Güncel Tıbbi Biyoloji ve Genetik Çalışmaları IV

Editör

Hüsnü Ümit LÜLEYAP

ISBN
978-625-399-130-2

Kitap Adı
Güncel Tıbbi Biyoloji ve Genetik Çalışmaları IV

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Sayfa ve Kapak Tasarımı
Akademisyen Dizgi Ünitesi

Yayıncı Sertifika No
47518

Baskı ve Cilt
Vadi Matbaacılık

Bisac Code
MED052000

DOI
10.37609/akya.2564

Kütüphane Kimlik Kartı
Güncel Tıbbi Biyoloji ve Genetik Çalışmaları IV / editör : Hüsnü Ümit Lüleyap.
Ankara : Akademisyen Yayınevi Kitabevi, 2023.
118 sayfa. : tablo, şekil. ; 135x210 mm.
Kaynakça ve İndeks var.
ISBN 9786253991302
1. Tıp--Mikrobiyoloji.

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Bölüm 1

SÜLFORAFAN VE KANSER

Dilek ÇEVİK[1]

GİRİŞ

Sülforafan (SFN), brokoli başta olmak üzere çeşitli krusifer sebzelerden elde edilen, antioksidan özellikli biyoaktif bir bileşendir. SFN, glukorafanin adı verilen bir glukozinolatın mirosinaz enzimi aracılığı ile hidrolize edilmesiyse oluşan bir izotiyosiyanattır (1). Kanserin gelişimi, sınırsız hücre bölünmesine yol açan hücresel mutasyonlar ve çevresel uyaranları içeren çok faktörlü bir süreçtir. Kanser dünya çapında morbidite ve mortalitenin önde gelen nedenlerinden biri olduğundan, bütün toplumlarda için önemli bir halk sağlığı problemi olarak öne çıkmaktadır. Kanser, geniş çapta ve çeşitlilikte genetik ve moleküler değişiklikler içerdiğinden dolayı tedavi seçenekleri halen kısıtlı kalmaktadır (2). Bu nedenle, tümör gelişimini önlemek, inhibe etmek veya tümörü tamamen ortadan kaldırmak için doğal bileşiklerin kullanılması için yapılan araştırmalar artış göstermektedir. Doğal bileşiklerin diyette kullanımı, kanser kemoprevensiyonu olarak bilinir ve temel amacı, kanser gelişiminin başlangıcını yavaşlatmak ve / veya büyümesini baskılamaktır. SFN, normal hücrelere karşı olumlu bir toksikoloji profilinin olması ve kanserin farklı aşamalarında rol oynamasından dolayı umut vadeden bir kanser önleyici ajan ve/veya tedavi amaçlı kullanıma uygun bir fitokimyasal olarak değerlendirilmektedir (3). Çok sayıda in vitro ve in vivo çalışma, SFN' nin sağlıklı hücreleri kimyasal ve/veya radyasyona bağlı karsinogeneze karşı

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moleküllerle kombinasyon halinde test eden, bir formülasyonun geliştirilmesine yol açabilecek ve azaltılmış yan etkilerle istenen biyolojik etkinliği gösterebilecek bir dizi araştırma yapılmaya devam edilmelidir. Sonuç olarak, son literatür, SFN'nin umut verici ve güvenli bir kemopreventif molekül olduğunu ve kansere karşı savaşmak için güçlü bir araç olduğunu çeşitli in vitro ve in vivo modellerde açıkça göstermiştir. SFN ile yapılan klinik çalışmalar, insanlarda olumlu bir toksikolojik profil, genotoksisite ve yüksek tolere edilebilirlik göstermiştir ve SFN'nin güvenli olduğunu bildirmiştir. Ancak SFN'nin yüksek etkinliği ve güvenirliği onun yeni bir kemopreventif veya kemoterapötik ilaç olarak insanlarda kullanım onayı alması için yeterli değildir. SFN için daha büyük ölçekli ve kapsamlı klinik çalışmaların yapılması gerekliliği devam etmektedir.

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Bölüm 2

ERKEK İNFERTİLİTESİNİN GENETİĞİ

Yunus ARIKAN[1]

ERKEK İNFERTİLİTESİ VE SPERMATOGENEZ

İnfertilite, normal yollarla en az 12 ay boyunca çocuk sahibi olamama olarak tanımlanabilir. Dünya genelinde her 6 çiftin 1'inde görüldüğü bu durumun yarısı erkek tarafından kaynaklanmaktadır (1,2).

Sperm parametreleri değerlendirildiğinde, fertil erkekler için her bir ejekülatta 39 milyon sperm ve mililitrede en az 15 milyon sperm bulunması durumu söz konusu olmalıdır. Bununla birlikte ejakülatta bulunan spermlerin en az %32'si ileri yönde hareket ediyor olmalı yine en az %58'i canlı ve en az %4'ü normal sperm morfolojisine sahip olduğunda ancak normozoospermi durumundan bahsedilebilir (3).

Erkek kaynaklı infertilitenin %10-15'inden sorumlu olan azospermi, ejakülatta hiç sperm bulunmama durumu ile karakterize olup genel populasyonun yaklaşık %1'inde görülür. Spermin epididimisten boşalma kanalına olan yolculuğundaki kanalların durumuna bağlı olarak tıkayıcı (obstrüktif) veya tıkayıcı olmayan (non-obstrüktif) etiyolojilere sahiptir (4,5). İnfertil erkeklerin yaklaşık %60'ında ise spermin sayısında veya yapısında bozukluklar bulunur. Sayı 15 milyonun altında ise oligozoospermi, Primer Siliyer Diskinezi (PCD) (MIM:244000) örneğinde olduğu gibi sperm hareketi yavaş ise astenozoospermi, gözle görülür durumda

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AZFb bölgesindeki büyük delesyonların varlığında hastaya TESE sonucu sperm elde edilememe riskinden bahsedilmelidir. AZFc bölgesi delesyonları olan bireylerde TESE ile sperm elde edilme oranı %36-73.3'dır (117,118). Klinefelter sendromu olan bireylerde TESE ile sperm elde edilip canlı doğumda başarılı dölleme oranı (%50), AZFc bölgesi delesyonu olan bireylere göre daha yüksektir (118). Bu da TESE ile sperm elde edilme oranındaki yüksekliğin elde edilen canlı doğum oranı arasında bir ilişki olmadığını göstermektedir (118). Erkek infertilitesinde genetik danışmanlık verilirken özellikle sperm sayısı ve kalitesini etkileyebilecek kolçisin gibi ilaçların kullanımı durumunda (119,120) infertilite tedavisi yapılırken kullanılan ilacın (kolçisin vb) doz ayarlaması yapılabilmesi için, genetik danışman ile ilgili ilacı preskribe eden doktorun iletişim haline olması gerektirebilir.

Son söz olarak yeni nesil dizileme tekniklerinin gelişmesi ile hem yeni genlerdeki dominant veya resesif karakterdeki kalıtsal mutasyonların hem de de novo mutasyonların ortaya çıkarılması sağlanacaktır. Bu sayede erkek infertilitesi hakkındaki bilgilerimiz artacak ve yardımcı üreme tekniklerinin de gelişmesiyle erkek infertilitesine bakışımız toplumsal bir sağlık sorunu olarak evrilecektir. Yeni nesillere bilerek aktarılmış olacak mutasyonlu genlerin de doğal seçilimi değiştirebilme potansiyelinin hem etik hem de biyolojik bir dilemma olarak değerlendirilmesi gerçeğini ortaya koymaktadır.

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Bölüm 3

REKOMBİNANT DNA TEKNOLOJİLERİ

Perçin PAZARCI[1]

GİRİŞ

Rekombinant DNA (rDNA) teknolojisi, farklı organizmalardan alınan genetik materyalin çeşitli laboratuvar yöntemleri kullanılarak kesilip daha sonra elde edilen DNA parçalarının birleştirilmesi sonucu normalde biyolojik organizmalarda var olmayan DNA dizilerinin elde edilmesine dayanan bir teknolojidir(1). İlk bakışta imkansız gibi görünen bu teknoloji tüm canlılarda bulunan DNA'nın aynı kimyasal yapıya sahip olmasından dolayı mümkündür ve aslında bu teknolojinin temeli olan rekombinasyon canlı organizmalarda sıkça görülür ve canlılar arasındaki çeşitliliğin en önemli etkenlerinden biridir(2).

Moleküler düzeyde rekombinasyon, farklı nükleotid dizilerine sahip iki DNA molekülünün homoloji gösteren bölgeleri arasında parça alışverişi sonucu meydana gelen yeni gruplamalardır(2). Bu yeni gruplamalar sonucunda orijinal DNA dizisi ile aynı olmayan ancak onlara ait nükleotid dizilerinin bir kısmını barındıran rDNA molekülleri oluşur. Canlılarda ise rekombinasyon eşeyli üremede mayozda gerçekleşen kromozomlar arası parça değişimleri ile, bakterilerde transformasyon, konjugasyon gibi mekanizmalarla meydana gelerek çeşitliliğe katkı sağlar. Hem moleküler düzeyde hem de canlılar düzeyinde bakıldığında rekombinasyonun temeli DNA molekülleri arasında homoloji olmasına dayanmaktadır ve

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monoklonal antikorlar kullanılarak hedefe özgü kemoterapi adı verilen, kanser ilaçlarının sadece belirli hedef dokuları etkilemesi için yapılan çalışmalar sürmektedir. Tri-fonksiyonel antikorlar ise yine kanser tedavisinde denenen ve rDNA teknolojileri kullanılarak üretilen antikorlardır. Temel olarak monoklonal antikorların bir tipi olan trifonksiyonel antikorlar, monoklonal antikorlardan farklı olarak iki farklı antijen içinde bağlanma bölgesi içerirler. Bu sayede bir yandan tümör hücrelerini tanıyabilirken diğer yandan T-hücrelerine ve makrofajlara aynı anda bağlanabilmekte, bu sayede tümör hücresini immün yanıt için işaretleyebilmektedir(19).

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Bölüm 4

OKSİDATİF STRES VE İNSAN SAĞLIĞI ÜZERİNE ETKİLERİ

Nazmiye BİTGEN[1]
Melike AKBULUT[2]

GİRİŞ

Oksidatif stres, hücrelerde ve dokularda oksijen reaktif türlerinin (ROS) üretimi ve birikmesi ile biyolojik bir sistemin bu reaktif ürünlerini detoksifikasyonu arasındaki dengesizliğin neden olduğu bir olgudur. ROS normalde oksijen metabolizmasının yan ürünleri olarak üretilir, buna rağmen çevresel stresörler (yani UV, iyonlaştırıcı radyasyonlar, kirleticiler ve ağır metaller) ve ksenobiyotikler (yani antiblastik ilaçlar) ROS üretimini büyük ölçüde artırmaya katkıda bulunur ve bu nedenle hücre ve doku hasarına (oksidatif stres) yol açan dengesizliğe neden olur.

Reaktif oksijen türleri veya serbest radikaller, normal hücresel metabolizma tarafından üretilebilir ve protein, lipid, DNA gibi biyomoleküllerle reaksiyona girerek hücresel hasara neden olurlar. Aynı zamanda dejeneratif değişikliklerden de sorumludurlar. Düşük konsantrasyonda serbest radikaller, fizyolojik düzenlemede ve hücresel sinyalleşme süreçlerinde hayati bir rol oynar, ancak yüksek seviyede hücrede zararlı değişikliklere neden olabilir. Bu bölümde, oksidatif stres ve insan sağlığı üzerine etkilerini vurgulayacağız.

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Bölüm 5

VARDİYALI HEMŞİRELERDE SİRKADİYEN RİTİM VE TELOMER UZUNLUĞU ARASINDAKİ İLİŞKİ

Hilal KOYUNCU[1]

GİRİŞ

Vardiyalı çalışma, standart çalışma saatlerinin (sabah 7 veya 8'den akşam 5 veya 6'ya kadar) dışında kalan zamanlarda sürekli veya dönemsel çalışma biçimi olarak tanımlanmaktadır. Gece vardiyası ise, gece 11 ile sabah 6 arasında en az 3 saatlik çalışmayı kapsayan özel bir vardiyalı çalışma türüdür. Sanayileşmiş toplumlarda, çalışanların yaklaşık %15-20' si vardiyalı olarak istihdam edilmektedir (1).

Vardiyalı çalışan populasyonlarda hastalık riskinin daha yüksek olmasının olası sebebi sirkadiyen ritimlerin bozulmasından kaynaklanan sirkadiyen uyumsuzluktur (2). Sirkadiyen uyumsuzluk ise fiziksel aktivite, uyku-uyanıklık, yeme, içme gibi davranışların, içsel fizyolojik sirkadiyen ritimlere göre yanlış sirkadiyen evrelerde gerçekleşmek zorunda kaldığında ortaya çıkar (3). Memelilerde bu ritimler, hipotalamusun suprakiazmatik çekirdeğinde (SCN) bulunan merkezi pacemaker tarafından senkronize edilir (4). SCN hem biyokimyasal, fizyolojik ve davranışsal süreçlerin günlük zamanlamasını hem de çeşitli doku ve organlardaki periferik sirkadiyen saatleri koordine eder (5). Çevresel ve/veya genetik manipülasyonlarla sirkadiyen sisteme müdahale edilmesi endok-

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Bölüm 6

İNSAN EMBRİYOLARINDA GENOM DÜZENLEME ARAŞTIRMALARIYLA İLGİLİ ETİK SORUNLAR

Ruşen AVŞAR[1]

GİRİŞ

Genom düzenleme organizmanın DNA'sında değişiklik yapma imkanı veren bir grup teknoloji olup genom düzenlemeyle ilgili bazı yaklaşımlar geliştirilmiştir. Bunlardan birisi CRISPR-Cas9'dur. CRISPR-Cas9 genom düzenleme (GD) sistemi, çeşitli organizmalarda ve hücre türlerinde DNA'nın kesin, verimli, nispeten ucuz ve hızlı modifikasyonuna olanak tanır. GD'nin, gen fonksiyon çalışmaları, gen terapi çalışmaları, ilaç geliştirme ve tarımda değiştirilmiş mahsullerin üretimi dahil olmak üzere birçok araştırma alanında uygulamaları olduğu bulunmuştur (1). 2015 yılında ilk kez CRISPR-Cas9 sistemi kullanılarak insan embriyoları üzerinde bir araştırma yapılmış ve bu çalışmada, CRISPR/Cas9'un yetişkin hemoglobinin bir alt birimini kodlayan ve β-talasemide mutasyona uğrayan insan β-globin genini etkili bir şekilde parçalayabildiği bulunmuştur (2).

Birçok ülkede, hamileliği oluşturmak için germline genom modifikasyonuna ilişkin yasal yasaklara rağmen (3), önde gelen bilim adamları tarafından germline genom düzenlemenin (GGD) klinik kullanımları tartışılmıştır (4,5). Tekniği çevreleyen etik sorunları ele almak için birçok toplantı ve grup toplanmış

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Bölüm 7

ODONTOJENİK KİSTLER VE TÜMÖRLERİN NEOPLASTİK KARAKTERLERİNİ DEĞERLENDİRME BELİRTEÇLERİ

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ODONTOJENİK KİSTLER VE TÜMÖRLER

Genel Bilgiler

Odontojenik kistler, oral ve maksillofasiyal dokuları etkileyen benzersiz bir hastalıktır. Diş oluşturma aparatının epiteli ile ilişkili enflamatuvar veya gelişimsel patojenik nedenlerin bir sonucu olarak ortaya çıkarlar. En sık görülen 4 odontojenik kist; periapikal kistler (PK), dentigeröz kistler, rezidüel kistler ve odontojenik keratokistlerdir. Amerika Birleşik Devletleri'nde bir diş hekimliği fakültesi patoloji servisinden alınan oral biyopsiler üzerinde yapılan bir çalışmada, kistik lezyonların prevalansının %10,7 olduğu belirtilmiştir.(1) Kanada'da yapılan demografik bir çalışmada, PC'lerin en yaygın odontojenik kistler olduğu (%65,15), bunu dentigeröz kist (%24,08) ve OKC'nin (%4,88) izlediği belirtilmiştir.(2) Birleşik Krallık'ta yapılan bir çalışmada, oral patoloji servisi tarafından alınan örneklerin %12,8'ine odontojenik kist tanısı konulduğu bildirilmiştir(3). Brezilya'da yapılan bir çalışmada odon-

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