Bölüm
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ANTİ HORMONAL TEDAVİLERE KARŞI GELİŞEN DİRENÇ MEKANİZMALARI

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GİRİŞ

Meme kanseri, kadınlarda en sık görülen kanserdir. Olguların yaklaşık %5-10'u tanıda metastatiktir ve erken evre hastalığı olan hastaların %30'una yakını metastatik hastalık ile nüks eder [1]. Meme kanseri vakalarının yaklaşık %70'i östrojen reseptörü (ER), progesteron reseptörü (PR) ya da her ikisini birden eksprese ederler ve hormon reseptörü pozitif (HR+) olarak adlandırılırlar [2]. Hormonal tedavi, erken evre meme kanseri tedavisinin temelini oluşturmaktadır. Fakat hastaların önemli bir kısmı primer veya sekonder endokrin direnç geliştirerek daha yeni tedavi seçeneklerine ihtiyaç duymaktadır [3].

ÖSTROJEN RESEPTÖRÜNÜN YAPISI

ER hariç steroid ailesinin çoğu reseptörü, klasik olarak "translokasyon reseptörleri" olarak görülür. Yani, hormon yokluğunda temel olarak sitoplazmik olarak dağılmış durumdan, hormonla uyarılmış hücrelerde ağırlıklı olarak nükleer bir lokalizasyona geçiş olur. Bununla birlikte, ER, hem hormon varlığında hem de yokluğunda ağırlıklı olarak nükleer lokalizasyonda görünmektedir. ER ligand bağımlı bir transkripsiyon faktörü olarak çalışır; ER'nin ligand bağlama alanına östrojenin bağlanması, ER'nin hedef genlerin promotöründeki östrojen yanıt elemanlarına (ERE) doğrudan bağlanmasına veya ilgili promotör bölgelerinde diğer transkripsiyon faktörleriyle protein-protein etkileşimine yol açar [4-7]. Daha sonra, hormon reseptör kompleksi, östrojen spesifik yanıt elemanlarına bağlanarak genlerin ekspresyonunu aktive eder veya baskılar. Böylelikle hormonun fizyolojik etkilerinden sorumlu olan protein ürünlerinin sentezleri düzenlenir. ER, nükleer reseptör süperailesinin diğer üyeleri ile birçok yapısal özelliği paylaşmaktadır. ER,

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