Bölüm
3

KARACİĞER MOLEKÜLER BİYOLOJİSİ İMMÜNOLOJİSİ, HEPATİT VE HEPATOSELLÜLER KARSINOMA

Sevgi KARABULUT UZUNÇAKMAK[3]

GİRİŞ

Karaciğer sindirim, detoksifikasyon, sıvı elektrolit dengesi, homeostazi gibi çok sayıda metabolik sürecin bir parçasıdır. Karaciğer görevleri sentezleme, safra üretme, detoksifikayon şeklinde sıralanabilir. Karaciğerin fonksiyonsuz kaldığı durumlarda toksin birikimi, koma ve ölüm gerçekleşir(1,2). Insan karaciğerinden portal ven ve hepatik arter aracılığıyla her dakikada 1.5 lt kan geçmektedir. Bu kanda hepatik immün sistemin tolere ettiği diet ile gelen antijenik yük ve genel ürünler bulunmaktadır.

Karaciğer, parenkimal hücrelerden (hepatosit) ve parenkimal olmayan (endotel hücreler, Kupffer hücreleri, lenfositler, stellat hücreler) hücrelerden oluşan kendini yenileyebilme kabiliyetine sahip nadir bir organdır. Hepatositler normal koşullar altında bölünmez hücre döngüsünün G0 fazında beklerler(3). Fakat karaciğer bütünlüğünü etkileyen ve karaciğerin normal ebatlarının küçüldüğüne dair bir uyarı almaları durumunda içerisinde bulundukları G0 fazından çıkıp hızla kaybolan hücrelerin yerine yenisini koymak üzere prolifere olurlar. Hepatositler, karaciğer kitlesinin %80'nini oluşturur. Çok miktarda mitokondri ve endoplazmik retikuluma sahip olan bu hücreler pıhtılaşma faktörleri, safra asidi, serum proteinleri gibi çok sayıda molekül üretmektedirler. Hepatositler içerdikleri detoksifikasyon enziminleri (p450) ile vücut metabolizması sonucu oluşan ya da vücuda alınan toksinlerin ayrışımını gerçekleştirir.

Dokular homeostaziyi koruyabilmek için ya var olan hücrelerin replikasyonunu sağlarlar ya da kök hücrelerin farklılaşmasını uyarırlar. Karaciğer küçüldüğüne dair bir uyarı aldığında homeostaziyi korumak için hem parakrin hem de otokrin yolla hücre sayısını arttırır. Hepatositler fonksiyonel heterojeniteye sahiptir. Farklı bölgelerdeki hepatositler farklı alt tip belirteçler eksprese eden en az üç tipe (periportal, midlobülar ve perisantral) ayrılmaktadır. Prolifere ve kendini yenileyebilen lobun merkez venine yakın hepatositler eksprese ettikleri *Tbx3, Axin2* Wnt/β-katenin hedef geni, gibi genler proliferasyon kapasitesinin diğer hepatositlerden fazla olduğunu gösterir(4). Hasarlanmamış karaciğerde azalan Wnt sinyalizasyonu azalan proliferasyon ve azalan organ kitlesiyle ilişkilidir(5). Periportal hepatositler SRY-box (Sox)9 gibi progenitor belirteçlere sahip olmalarının yanısıra safra kanalı spesifik genlerce ve hepatosit nükleer faktör (*Hnf)4α* gibi hepatosit spesifik transkripsiyon faktörlerince zengindirler. Bu hepatositler kronik hasar durumunda karaciğer kitlesini yeniden oluştururlar(6). Karaciğer lobülündeki hepatositler farklı genomik içeriğe de sahip olabilirler. Bu onların proliferasyon kapasitesini etkileyebilmektedir(4).

İmmün olgunlaşma ve farklılaşmaya bağlı olarak karaciğer bazı immünite ilişkili değişimlere de gitmektedir(7). Alınan antjenik uyarılara binaen karaciğer bünyesinde bulunan ya da oluşan sinyallere bağlı olarak karaciğere göç eden hücreler karaciğerin savunmasını sağlmaktadır-

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P53 yolağı, aflatoksin ilişkili HCC gelişimine birçok aşamada etki etmektedir. Aflatoksin ilişkili vakaların %50'nde p53 geni mutasyonları tespit edilmiştir. p14ARF mikrodelesyonu p53 mutant HCC vakalarında %15-20 oranında görülmüştür(185). Artan MDM2 ekspresyonu, gankyrin aşırı ekspresyonu HCC'li hastalarda sıklıkla görülen değişimlerdir(186).

Sonuç

Karaciğer, vücutta çok farklı görevleri yapan birden fazla fonksiyona sahip hayati bir organdır. Homeostazi için bu kadar önemli olması onun kendini koruması ve devam ettirebilmesi için ona hem fiziki hem de hücresel düzeyde avantajlar kazandırmıştır. Barındırdığı farklı türdeki hücrelerin yanısıra aynı hücrelerin farklı fonksiyonları yerine getirip multifonksiyonlu olması da kendi devamlılığının garantisi niteliğindedir. Çok sayıda sahip olduğu avantajlara rağmen genetik ve çevresel etkenler karaciğerde bazı hastalıklara sebep olmaktadır. Tüm hastalıklarda olduğu gibi karaciğerde oluşan hastalıkların temelinde moleküler mekanizmalardaki değişimler yatmaktadır. Gen ekspresyon değişimleri, yapısal bozulmalar, polimorfizmler, gen insersiyon ya da delesyonları birçok hastalıkta olduğu gibi karaciğerde de görülmektedir.

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