşımaktadır.

Son yıllarda, AH'nin patogenezinde genetik ve epigenetik düzenleyicilerin önemli bir rol oynadığı gösterilmiştir. Bu bağlamda, mikroRNA'lar (miRNA'lar) gibi küçük, kodlanmayan RNA moleküllerinin, gen ekspresyonunu post-transkripsiyonel seviyede düzenleyerek hastalığın ilerleyişine katkıda bulunduğu anlaşılmıştır. miRNA'ların, nörodejeneratif hastalıkların biyolojik süreçlerinde yer aldığına dair kanıtlar artmakta olup, özellikle AH'nin patofizyolojisi üzerindeki etkileri giderek daha fazla araştırılmaktadır. miRNA'lardaki değişikliklerin, hastalığa özgü nöropatolojik oluşumlar, beyinde amiloid plaklar, nörofibriler yumaklar ve AH ile ilişkili bazı moleküllerin ekspresyon seviyeleriyle bağlantılı olduğu bulunmuştur. miRNA'ların işlevlerinin daha iyi anlaşılması hem AH'nin moleküler mekanizmalarının aydınlatılmasına hem de erken teşhis için biyobelirteç olarak değerlendirilmesine katkı sağlayabilir. Ayrıca, miRNA'ların terapötik hedefler

[1] Dr. Öğr. Üyesi, Lokman Hekim Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya AD., yasemin.atici@lokmanhekim.edu.tr ORCID iD: 0000-0003-1833-7595
[2] Tıp Fakültesi Dönem VI Öğrencisi, Lokman Hekim Üniversitesi, Tıp Fakültesi, 211110201@lhu.edu.tr, ORCID iD: 0009-0002-9578-9958
[3] Tıp Fakültesi Dönem VI Öğrencisi, Lokman Hekim Üniversitesi, Tıp Fakültesi, 181110074@lhu.edu.tr, ORCID iD: 0009-0007-3380-6720

SONUÇ

AH, zamanla biriken nöropatolojik değişikliklerle şekillenen bir süreç olarak tanımlanır. AH, klinik semptomlar yerine biyobelirteçler aracılığıyla in vivo veya otopsi sonrası incelemelerle teşhis edilmektedir. Bu biyobelirteçler, özellikle nörogörüntüleme teknikleri ile Aβ ve Tau proteinlerine odaklanmaktadır. Ancak, bu biyobelirteçler tek başına AH teşhisi koymak için yeterli değildir ve genellikle hastalığın ileri evrelerinde tespit edilebilmektedir. Bu nedenle, güvenilir, etkili ve zamanında teşhis sağlayabilecek biyobelirteçlerin keşfi büyük önem taşımaktadır.

AH, karmaşık ve çok faktörlü bir nörodejeneratif hastalık olup, günümüzde kesin bir tedavisi bulunmamaktadır. Hastalığın altında yatan moleküler mekanizmaların daha iyi anlaşılması, yeni terapötik yaklaşımlar geliştirilmesi açısından kritik bir öneme sahiptir. Son yıllarda yapılan çalışmalar, mikroRNA'ların AH'nin patogenezinde önemli roller oynadığını göstermiştir. miRNA'lar, gen ekspresyonunu düzenleyerek nöronal fonksiyonların korunmasında ve hastalığın ilerleyişinde etkili olmaktadır. Bu nedenle, miRNA'lar hem biyobelirteç hem de terapötik hedef olarak umut vadetmektedir. Gelecekte, miRNA temelli biyobelirteçlerin klinik pratiğe entegrasyonu, hastalığın erken teşhis edilmesine ve bireyselleştirilmiş tedavi yaklaşımlarının geliştirilmesine olanak sağlayabilir. Ayrıca, miRNA'lara yönelik terapötik müdahalelerin etkinliği üzerine yapılacak çalışmalar, AH'nin tedavisine yeni bir bakış açısı kazandırabilir. Bu doğrultuda, genetik ve epigenetik mekanizmaların daha kapsamlı araştırılması, hastalığın daha iyi anlaşılması ve yeni tedavi stratejilerinin geliştirilmesi açısından büyük önem taşımaktadır.

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BÖLÜM 6

ENDOPLAZMİK RETİKULUM STRESİ VE NÖRODEJENERATİF HASTALIKLARDAKİ ROLÜ

Yasemin ATICI [1]

GİRİŞ

Endoplazmik retikulum (ER), hücresel homeostazın sürdürülmesinde kritik işlevlere sahip özelleşmiş bir organeldir. ER'nin temel fonksiyonları arasında protein sentezi ve transportu, proteinlerin doğru şekilde katlanması, lipit biyosentezi, kalsiyum (Ca^{+2}) homeostazının düzenlenmesi ve redoks dengesinin korunması yer almaktadır. ER bütünlüğünün bozulması, yanlış katlanmış veya katlanmamış proteinlerin birikmesi, Ca^{+2} metabolizmasındaki değişiklikler ve redoks dengesindeki düzensizlikler, hücresel düzeyde ER stresinin ortaya çıkmasına yol açmaktadır. Bu stres yanıtı, protein kinaz RNA-benzeri ER kinaz (PERK), aktive edici transkripsiyon faktörü–6 (ATF6) ve inositol gerektiren protein–1 (IRE1) olmak üzere üç temel sensör aracılığıyla katlanmamış protein yanıtı (UPR) mekanizmasını başlatarak ER homeostazını yeniden tesis etmeye çalışır. Ancak, ER stresinin aşırı ve uzun süreli aktivasyonu, hücresel işlevlerin geri döndürülemez şekilde bozulmasına ve nihayetinde apoptozun indüklenmesine neden olmaktadır.

Yapılan çalışmalar, ER stresinin Alzheimer hastalığı, Parkinson hastalığı, diyabet, kanser, tüberküloz ve sıtma gibi çeşitli hastalıkların patogenezinde önemli bir rol oynadığını göstermektedir. ER stres yanıtının modülasyonu, hastalığa özgü koşullara bağlı olarak terapötik bir strateji olarak değerlendirilmektedir. ER stresinin aktivasyonu bazı hastalıkların tedavisinde faydalı olabilirken, sürecin inhibe edilmesi diğer hastalıkların tedavisinde yararlı olabilir. ER stresine ilişkin moleküler mekanizmaların daha derinlemesine anlaşılması, özellikle nörodejeneratif hastalıkların tedavisine yönelik yeni farmakolojik hedeflerin geliştirilmesine katkı sağlayabilir.

[1] Dr. Öğr. Üyesi, Lokman Hekim Üniversitesi, Tıp Fakültesi, Tıbbi Biyokimya AD., yasemin.atici@lokmanhekim.edu.tr ORCID iD: 0000-0003-1833-7595

ilk evrelerinde protein sentezini geçici olarak baskılayarak ER üzerindeki yükü azaltır. PERK, eIF2α'yı fosforile eder ve bunun sonucunda ATF4'ün translasyonunu destekler. ATF4, oksidatif stres ve amino asit metabolizması gibi süreçleri düzenlerken, aynı zamanda CHOP aracılığıyla apoptozu indükleyebilir. PERK yolu, diyabet, kanser ve nörodejeneratif hastalıklar gibi birçok patolojik durumda hücrenin yaşam ve ölüm kararlarında belirleyici bir rol oynar. ATF6 yolu ise golgi aygıtına taşındıktan sonra proteolitik olarak aktif form olan ATF6f'ya dönüştürülür. ATF6f, çekirdekte şaperon proteinleri ve ERAD bileşenlerini kodlayan genlerin ekspresyonunu artırarak proteostazı yeniden sağlamayı amaçlar. Çoğu zaman koruyucu bir yanıt oluştursa da bazı durumlarda özellikle kanser hücrelerinde stres toleransını artırarak terapötik dirence katkı sağlayabilir. Bununla birlikte, ER stresinin çeşitli hastalıklardaki spesifik etkileri ve moleküler mekanizmaları halen tam olarak aydınlatılamamıştır. Ancak eldeki veriler, bu sinyal yollarını hedef alan küçük moleküller ya da genetik düzenleyicilerin, hastalıkların ilerleyişini durdurma veya yavaşlatma potansiyeline sahip olduğunu göstermektedir. Sonuç olarak, ER stresi ve onunla ilişkili olan IRE1, PERK ve ATF6 sinyal yolları, hücresel yanıtın dinamik düzenleyicileri olarak adaptasyon ve dejenerasyon süreçlerinde kritik roller üstlenmektedir. Bu yolların detaylı olarak anlaşılması, Alzheimer, Parkinson, diyabet, kanser ve enfeksiyöz hastalıklar gibi çok sayıda hastalığın tanı, prognoz ve tedavisinde yeni ufuklar açabilecek yenilikçi stratejilerin geliştirilmesine olanak sağlayacaktır.

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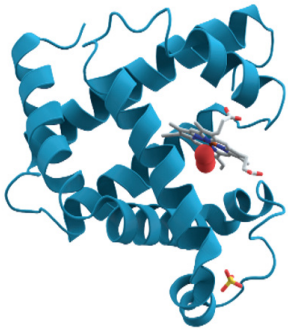
BÖLÜM 7

PROTEİN GLİKASYONU

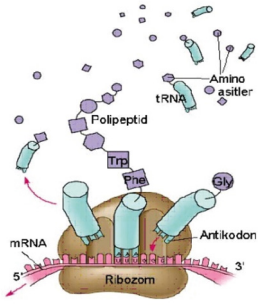
Cemal NAS[1]

GİRİŞ

Tek ya da daha fazla amino asit zincirlerine sahip olan proteinler, bu amino asit zincirlerinin polimerleşmesi ile oluşan biyo-makro moleküler yapılardır. Protein sentezi, protein ve rRNA'lardan oluşan ribozomlarda gerçekleşir (Şekil.1-2). Tüm proteinlerin yapısında spesifik özellikler sağlayan özel amino asit dizilimleri mevcuttur. Proteinlerin fonksiyonları, yapısındaki amino asitlerin özelliklerinin belirlenmesiyle ortaya çıkarılabilir. Proteinlerin organizmalarda metabolik reaksiyonları katalize etmek, DNA'yı çoğaltmak, uyaranlara yanıt vermek, hücresel temelde organizmalara yapı sağlamak ve molekülleri bir yerden başka bir yere taşımak gibi çok çeşitli fonksiyonları vardır (1). Çoğunlukla hücrelerde sudan sonra en fazla bulunan ve hücre kütlesinin %10-20'sini oluşturan proteinler, yapısal ve fonksiyonel proteinler diye ikiye ayrılabilir. Hücrelerde var olan uzun filamentler genellikle protein molekülünün polimeri şeklindeki yapısal proteinlerdir. Tamamen farklı tipte olan fonksiyonel proteinler ise birkaç molekülün birleşmesiyle oluşan, tübüloglobüler yapılardır (2).



Şekil 1. Protein 3D formu



Şekil 2. Ribozom tRNA bağlanması

[1] Tıbbi Biyokimya Uzmanı, MD, drcemalnas@gmail.com, ORCID iD: 0000-0002-5616-8625

için AGE'ler ile hastalıkların mekanizmaları arasındaki ilişkiye odaklanan, mikro ve makro moleküllere dönük kanıta dayalı daha geniş kapsamlı ileri çalışmalara ihtiyaç vardır.

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