KANSER GENOMİĞİ VE İLAÇ DİRENCİ

35. BÖLÜM

Burcu GÜLBAĞCI[1]

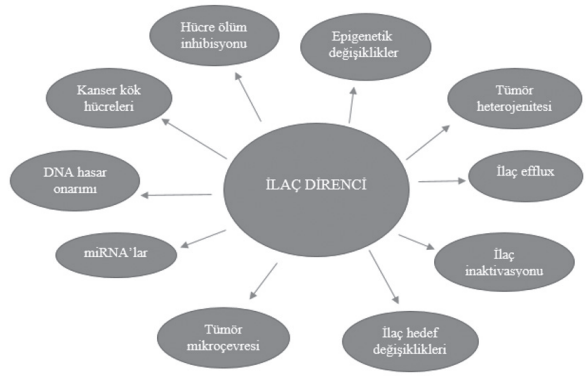
GİRİŞ

Son yüzyılda hücre genomuna ait elde edilen veriler ışığında artık bilmekteyiz ki kanser, genetik bir hastalıktır. Kanser hücrelerinin genomundaki mutasyonların ve anormal gen işleyişlerinin keşfi hem kanser oluşumu ve metastaz gelişimine dair hem de tedavi seçimi ve süreci hakkında bize yeni ufuklar açmıştır (1).

Yirminci yüzyılın başlarında ilk olarak David von Hanseman (2) ve Theodor Boveri (3) tarafından kanser hücrelerinin birtakım kromozomal anormallikler içeren kontrolsüz çoğalan hücre klonları olduğu fikri ortaya atılmıştır. Kanser hücrelerinde genetik anormalliklerle ilgili giderek artan bilgilerle bazı kanser türlerinde spesifik kromozom anormallikleri keşfedilmiştir. Kronik myeloid lösemide Philedelphia kromozomunun t(9:22) bulunması (4), ilerleyen süreçte kolon kanseri ve melanomda sık mutasyona uğrayan genlerin ortaya çıkarılması (5,6), akciğer kanserinde sıklıkla mutasyona uğrayan ve tedavi yanıtını etkileyen genlerin keşfi (7); kanser genom atlası projesini doğurmuştur. U.S. National Cancer Instutite tarafından 2009 yılında *The Cancer Genome Atlas* 15 ülkeden çok sayıda araştırmacının katılımı ile başlatılmıştır (8).

Gelişen teknoloji ve yeni nesil sekanslama yöntemleri sayesinde kanser genomiği hakkında her geçen gün yeni bilgiler elde etmemize rağmen tedavideki başarısızlığın en önemli nedeni ilaç direncidir. Sitotoksik tedavi sırasında kanser hücrelerinin bir kısmı ölürken, bir kısmı çeşitli mekanizmalar kullanarak tedaviye dirençli klonlar oluşturup nükse ve metastaz oluşumuna neden olmaktadır (9). Kansere bağlı ölümlerde ikinci sırada yer alan kolorektal kanserde, hastaların % 90'ından fazlasında tedavi başarısızlığının ilaç direncine bağlı olduğu tahmin edilmektedir (10).

Kanser tedavisindeki ilaç direncinden pek çok farmakogenomik mekanizma sorumludur (Şekil:1).



Şekil 1. İlaç direnci, multifaktöriyel bir fenomen olup, her bir mekanizma tek başına etkili olabileceği gibi birlikte de bulunabilirler

KANSER TEDAVİSİNDE İLAÇ DİRENCİNDE ROL OYNAYAN MEKANİZMALAR

1.1. DNA Hasar Onarımı

Kemoterapotik ajanların (Örn: platin bazlı ilaçlar, alkilleyiciler, vb.) etki mekanizmalarından

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baskılayıcı protein p53 (*TP53*) tarafından apopitoz indüklenir. Kanserlerin %50'sinde *TP53* geni mutasyona uğramıştır. Bu genin mutasyonu veya delesyonu ise p53 proteinindeki fonksiyon kaybı ile ilaç direncine neden olmaktadır (76,77). Alternatif olarak, kaspaz-9 ve kofaktörü, *apopitotik proteaz aktive edici faktör 1* (Apaf-1) gibi p53 düzenleyicilerinin inaktivasyonu da ilaç direncine yol açabilir (78).

KANSER TEDAVİSİNDE İLAÇ DİRENCİNE YAKLAŞIM

Kanser tedavisinde ilaç direnci; ilaç inaktivasyonu, ilaç hedef değişikliği, ilaç effluxu, DNA hasarı onarımı, hücre ölümü inhibisyonu, hücre heterojenliği, epigenetik etkiler veya bu mekanizmaların kombinasyonu ile gelişen karmaşık bir fenomendir. Mevcut bilgilerimiz ile kombinasyon tedavisinin en uygun tedavi seçeneği olduğunu söyleyebiliriz; çünkü ilaç direncini azaltma konusunda tek başına herhangi bir ilaçtan daha etkilidir (49,79,80). Bu nedenle farklı kombine tedavi stratejileri, artan ilaç direnci prevalansına karşı koymak için geliştirilmelidir.

Kanser progenitör hücreleri genellikle ilaca dirençlidir. Bu progenitör hücreler, görünüşte remisyonda olan hastalarda varlığını koruyabilir ve metastaz sırasında diğer organlara göç edebilir. Bu nedenle kanser progenitör hücreleri, tümör bölgesinde veya uzak organlarda nükse neden olabilir. Antikanser tedavisi geliştirmenin bir sonraki adımı, bu tür kanser progenitör hücrelerinin ortadan kaldırılmasını hedeflemelidir. Ek olarak, ilaca dirençli küçük bir hücre klonunun varlığı, ele alınması zor olan başka bir karmaşıklığı ortaya çıkarmaktadır (81,82). Bu ilaca dirençli kanser hücreleri, belirgin bir remisyondan sonra kanserin nüksetmesine de katkıda bulunur. Kanser progenitör hücrelerinin veya ilaca dirençli kanser hücrelerinin ilaç direnci oluşturmaya ne kadar katkı sağladığını belirlemek güç bir konudur. Bu nedenle, ilaç direncinin altında yatan mekanizmaları anlamak ve mevcut tedavilere artık duyarlı olmayan kanseri tedavi edebilecek yeni yaklaşımlar belirlemek önemlidir. Epigenetik değişikliklerin, ilaç direncine neden olabildiği gibi kanser hücrelerini diğer ilaçlara duyarlı hale getirebiliyor olduğunun gözlenmesiyle ilaca dirençli kanserlere yaklaşım ve tedavi stratejileri yeni bir boyut daha kazanmıştır (83,84,85).

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