

## Bölüm 2

# KRONİK HASTALIKLARDA POTANSİYEL BİYOBELİRTEÇ OLARAK CircRNA'LAR

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### GİRİŞ

Kodlayıcı olmayan RNA'lar (ncRNA'lar) ökaryotlarda gen ifadesinin düzenlenmesi ve protein sentezinde önemli rol oynar (1). Uzun kodlayıcı olmayan RNA'lar (lncRNA'lar) sınıfında yer alan dairesel RNA'lar (circRNA'lar), poli-A kuyruğu ve 5' başlığı bulunmayan, iki ucu kovalent olarak kapalı, dokuya özgü ifadesi olan endojen RNA'lardır (2-4). CircRNA'lar, ilk keşfedildiklerinde mRNA'ların uçbirleştirme (splicing) ile işlenmesi esnasında ortaya çıkan yan ürünler olarak düşünülmüştür (5). Yüksek ölçekli RNA dizileme ve biyoinformatik araçların gelişmesi ve yaygınlaşması ile circRNA'ların biyogenezi, işlevleri ve özgünlüğü hakkında çok sayıda güncel verinin üretilmesi sağlanmıştır (6, 7). Şimdiye kadar, prokaryotlar, tek hücreli ökaryotlar, balıklar ve memeliler olmak üzere farklı canlı türlerinin tümünde circRNA'ların varlığı gösterilmiştir (8-11).

CircRNA'lar, bilindik uçbirleştirme ile işlenen mRNA'lardan farklı olarak, tersine uçbirleştirme (back-splicing) mekanizması ile 5' ve 3' uçların kovalent olarak birleştirildiği kimyasal bir süreç ile üretilmektedir. Köken aldıkları genlerin transkripsiyonu esnasında RNA polimeraz II (Pol II) tarafından sentezlenirler (12, 13). Öncü-mRNA'dan köken aldıkları dizi içeriğine göre circRNA'lar genel olarak üç kategoride sınıflandırılmaktadır (Şekil 1'de); eksonik circRNA'lar (ecircRNA'lar), intronik circRNA'lar (ciRNA) ve ekson-intron circRNA'lar (ElciRNA'lar) (14). Lokalizasyonları görev aldıkları yere göre değişiklik göstermektedir. Bazıları çekirdekteki süreçlere katılırken bir kısmı sitoplazmada hedef molekülleri ile etkileşime geçmektedir; bununla birlikte eksozomlar aracılığı ile vücut sıvılarına ve diğer hücrelere aktarılan circRNA'lar da bulunmaktadır (15, 16) Henüz

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arasından circ\_0005008 ve circ\_0005198'in ifadelerinin istatistiksel olarak en anlamlı ifade farklılığı sergilediği belirlenmiştir. Sonrasında sistemik lupus eritematozus (SLE) ve sağlıklı bireylere göre RA hastaların plazmasında circ\_0005008 ve circ\_0005198'in ifadesinin daha yüksek olduğu tespit edilmiştir (112). RA hastalarında yapılan benzer çalışmada, 24 RA hastası ve 24 sağlıklı bireylerin PBMC hücrelerinde RT-qPCR analizi ile 6 circRNA (hsa\_circ\_0082689, hsa\_circ\_0087798, hsa\_circ\_0000175, hsa\_circ\_0008410, hsa\_circ\_0049356 ve hsa\_circ\_0032959) tespit edilmiştir. Sağlıklı bireylere göre RA hastalarının PMBC hücrelerinde hsa\_circ\_0000175 ve hsa\_circ\_0008410'un istatistiksel olarak en anlamlı ifade farklılığına sahip oldukları tespit edilmiştir. Devamında yapılan geniş kapsamlı kohort çalışmaları sonucunda sağlıklı bireyler ve diğer romatizmal rahatsızlık bulunan hastalara göre RA hastalarında hsa\_circ\_0000175 ve hsa\_circ\_0008410'un ifadelerinin yüksek olduğu belirlenmiştir (113).

## **SONUÇ**

Kardiyovasküler hastalıklar, kanser, diyabet ve nörodejeneratif bozukluklar gibi çeşitli kronik hastalıkların moleküler patogeneze katılan genlerin ifadesini düzenleyen ve ilgili hücreyel yollardaki çeşitli moleküllerle doğrudan etkileşime giren birçok circRNA tanımlanmıştır. Hastalıkla ilişkili olarak ifade değişimi sergileyen bu circRNA'ların, aynı zamanda kararlı ve uzun ömürlü olmalarından dolayı sıvı biyopsilerde tespit edilebilir olduklarının gösterilmesi, circRNA'ları bu tür hastalıkların tanı ve tedavi süreçlerinin takibinde önemli bir biyobelirteç adayı yapmıştır. Şimdiye kadar birçok kronik hastalık için çok sayıda circRNA'nın bir biyobelirteç olarak kullanılabileceğinin gösterilmiş olması yakın zamanda bu moleküllerin hastalıkların takibinde kullanılabileceğine işaret etmektedir.

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