Bölüm
16

TÜMÖR MİKROÇEVRESİ

Elif POLAT[1]

GİRİŞ

Tümör mikroçevresi (tumor microenvironment; TME), kanser dışı hücreler ve bunların stromalarından oluşan, kanserin büyümesini etkileyen önemli bir faktör olarak kabul edilir. Mikroçevre ve orada yer alan hücreler arasındaki çift yönlü iletişim, hem tümör büyümesi hem de normal doku homeostazı için önem arzeder[1]. Özellikle, tümör hücreleri ve tümörle ilişkili stroma arasındaki etkileşimler, hastalığın başlangıcını, ilerlemesini ve prognozunu etkileyen güçlü bir ilişki ile sonuçlanır[2]. Kanser, önceleri tümör hücrelerinde anormal mutasyonlar içeren heterojen bir hastalık olarak görülmesine rağmen, daha sonraları tümörlerin aynı zamanda mikro-çevresel oluşumlarının doğası ve stromal hücre oranları veya aktivasyon durumları gereği çeşitlilik gösterdiği bilinir[3, 4].

Tümör ve mikroçevre arasındaki etkileşimlerle ilgili ilk çalışmalardan biri, Rudolph Virchow tarafından 1863 yılında lökosit infiltrasyonunun solid tümörlerde karakterize edildiğini ortaya koymasıyla gerçekleştirildi[5]. Steven Paget[6] 1889'da meme kanseri metastazının organ tercihlerini analiz ederken, metastatik kolonizasyonun organın özelliklerine bağlı olduğunu göstermiştir. Bu prensip ayrıca primer tümörler ve mikroçevre arasındaki ilişkinin temelini oluşturur ve tümör evrimini etkiler[7]. Paget, bu nedenle tümör mikroçevresi kavramının öncüsü olarak bilinir[8]. TME araştırmaları 1970'lerden sonra artık tümör hücrelerinden türetilen sinyallere yanıt olarak TME'nin kanserin ilerlemesini aktif olarak etkilediği kabul edilir.

Tümor stroması, kan ve lenfatik dolaşım sistemleri, perisitler, fibroblastlar/miyofibroblastlar, glial, epitel, adiposit, vasküler, düz kas, bağışıklık hücrele-

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zal membran, kollajenler, glikoproteinler, hiyalüronan, glikozaminoglikanlar, lamininler, proteoglikanlar, büyüme faktörleri ve kemokinlerinden oluşmaktadır. ECM hücresel yapılara destek sağlar. Ayrıca ECM bileşimindeki değişikliklerin metastazda da önemli bir rol oynadığı düşünülmektedir[100].

TME'DE TERAPÖTİK YAKLAŞIMLAR

Kansere karşı birçok terapötik yaklaşım, tümör hücrelerinin çeşitli yönlerini hedeflemeyi amaçlar. Ayrıca TME'de bulanan stromal hücreler tümör hücrelerine göre genetik olarak stabildir. Bu yüzden klasik terapötik direnç mekanizmalarına karşı daha az duyarlı oldukları bilinir. Çeşitli anjiyogenez inhibitörleri ve stroma hücrelerini tüketmeyi hedefleyen tedaviler[88], TME'nin protümörjenik etkilerini ortadan kaldırdıkları için yararlı olamamaktadır. TME-yönelimli tedavilerin ortaya çıkan diğer bir örneği, tümör ile ilişkili kronik inflamasyonu nötralize etmeye yöneliktir[101]. Bu amaçla hedeflenen hücre tipleri arasında, CSF-1R, CCR2 ve CXCR2 sayılabilirken sinyal moleküllerinden de bağışıklık hücresi fonksiyonunu sağlayan NF-κB yolağı veya anahtar sitokin yollarının inhibisyonunu bloke eden stratejilerden söz edilebilir[102].

SONUÇ

Hücreler, yapısal proteinler ve sinyal moleküllerinden oluşan tümör stromasının; tümör başlangıcı, ilerlemesi ve metastazında merkezi bir rol oynadığı kabul edilmektedir. Bu nedenle tümör mikroçevresindeki kanser hücreleri ve stromal hücreler arasındaki etkileşimin belirlenmesi gelecekte kanser tedavisine büyük katkılar sağlayabilir.

Anahtar Kelimeler: Tümör mikroçevresi, stroma hücreleri, kanser, hücre dışı matriks, metastaz

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