Bölüm
2

AKCİĞER KANSERİNDE GENETİK VE EPİGENETİK DEĞİŞİKLİKLER

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GİRİŞ

Akciğer kanseri kansere bağlı ölümlerin en sık nedenidir(1). Tüm evreler için tanıdan sonra 5 yıllık beklenen yaşam oranı %18dir(2). En sık etyolojik neden sigaradır(3). Dünya Sağlık Örgütü (DSÖ) klasifikasyonuna göre 2 major gruba ayrılır:1. Küçük hücreli dışı akciğer kanseri(KHDAK)(%85)2. Küçük hücreli akciğer kanseri(KHAK)(%15). KHDAK skuamöz hücreli akciğer kanseri, akciğer adenokanseri ve büyük hücreli subtiplerine ayrılır(4). Konvansiyonel sisplatin bazlı kemoterapiler ile beraber antianjiojenik ajanların kullanımı ılımlı bir yarar sağlarmıştır(5). Bununla beraber tirozin kinaz inhibitörleri(EGFR mutasyonu, ALK ve ROS rearanjmanı)ile klinik sonuçlar %15-20 daha iyileşmiş olup anti-PD-1/PDL-1 töropatik antikorlar ile immunoterapi KHDAK tedavisinde başarılı sonuçlar doğurmuştur (6-9). Bununla beraber primer ve sekonder ilaç direnci tedavi başarısızlığına yol açar(10,11). Akciğer karsinogenezini açıklamak için çok aşamalı sıralı genetik ve epigenetik anormalliklerin birikimi en önde gelen hipotezdir. Bu süreçte epigenetik biyomarkırlar göz önüne alındığında doku ve vücut sıvılarındaki tespiti erken tanıda değerli olabilir (12).

Epigenetik değişiklikler anormal DNA metilasyonu (hipo veya hipermetilasyon), histon modifikasyonları ve non-koding RNA regülasyonlarıdır(13).DNA dizisinde değişiklik olmadan gen ekspresyonunda gelişen kalıtımsal değişikliklerdir(14). Epigenetik mekanizmalar geri dönüşümlü ve geçici olabilmektedir. DNA metilasyonu en çok araştırılmış epigenetik değişikliktir. DNA metilasyonunun bilinen en önemli iki görevi gen ifadesinin baskılanması ve genomun yapısal bütünlüğünün korunmasıdır. DNA dizisinde bulunan sitozin ve guanin bazlarının bir araya geldiği alanlar CpG adaları olarak adlandırılır. CpG adaları tüm genom-

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dir(58). Preklinik çalışmalar göstermiştirki DNMTİ ve HDAC tümör immunitesini güçlendirir ve immun cevabı arttırır(59-65). Günümüzde birçok çalışma konvansiyonel kemoterapi veya immunoterapi ile epigenetik ilaçların kullanımını test etmektedir(66).

Epigenetik moleküller KHDAK 'de kemoterapi tedavisine yanıtı ön görmede belirteç olarak kullanılabilir. Böylece uygun rejimler için hastaları sınıflamak, cevap olasılığı yüksek olanlarda bu tedavileri vermek ve yarar vermeyecek ilacın toksisitesinden korunma amaçlı kullanılabilir. MiR-181b overekspresynu sonucu bcl-2 proteini azalır ve çoklu ilaç dirençli akciğer kanserinde hücreleri sisplatin kaynaklı apopitoza duyarlaştırır(66).

Akciğer kanseri gelişiminde ortaya çıkan onkomirlerin ve tümör baskılayıcı akviteye sahip miRNA'ların ekspresyon profillerin daha iyi anlaşılması, miRNA temelli tedaviler için oldukça aydınlatıcı olacaktır. Şimdilik erken dönemde preklinik calışmalar gelecek için umut vaat etmektedir.

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