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Bölüm 1

NÖRODEJENERATİF HASTALIKLARDA SİRTUİNLER VE MİTOKONDRİYAL AKTİVİTE

Yasemin ATICI[1]
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1. SİRTUİNLERİN YAPISI, LOKALİZASYONU VE ENZİMATİK AKTİVİTELERİ

Sessiz bilgi düzenleyici 2 (Sir2) proteinleri olarak da bilinen sirtuinler ilk olarak mayada (Saccharomyces cerevisiae) tanımlanmıştır. Nikotinamid adenin dinükleotid (NAD) bağımlı protein deasetilazlar ailesinin bir alt tipidir ve sınıf III histon deasetilazlar (HDAC'ler) olarak kategorize edilirler. Sirtuinler (SIRT), histonlardan, transkripsiyon faktörlerinden, enzimlerden, histon olmayan proteinlerden asetil grubunu çıkarır. İnsanlarda ve diğer memelilerde yedi farklı sirtuin vardır. SIRT 1'den SIRT 7'ye kadar tanımlanan sirtuinlerden SIRT1 en iyi tanımlanmış olanıdır (1).

SIRT'ler, C- ve N-terminal alanlarında uzunluk ve dizi bakımından farklılık gösterir. Bu nedenle hücrenin farklı yerlerinde lokalize olurlar. SIRT1 ve SIRT2 nükleusta ve sitoplazmada lokalize olurken, SIRT3-SIRT5 mitokondride lokalize olur (Şekil 1) (2,3).

Sirtuinler, NAD+ bağımlı lizin deasetilasyonu yaparlar. Aynı zamanda yapılardan süksinil, malonil ve uzun zincirli açil gruplarını da çıkardıkları gösterilmiştir (5,6). Bu enzimler, hücre sağkalımı, proliferasyon, yaşlanma, apoptoz, DNA onarımı ve kalori kısıtlaması gibi çeşitli biyolojik süreçlere dahil olmuşlardır (7,8).

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stresle mücadelede rol oynayabilir, enerji metabolizmasını düzenleyebilir ve DNA onarım mekanizmalarını etkinleştirebilir. Bu nedenle, SIRT1'in potansiyel olarak yaşlanma süreçleri ve çeşitli hastalıklar üzerinde olumlu etkileri olabileceği düşünülmektedir. Sirtuin aktivitesinin artırılması, yaşlanma süreçlerini geciktirme ve yaşa bağlı hastalıkların gelişimini önleme potansiyeline sahip olabilir. Ancak, bu konudaki araştırmalar henüz tam olarak netleşmemiş olup, sirtuinlerin fonksiyonları ve potansiyel uygulamaları üzerindeki çalışmalar devam etmektedir. Sirtuinler arasındaki kesin moleküler mekanizmaları aydınlatmak için gelecekteki çalışmalara ihtiyaç vardır. Ayrıca, yeni sirtuin modülatörlerinin keşfi ve hücreler, hayvanlar ve klinik deneylerin karşılaştırmalı çalışmalarının geliştirilmesi, etkili anti-nörodejenerasyon ilaçlarının keşfi ve geliştirilmesine katkıda bulunabilir.

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Bölüm 2

LİPİT METABOLİZMASININ VE APOLİPOPROTEİNLERİN ALZHEIMER HASTALIĞINA ETKİSİ

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1. GİRİŞ

Alzheimer Hastalığı (AH), normal yaşlanma süreci dışında düşünme ve hafıza becerilerini zamanla azaltan, birçok işlevin tek başına gerçekleştirilmesini geri dönüşümsüz bir şekilde engelleyen; davranışsal ve fonksiyonel bozukluklarla devam eden özellikle hipokampus üzerinde etkili olan bir beyin hastalığıdır. AH bilişsel işlevlerin kaybıyla kendini gösteren demansın en yaygın tipi olan nörodejeneratif bir hastalıktır. AH'nin belirtileri arasında beyinde hafıza ve işlevsel bozukluklar meydana gelmektedir. Hastalığın kendine özgü görülen önemli patolojik bulguları vardır. Bunlar; amiloid beta (Aβ), Tau proteinlerinin hiperfosforile olması ve hücre içerisinde çözünemeyen nörofibril yumak (NFY)'lerin birikimi ile birlikte sinaptik disfonksiyondan kaynaklanan bozukluklardır (1).

Lipitler beynin kuru ağırlığının büyük kısmını oluşturmaktadır. Beyin, lipitleri glukozdan gerekli enerjiyi sağlayamadığı durumlarda kullanır. Genetik faktörler ve yaşam tarzı lipit metabolizmasını önemli derecede etkiler ve lipit metabolizmasında görülen tüm değişiklikler AH ile ilişkilendirilmektedir (1). Lipit metabolizmasında ve lipitlerin hücre içerisinde taşınmasında önemli rol oynayan apolipoprotein E4 (APOE4) hastalığın bilinen en yaygın genetik faktörüdür. Ek olarak lipit metabolizması AH'de etkili olan kan-beyin bariyerinin işlevi, amiloid öncül proteininin (APP) işlenmesi, miyelinasyon, membran yeniden modellemesi,

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Kolesterolün serebral ve hipokampal kortekste artması, hafıza ve öğrenmeyi geri dönüşümü olmayacak şekilde etkilemektedir. Orta yaşlarda yüksek kolesterollü diyet uygulanması AH için risk faktörü oluştururken, ileri yaşlardaki yüksek kolesterolün AH ile bağlantısı bulunamamıştır. Kolesterolün AH için koruyucu bir etkiye sahip olup olmadığı henüz tam anlamıyla belirlenememiştir. Bunun yanında, AH ile kolesterol arasındaki ilişkinin yaşa ve doza bağımlı olarak farklılık gösterdiği belirtilmektedir.

Normal yaşlanmada lipit homeostazı beynin temel işlevlerinin karşılanmasını sağlar. AH'de lipit metabolizmasında homeostazın bozulması söz konusudur ve bu durum AH'nin ilerlemesini karakterize eden anormal beyin fonksiyonlarıyla sonuçlanır. AH'nin daha kapsamlı mekanizmalarını, spesifik biyobelirteçlerini ve yeni tedavilerini ortaya çıkarmak için beyin lipit homeostazının araştırılacağı daha kapsamlı çalışmalara ihtiyaç vardır.

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Bölüm 3

ALZHEIMER HASTALIĞININ PATOFİZYOLOJİSİ VE OKSİDATİF STRES

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1. ALZHEIMER HASTALIĞI VE OKSİDATİF STRES

Alzheimer hastalığı (AH), yaşlı nüfusta demansın yaygın prevalansından sorumlu olan ilerleyici nörodejeneratif bir bozukluktur (1). Dünya Sağlık Örgütü'nün verileri, dünya çapında demanstan etkilenen yaklaşık 55 milyon birey olduğunu göstermektedir. Her yıl neredeyse 10 milyon yeni AH vakası, demans teşhisi almaktadır. AH'nin küresel yükünün 2050 yılına kadar iki katına çıkması tahmin edilmektedir (2). Bu nedenle AH'nin klinik belirtilerini hafifletmek için potansiyel terapötik müdahalelere ihtiyaç vardır.

Amiloid-β protein öncülünün (AβPP) işlenme ve imha mekanizmasındaki kusurlar, çözünür amiloid-β 40 (Aβ40), çözünmez Aβ42 ve beyindeki C-terminal parçaların birikimi, AH'nin patolojisi ile ilişkilendirilmiştir. Ayrıca amiloid plakların aracılık ettiği biyokimyasal, metabolik, moleküler ve hücresel olaylar nörodejenerasyona ve hipokampüsteki nörojenik süreçlerde zararlı etkilere neden olabilmektedir (3). Demansın potansiyel nedeni olarak tanımlanan nöral rejeneratif plastisitenin, nöral kök hücrelerin (NKH) hücre döngüsündeki kusurlar ve hipokampüste yeni gelişen nöronlarda apoptoz nedeniyle bozulduğu belirlenmiştir [4].

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faktördür. Oksidatif stres, antioksidan savunmanın yetersiz olduğu durumlarda reaktif türlerin birikmesine neden olur. Bu durum, lipid peroksidasyonu, protein ve nükleik asitlerin oksidatif modifikasyonu gibi biyokimyasal değişikliklere yol açabilir. Oksidatif stres, Aβ birikimi, mikroglia aktivasyonu, redoks aktif metal iyonlarının düzensizliği ve mitokondriyal fonksiyon bozukluğu gibi AH ile ilişkilendirilen belirtilerle bağlantılıdır. Mikroglia ve astrosit gibi hücreler, AH'nin histopatolojik belirtileri olan nöroenflamasyona katkıda bulunabilir. Aktive edilen mikroglialar, proenflamatuvar sitokinleri üreterek ve Aβ birikimine yanıt olarak nöronal hasara aracılık ederek AH patofizyolojisinde rol oynar. Mitokondriyal disfonksiyon da AH ile ilişkilendirilen bir başka önemli faktördür, çünkü mitokondriler reaktif oksijen türlerinin ana kaynağıdır. Metal iyonlarının özellikle bakır ve demir düzensizliğinin, AH ile ilişkilendirilen oksidatif stresi artırabileceği ve Aβ'nin nörotoksisitesini etkileyebilecği belirtilmiştir. AH'nin kompleks patogenezinde oksidatif stresin önemli bir rol oynadığı ve bu süreçlere müdahale eden terapötik stratejilere ihtiyaç olduğu vurgulanmıştır.

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Bölüm 4

İNME BİYOBELİRTEÇLERİ

Yeşim GÜVENÇ DEMİRAĞCI[1]

GİRİŞ

İnme, merkezi sinir sisteminin vasküler hasarına atfedilen ve klinik olarak tanımlanmış akut, fokal nörolojik defisit sendromudur. Beynin fokal hasarına bağlı olarak hızla gelişmiş olan klinik bulgular 24 saatten daha fazla sürmektedir. Ülkemizde ve Batı'da morbiditenin ve mortalitenin üçüncü nedenidir. Hayatta kalan hastalar beş yıl içinde yeniden inme geçirmektedir. Yaşlıların hastalığı olarak sınırlandırılmamalıdır. Bütün yaşlar inme açısından risk altındadır (1).

İNME SINIFLANDIRMASI

İki çeşit inme tipi bulunmaktadır:

İskemik İnme

Hemorajik İnme

İnmelerin %80'ini iskemik nedenler oluşturmaktadır. Bunların %50'si intrakraniyal tromboz (ateroskleroz), %30'u da ekstrakraniyal embolilerle meydana gelmektedir. Hemorajik inmeler (%20) intraserebral kanama (ISK) ve subaraknoid kanama (SAK) nedeniyle meydana gelmektedir. İntraserebral kanamalar çoğunlukla rüptür ve hematom oluşturan zayıflamış damarlardan meydana gelmektedir. Subaraknoid kanamalarda kanama beynin dışına ya da BOS içine olmaktadır (2).

Geçici iskemik atak (GİA) mini-stroke olarak adlandırılmaktadır. İskemik inmeye benzemekle birlikte fokal nörolojik defisitler 24 saatten kısa sürmektedir (1).

İNME FİZYOPATOLOJİSİ

İskemik olaylarda serebral hipoperfüzyon, hücresel biyoenerji yetmezliği, oksidatif hasar, kan-beyin bariyeri disfonksiyonu, mikrovasküler hasar, hemostatik

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Bölüm 5

KANSERDE TERAPÖTİK HEDEF OLARAK AXL RESEPTÖRÜ VE AXL İNHİBİTÖRLERİ

Hatibe KARA[1]

GİRİŞ

Kanser hücrelerinde ve tümör mikro çevresinde farklı sinyal yollarının düzensiz işlediği görülür. Transmembran proteinler olarak karakterize edilen Reseptör Tirozin Kinaz (RTK)'ların anormallikleri de birçok malignitede yer almaktadır. Bir RTK üyesi olan AXL'ın aşırı ekspresyonu kanserde kötü prognoz ve tümör büyümesiyle ilişkilidir. AXL, K vitaminine bağımlı protein ailesinde yer alan Büyüme Durdurma Spesifik Protein 6 (GAS6)'nın bağlanmasıyla aktive olur. GAS6/AXL sinyal yolu PI3K/AKT, MAPK/ERK ve STAT3 dahil olmak üzere aşağı akış yollarını aktive ederek kanserin ilerlemesi, metastazı, kemoterapötik direnci ve immün bağışıklıktan kaçınmayı teşvik eder. Kanserin farklı süreçlerinden sorumlu tutuluyor olması AXL'ı kemoterapötik hedef haline getirmiş ve AXL'a özgü pek çok terapötik ajan geliştirilmesinde etkili olmuştur. Bu ajanların tek başına veya kombine rejimler halinde kullanımı hem preklinik hem de klinik ortamlarda ümit verici sonuçlar ortaya koymuştur. Bu bölümde, AXL reseptörü hakkında kısaca bilgi verilecek ve AXL'a özgü geliştirilen tedavi stratejilerine değinilerek, kanser tedavisinde değerlendirmeye alınan AXL inhibitörleri tanıtılacaktır.

AXL'ın Yapısı ve İşleyişi

AXL, RTK'lerin TAM (TYRO3, AXL ve MERTK) alt ailesinin bir üyesidir. ANXELKTO adı, "kontrol edilemez" anlamına gelen ve Yunanca "anexelekto" kavramından gelmektedir (1). AXL ilk olarak 1988'de kronik miyeloid lösemi hücrelerinden (KML) izole edildi (2). AXL proteininin yapısı; i) iki immünoglobulin benzeri alan ve iki fibronektin III alanı içeren membran dışı bölge; ii) bir transmembran alan; iii) bir hücre içi kinaz alanı olmak üzere üç kısımdan oluşur (3). AXL molekülü, K vitaminine bağımlı protein ailesinden olan GAS6 tarafından aktive edilir. Bu aktivasyonda bir AXL molekülü bir

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bulunmuştur. Bu çalışmadan elde edilen gözlemler, KHDAK hastalarında glesatinib ile ilgili bir faz II çalışmasının başlatılmasını sağlamıştır (78).

SONUÇ

AXL kanserde, hücrenin hayatta kalması, EMT, metastaz ve terapötik direnç mekanizmalarında önemli bir oyuncudur. Son on yılda, TKI'ler, mAb'ler, ADC'ler ve çözünebilir reseptörler dahil olmak üzere bir dizi spesifik AXL hedefli tedavi, klinik gelişime dahil olmuştur. Özellikle, AXL inhibitörleri ön çalışmalarda umut verici sonuçlar ortaya koymuştur. Gün geçtikçe artan araştırma sonuçları, AXL inhibisyonunu potansiyel kanser tedavi stratejilerinden biri yapmaktadır. AXL inhibitörlerinin keşfi ve araştırılması, özellikle ilaç direncindeki etkinliğinin ortaya çıkmasıyla birlikte kanser tedavisi seçeneklerinin iyileştirilmesi açısından kritik önem taşımaktadır. Bu bölümde AXL'ın kanserdeki rolüne kısaca değinilmiş ve AXL'ı hedef alan tedavi stratejilerinden AXL inhibitörleri tanıtılmıştır.

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Bölüm 6

PROSTAT KANSERİ BİYOBELİRTEÇLERİ

Gamze GÖK[1]

PROSTAT KANSERİ

Kanser, hücrelerdeki kontrolsüz bölünme ve çoğalma neticesinde oluşur. Çevresel ve genetik unsurlardan etkilenir. Kanserin günümüzde 100'den fazla türü tanımlanmıştır. Bazı kanser türlerine yaklaşım için standartlar oluşturulmasına rağmen, kanserli her olgu özgün değerlendirilmelidir (1).

Erkeklerde ikinci en fazla görülen kanser türü olan prostat kanserinin tüm kanserler içerisinde görülme oranı yaklaşık olarak %15'tir. Prostat kanseri teşhis edildiğinde lokalize ise kürün tam sağlanabilmesi mümkündür (2). Kaynağını prostatik bezden ya da kanal asinilerinden alan prostat kanseri en çok mortaliteye sebep olan kanserler içinde ilk beşte yer almaktadır (3). Prostat kanserine yaklaşım gelişme göstermektedir. Prostat kanseri özellikle 50 yaş üstü erkeklerin sağlıkları için ciddi risk içerir. Bu hastalığın klinik çeşitlilikleri farklı tedavi seçeneklerini beraberinde getirir (4).

Coğrafik ve etnik nedenlerden dolayı prostat kanserinin görülme sıklığı bölgeler arasında değişmektedir (5). Prostat kanseri görülme oranları Kuzey Amerika, Avustralya ve Avrupa'da yüksek iken; Asya'da düşüktür (6). Prostat kanserinin Türkiye'de görülme sıklığı Amerika'dan daha düşük olmasına rağmen artış görülmektedir. Bu artış; ülkemizde yaşam tarzında meydana gelen değişiklikler, nüfusun yaşlanması ve prostat kanseri için yapılan taramaların yaygınlaşması nedenleri ile olabilir (7).

Aile öyküsü, ileri yaş, genetik faktörler ve ırk prostat kanseri risk faktörlerindendir. Obezite, diyet, yeterli fiziksel hareketin olmaması, kan glukozunda yükseklik, enfeksiyonlar ve enflamasyon prostat kanseri ile pozitif ilişki gösteren etmenlerdir (8).

Prostat kanseri genellikle yavaş ilerler. Periferik zonda oluşan odaklar küçüktür bu nedenle prostat kanserleri erken evrede genellikle semptom göstermezler (4).

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TMPRSS2-ERG

2005 yılında, prostat kanserinde v-ets erythroblastosis virus E26 onkogen homologu (ERG) mRNA'nın aşırı eksprese olduğu bildirilmiştir (32). ERG'yi aktive eden etken transmembran proteaz serin 2 (TMPRSS2)'dir. Androjenler, TMPRSS2 vasıtasıyla ERG'nin expresyonunu indükler. Bu durumun sonucunda protoonkogen ERG aşırı eksprese olur (33). ERG in vitro ve in vivo prostat kanserinde hem kanserin onkogenezini hem de metastazını uyararak başlatır (34) . TMPRSS2-ERG füzyonu etnik köken ile ilişkilidir. Etnik grupları farklı olan bireyler arasında %7 ile %83 aralığında farklılık mevcuttur (35). Prostat kanseri ile teşhis edilen Kafkas hastaların yaklaşık yarısında TMPRSS2-ERG füzyonu vardır (13).

SelectMDx

SelectMDx testi, idrar prostat kanseri beliriteçlerinden biri olarak geliştirilmiştir. DLX1 geni, HOXC6 geni ve TDRD1geninin kombinasyonu, Gleason ≥ 7 olan yüksek dereceli prostat kanserlerinin doğru tespit edilmesinde yüksek doğruluk içermektedir. Ticari kiti mevcuttur (13).

SONUÇ

Prostat kanserinin tanısı için yeni biyobelirteçlerin ortaya çıkarılması, biyobelirtçelerin ölçümlerinin hassas, doğru, ulaşılabilir olması tedavi oranlarında iyileştirilme sağlayabilir. Yalnızca prostat kanserinde artış gösterip, diğer benign hastalıklarda ortamda bulunmayan ve böylece hastaları gereksinim dışı biyopsilerden kurtaran biyobelirteçlere ihtiyaç devam etmektedir.

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Bölüm 7

OTOİMMÜN TİROİD HASTALIKLARI VE TİROİD FONKSİYON TESTLERİ

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GİRİŞ

Tiroid bezi embriyonik büyüme, organ gelişimi, nörolojik gelişim, enerji metabolizması, üreme, termoregülasyon, glukoz alımının düzenlenmesi, redoks homeostazisi ve iyodür alımı gibi fizyolojik süreçlerde rol oynayan endokrin bir organdır. Bu görevleri tiroksin (T4) ve triiyodotironin (T3) adlı tiroid hormonlarını (TH) üreterek gerçekleştirmektedir. (1,2).

TH tiroid bezinde üretilen ve iyot içeren özel bileşiklerdir. T4 bir prohormondur. T3 ise dolaşımda aktif hormon olarak bulunmaktadır. T4 dolaşımda nispeten daha yüksek konsantrasyonda bulunmaktadır. TH'ler vücuttaki çoğu dokuya etki eder ve T3 üretiminin büyük kısmı dokularda T4'ün enzimatik deiyodinasyonu yoluyla gerçekleşir. Ayrıca TH'lerin üretimi TSH tarafından düzenlenir (3).

Hashimoto tiroiditi ve Graves hastalığı olarak adlandırılan otoimmün tiroid hastalıkları bağışıklık sisteminin tiroid bezine saldırısı ve anormal lenfosit aktivitesi ile karakterize bir grup hastalıktır. Tiroid antijenlerine karşı reaktif T ve B hücrelerinin tiroide infiltrasyonu, tiroid otoantikorlarının üretimi ve anormal tiroid fonksiyonu ile oluşmaktadırlar. Otoimmün tiroid hastalıkları heterojen bir hastalık grubudur. Hastalar subklinik biyokimyasal anormalliklerden şiddetli hipertiroidizme veya şiddetli hipotiroidizme kadar geniş bir yelpazede yer alabilmektedir. (4,5,6,7).

T4, başta tiroid bağlayıcı proteine (TBG) (%60-75) olmak üzere, transtiretin (TTR/TBPA) (%15-30) ve albümin (~%10) olmak üzere %99,97 oranında plazma proteinlerine bağlı olarak dolaşır. T3'ün ise, yaklaşık %99,7'si TBG'e bağlanır. Total tiroid hormonlarının (tT4 ve tT3), toplam (serbest + proteine

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Gebelerde %5-10 oranında görülen postpartum tiroiditin olasılığını tahmin etmek için, hamileliğin erken döneminde Anti-TPO testi kullanılabilir. Anti-TPO pozitif olan gebelerin yaklaşık %50'sinde tiroidit gelişir. Postpartum tiroidit genellikle geçicidir. Bu hastaların %67'sinde klinik semptomlar görülürken, %33'ünde TSH anormal olsa bile semptomlar subklinik kalır. Anti-TPO testi infertilitenin değerlendirilmesinde de yararlı olabilir. Çünkü yüksek Anti-TPO düzeyleri düşük yapma riskinin artmasıyla ve başarısız in vitro fertilizasyon tedavisiyle ilişkilendirilmiştir (8,59).

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Bölüm 8

PARAOKSONAZ ENZİM AİLESİ ENZİMLERİNDEN HOMOSİSTEİN TİYOLAKTONAZ, PARAOKSONAZ VE ARİL ESTERAZ AKTİVİTELERİNE GENEL BİR BAKIŞ

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GİRİŞ

Homosistein sülfür içeren doğal vaskülotoksik ve trombojenik bir amino asittir. Yapılan çalışmalar, yüksek plazma homosistein ve homosistein metabolizması sonucu oluşan homosistein tiyolakton seviyelerinin doğrudan toksisite ve vasküler endotel hasarına neden olabileceğini göstermektedir (1). Hiperhomosisteinemi homosisteinilasyon ve tiyolasyon yoluyla reaktif oksijen türlerinin (ROS) birikmesine ve proteinlerin posttranslasyonal modifikasyonlarına yol açarak zararlı etkilere sebep olur (2). Hatalı posttranlasyonal değişikliklere uğrayan bu toksik proteinler apoptoza, kazanılmış immun cevaba (LDL oksidasyonuna ve buna bağlı makrofaj cevabındaki artışa) ve tromboza sebep olur (3). Yakın dönemdeki çalışmalarda ise homosistein tiyolaktonun özellikle kromatin organizasyonu, tek karbon metabolizması ve lipit metabolizmasıyla ilgili gen ekspresyonunu da indüklediği gösterilmiştir (4). İnsan paraoksonaz enzimi (PON-1) ise paraoksonaz (PON), homosistein tiyolaktonaz (HTLaz) ve arilesteraz (ARE) enzim aktiviteleri sayesinde hatalı postranslasyonal modifikasyonlara uğramış zararlı proteinleri inaktive eder. Bu etkiler aracılığıyla PON-1 enziminin vasküloprotektif, antienflamatuvar ve antioksidan özellikleri ortaya çıkar. Bu

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edilmesi, homosistein düzeylerinin düzenlenmesi ve oksidatif stresin azaltılması gibi birçok biyolojik süreçte kritik bir rol oynar.

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