Bölüm 14

KANSERDE YENİ BİR TERAPÖTİK-HEDEF MOLEKÜL: CRM1'İN YAPISI, FONKSİYONU VE EKSPRESYONU

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NÜKLEOSTOPLAZMİK TAŞINIM

Birçok molekül çekirdek ve sitozol arasında taşınmaktadır. Hücre çekirdeğine moleküllerin giriş ve çıkışı nükleer por kompleksleri (NPC) tarafından sıkıca kontrol edilir. Küçük moleküller (≤ 30 kDa) NPC'yi difüzyon ile geçebilmektedir. Ancak RNA ve proteinler gibi büyük boyutlu moleküllerin hücre çekirdeğine giriş-çıkışı transport faktörleri olan "karyoferinler" isimli proteinler aracılığıyla gerçekleşir (Wente, 2000). Karyoferin (nükleer-sitoplazmik transport reseptör ailesi), ökaryotik bir hücrenin sitoplazması ve çekirdeği arasındaki moleküllerin taşınması ile ilgili reseptör ailesi olup, 19'dan fazla (İmportinler, Eksportinler ve Transportinler) üyesi vardır (Wente, 2000; Watson vd., 2004). Çekirdeğin içinde yani karyoplazmada (veya çekirdek plazması) bulundukları için "karyoferinler" olarak adlandırılırlar. İmportinler, kargo molekülünü sitoplazmadan-nükleusa taşırken, Eksportinler taşınım sürecini tersine çevirerek, kargo molekülünü nükleustan-sitozole taşırlar, ancak Transportinler ise hem nükleustan-sitoplazmaya hem de sitoplazmadan-nükleusa taşıyabilir (Izaurralde vd., 1998; Misteli, 2008).

Karyoferinler kargo molekülünü hedef dizilerinden tanıyarak, seçer ve nukleer mebran boyunca taşır (Wente, 2000; Watson vd., 2004). Nükleer hedef dizisi, kısa amino asit dizisi olup, kargo molekülünün nukleusa giriş-çıkışı için, taşıyıcı karyoferinler tarafından tanınmasını sağlayan bir etiket olup, taşınım yönünü belirler (Chook ve Blobel, 2001). Kargo molekülü sitoplazmadan-nükleusa taşınırken İmportinler tarafından tanınan bu nükleer hedef dizisi, "nükleer lokalizasyon sinyali" (NLS) olarak adlandırılır ve taşınım için İmportinlerin tanıdığı bir etiket gibi davranır. NLS dizisi yaygın olarak hidrofilik amino asidlerden (özellikle lizin amino asidi) oluşur (Watson vd., 2004; Izaurralde ve Adam, 1998). Kargo molekülü nükleustan-sitoplazmaya taşınırken Eksportinler tarafından tanınmasını sağlayan bu hedef diziye ise "nükleer eksport sinyali" (NES) denir (Watson vd., 2004.

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re-döngüsü G1 fazında tutuklar (Etchin vd., 2013; Lapalombella vd., 2012).

KOS-2464, en etkili LMB analogu olup, düşük nanomolar konsantrasyonlarda apoptozisi indüklediği bildirilmiştir (Mutka vd., 2009; Turner ve ark., 2012). KOS 2464 düşük toksisite ve yüksek anti-tümör aktivitesi çeşitli kanser hücre hatlarında ve ksenogreft fare modellerinde gösterilmiştir (Mutka vd., 2009).

CBS9106 CRM1'in reaktif bölgesine bağlanarak degrade olmasına neden olan faklı bir inhibitörü olup, in vitro çeşitli kanser hücre hatlarında ve in vivo ksenograft hayvan modelde anti-tümör aktivitesi gösterilmiştir (Turner vd., 2012).

Ratjadon, *Sorangium cellulosum*'dan izole edilmiş olup inhibisyon mekanizması LMB'ye benzer ve anti-proliferatif etkilere sahiptir (Meissner vd., 2004).

Anguinomisinler, güçlü inhibitörler olup, transforme hücrelere seçici sitotoksisite gösterirler (Hayakawa vd., 1995).

PKF050-638, HIV-1 Rev proteininin nükleer ihracatını engelleyerek HIV-tedavisinde kullanılan bir CRM1-inhibitörü olup, anti-kanser etkisi henüz araştırılmamıştır (Daelemans vd., 2002; Turner vd., 2012).

SONUÇ VE ÖNERİLER

Yapılan çalışmalar, CRM1'in karsinogenezdeki kritik rolü ve terapötik hedef olma potansiyelinin göstermiş ve bu nedenle son yıllarda CRM1 yeni tümör-tedavi stratejilerinin geliştirilmesi çabalarının odak noktası haline gelmiştir. Bu çabalarla geliştirilen yeni nesil spesifik CRM1-inhibitörlerinin ve diğer ajanlarla kombinasyonlarının tedavi amaçlı klinik kullanımları oldukça umut vericidir. Spesifik inhibisyonu veya interferans teknikleriyle gen ifadesinin baskılanması yoluyla gerçekleştirilen artan sayıda çalışmalarla, CRM1'in malignitelerdeki biolojik fonksiyonu, ilişkili hücre içi mekanizmaları açıklığa kavuşturulmakta ve tedavi sırasında gelişen ilaç-direnç mekanizmaları daha iyi anlaşılmaktadır. CRM1'in hedeflenmesi, çeşitli apoptotik yolakların aktive olmasına neden olarak, ilaç-direnç mekanizmalarının gelişmesinin önüne geçerek tedavi stratejilerinde birçok avantaj vadetmektedir.

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