BÖLÜM

4

Diferansiye Tiroid Kanseri Gelişim Mekanizmaları

- Prof. Dr. Didem ÖZDEMİR
- Prof. Dr. Bekir ÇAKIR

Özet

Diferansiye tiroid kanserlerinin (DTK) gelişimi günümüze kadar üç farklı mekanizma ile açıklanmaya çalışılmıştır. Bunlardan ilk ortaya atılmış olan çok basamaklı karsinogenez modelinde bazı genetik değişiklikler ve çevresel etkenlerle papiller tiroid kanseri (PTK) veya folliküler tiroid kanseri (FTK) geliştiği, bu tümörlere eklenen farklı genetik değişikliklerle de az diferansiye veya anaplastik tiroid kanserine dönüştükleri kabul edilmektedir. Kanser kök hücre modelinde küçük bir hücre grubunun tümörün oluşmasına, büyümesine ve yayılmasına neden olduğu öne sürülmektedir. Bu hücreler diğer kök hücrelerin özelliklerini taşırlar ve belirgin bir kendini yenileme, tümör büyümesini devam ettirme kapasiteleri vardır. Üçüncü model tiroid kanserinin olgun folikül hücrelerinden değil fetal hücre kalıntılarından köken aldığı modeldir. Fetal hücre karsinogenez adı verilen bu modelde anaplastik tiroid kanserinin fetal tiroid kök hücrelerden, PTK'nın tiroblastlardan ve FTK'nın protirositlerden kaynaklandığı savunulmaktadır. Hücre, hayvan ve insan çalışmalarında her üç modeli de destekleyen veya karşı çıkan bulgular elde edilmiştir. Bütün bu modellerde spontan veya çevresel uyarılarla oluşan genetik ve epigenetik değişikliklerin tiroid kanser gelişiminde ve ilerlemesinde anahtar rol oynadığı kabul edilmektedir. Foliküler hücrelerin proliferasyonunu, diferansiyasyonu, migrasyon ve apoptozunu etkileyen bu genetik değişiklikler en sık mutasyon ve yeniden düzenlenme şeklinde görülmektedir. BRAF ve RAS mutasyonları, RET/PTK yeniden düzenlenmesi ve PAX8/PPARγ gen füzyonu DTK gelişimde rol oynayan en sık genetik değişikliklerdir. Bunların dışında tiroid kanserlerinde gen amplifikasyonları ve kopya sayı kazanımları, anormal gen metilasyonları ve farklı mikroRNA profilleri de bildirilmiştir. Genetik değişiklikler mitogen-activated protein kinases-extracellular regulated kinase (MAPK) ve fosfotidilinositol 3-kinaz (PI3K-AKT) sinyal yolakları başta olmak üzere birçok farklı hücre içi sinyal yolağı üzerinden tümör gelişimi ve ilerlemesine neden olabilir.

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