

## BÖLÜM 13

# MAKROLİDLERE VE LİNKOZAMİDLERE DİRENÇ MEKANİZMALARI

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### Giriş

Yapısal olarak ilgileri olmayan ancak etki ve direnç mekanizmaları yönünden benzerlik gösteren makrolidler ve linkozamidler bakteriyel ribozomun 50S alt birimini hedef alan bakteriyostatik etkili antibiyotiklerdir. Makrolid grubu antibiyotikler, 65 yılı aşkın süredir klinik kullanımda olan en eski antimikrobiyal ajanlar arasındadır (1). Bu grubun en iyi bilinen üyesi olan eritromisin, 1952 yılında *Saccharopolyspora erythraea* (eski adıyla *Streptomyces erythraeus*)’dan elde edilmiştir (2). Kimyasal yapı olarak 14 üyeli makrolakton halkasına sahip olan eritromisinden türetilen diğer makrolidler arasında klaritromisin, diritromisin, roksitromisin ve nitrojen eklenmesiyle oluşmuş 15 üyeli bir halkaya sahip olan azitromisin yer alır. Klinik kullanımı olan spiramisin, josamisin, midekamisin ve miokamisin gibi 16 üyeli halkaya sahip makrolidler de mevcuttur (3). Makrolidler, bakteriyel ribozomlara olan yüksek afinitesi nedeniyle geniş spektrumlu etkiye sahip olsalar da esas olarak Gram-pozitif bakterilere karşı etkinlik gösterirler (4).

Linkozamidler, linkomisin, klindamisin ve pirlimisin olarak kullanımda olan L-prolinden ve bir amid bağıyla bağlanan şekerden oluşur. Çoğu anaerobik bakteriye, stafilokok ve streptokoklara etkilidirler (5).

### Direnç Mekanizmaları

Makrolidlere karşı artan direnç, bunların Gram-pozitif bakteriyel enfeksiyonların tedavisinde yaygın olarak kullanılmalarının bir sonucudur ve genellikle linkoza-

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Stafilokok izolatlarında linkozamidlerin eflüks pompa direnci, *lsa* benzeri proteinlerin aracılık ettiği fenotipe benzer düşük seviyeli bir dirençten sorumlu ABC proteinlerini de kodlayan *vga* gen ailesine ait plazmid genlerinin edinilmesinden kaynaklanır. Bu gen ailesinde ABC-F proteinlerini kodlayan *vgaA*, *vgaA* (V), *vgaA* (LC) ve ek olarak *vgaB*, *vgaC*, *vgaE* ve *vgaE* (V) genleri tespit edilmiştir. Hepsinin substrat spektrumu streptogramin A antimikrobiyal ajanlarını içerirken, *vgaB*'nin dışındakilerinin substrat spektrumu ayrıca linkozamidleri ve pleuromutilinleri de içerir (5). *Sala* geni ise ABC-F protein ailesinin başka bir üyesini temsil edebilen bir ABC proteinini kodlar (34). Başlangıçta *S. sciuri* kromozomal DNA'sında tanımlanmıştır ve linkozamidlere ve streptogramin A bileşiklerine direnç kazandıran bir gen olarak bildirilmiştir (44). *Sala* genlerinin çevresinde insersiyon dizileri veya transpozonlar gibi gen transferinde rol alan hiçbir element tanımlanmamıştır. Ancak yapılan çalışmalarda stafilokokların üç farklı türünde bu genlerin tanımlanması, yatay bir gen transferini düşündürmüştür (5).

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