BÖLÜM 35

İNDÜKLENMİŞ PLURİPOTENT KÖK HÜCRELERİN (İPSC) ÇOCUK NÖROLOJİ PRATİĞİ İÇİN NADİR HASTALIKLARA MODELLEMESİ VE KÖK HÜCRE TEDAVİSİNDE YENİ UFUKLAR

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GİRİŞ

Çocukluk çağı nörolojik hastalıklarının altında yatan patofizyolojik mekanizmalar, insan patogenezini yansıtan uygun hastalık modellerinin bulunmaması nedeniyle belirsiz kalmıştır. Tür çeşitliliği ve nörolojik hastalıkların hayvan modelleri arasındaki farklılıklar nedeniyle, hayvan ve hücre kültürü hastalık modellerinin insan hastalıklarını doğru şekilde modelleyip modelleyemeyeceği tartışma konusudur. 2006 yılında Kyoto Üniversitesi'nden Takahashi ve Yamanaka embriyonik kök hücrelere (ESC'ler) benzer pluripotentlik potansiyeli sergileyen, indüklenmiş pluripotent kök hücrelerin (iPSC'ler) türetilmesini ilk kez raporladılar.[1] Günümüzde, iPSC çalışmaları hastalık araştırmalarının birçok sektörüne nüfuz etmektedir. Hasta numunesinden türetilen iPSC'ler, hastalık gelişiminin patojenik mekanizmalarını aydınlatmak ve yeni terapötik stratejileri test etmek için kullanılmaktadır.

RETT SENDROMU

Rett sendromu, neredeyse sadece kadınlarda görülen nörogelişimsel bir bozukluktur. Hastalığa, Xq28 ile eşleşen ve metil-CpG bağlayıcı protein 2'yi (MeCP2) kodlayan MECP2 genindeki patojenik varyantlar neden olur[1]. MECP2' deki patojenik varyantlar, klasik sporadik Rett Sendromu vakalarının yaklaşık yüzde 95'inden, atipik Rett Sendromu vakalarının ise yüzde 75'inden sorumludur[2]. Bunun dışında az sayıda hasta, CDKL5 veya FOXG1'deki patojenik varyantların neden olduğu atipik Rett Sendromuna sahiptir.[3,4] MECP2'deki patojenik varyantların hastalığa nasıl yol açtığı tam olarak belirlenememekle birlikte önde gelen hipotez, MeCP2 eksikliğinin korteksteki sinaptik maturasyon ve plastisitede bozulmaya yol açtığıdır.[5] Hastalığın tahmini prevalansı 100.000 kız çocuğunda 7,1'dir.[6]

Hastalığın klinik bulguları; yaşamın ilk 6-18 ayındaki normal bir nörolojik ve fiziksel gelişim dönemini takiben erken çocukluk döneminde ortaya çıkmaya başlar. Rett sendromunun karakteristik özellikleri; edinilmiş konuşma ve motor becerilerin kaybı, tekrarlayan el hareketleri, solunum düzensizlikleri ve nöbetleri içerir. Bunun dışında hastalar uyku bozuklukları, bruksizm, solunum anormallikleri, otonomik disfonksiyon, uygunsuz kahkaha veya ağlama gibi psödobulber semptomlar, azalmış ağrı tepkileri, sporadik gastrointestinal problemler, erken başlangıçlı

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birikmesinin neden olduğu en yaygın nörodejeneratif hastalıktır. Ailesel geçişli veya sporadik olabilir. Presenilin 1 (PS1) ve presenilin 2 (PS2) mutasyonları, otozomal dominant erken başlangıçlı ailesel AH'na neden olan faktörlerdir. Klinikte karşımıza tipik olarak 65 yaş üzeri bireylerde, sinsi başlangıçlı, yavaş ve progresif bellek bozukluğuna zaman içinde diğer kognitif alanlardaki bozuklukların da eşlik ettiği ve nihayet günlük yaşam aktivitelerindeki bağımsızlığın ve işlevselliğin bozulduğu bir tablo ile çıkar.[137] Olası AH demansının tanısına yönelik kriterler, Ulusal Yaşlanma Enstitüsü ve Alzheimer Derneği (NIA-AA) tarafından oluşturulmuş ve en son 2011'de güncellenmiştir.[138] Mevcut tedavilerin hiçbiri AH'nda bilişsel ve hafıza bozukluklarını iyileştirmede etkili değildir.[139]

İndüklenmiş pluripotent kök hücre (iPSC) teknolojisi, hastalıkları modellemek, hücresel mekanizmaları incelemek ve nörodejeneratif hastalıklar da dahil olmak üzere çeşitli hastalıklara karşı terapötik stratejiler oluşturmak için için kullanılabilir. Yagi ve ark. 2011 yılında PS1 ve PS2'de mutasyon bulunan ailesel Alzheimer's hastalarının fibroblastlarından iPSC'ler türettiler ve bu hücrelerin nöronlara farklılaşmasını sağladılar. Ailesel AH-iPSC'den türetilen farklılaşmış nöronların amiloid β42 salgısını arttırdığı raporlandı. Ayrıca mutant presenilinlerin moleküler patogenezi de incelendi. Çalışma sonucunda ailesel AH-iPSC'den türetilmiş nöronun geçerli AH modeli olduğu ve yaşa bağlı nörodejeneratif hastalıkların incelenmesi için yenilikçi bir strateji sağladığı gösterildi.[140] 2012 yılında Israel ve ark. hem ailesel hem sporadik Alzheimer's hastalarından alınan iPSC'lerden türetilmiş nöronlarla AH benzeri fenotipler oluşturdular.[141] Sporadik AH hatlarının dahil edildiği farklı bir çalışmada ise ailesel AH hücrelerine benzer hastalık fenotipleri gözlemlendi.[142] Sporadik geç başlangıçlı AH, vakalarının büyük çoğunluğunu temsil etmesine rağmen çok az sayıda çalışma sporadik AH çizgilerini içermektedir. Bu nedenle bu yönde pek çok çalışma başlatılmıştır ve büyük ölçekli insan genomu çalışmaları (GWAS) ile birleştirilerek varyantların sürekli olarak artan AH riskiyle ilişkili olduğu gen listeleri türetilmektedir.[143] 2015 yılında Young ve ark. iPSC'lerden türetilen nöronlarda sporadik AH ile ilişkili genetik varyantlardan kaynaklanan bir fenotipi tanımlayan ilk çalışmayı yayınladılar[144]. Yapılan çalışmalar ışığında iPSC'lerden AH benzeri fenotipler geliştirilerek, AH tedavilerine yönelik klinik öncesi ilaç denemelerinde hızlı ilerleme kaydedilmektedir. Bu hücresel modellerden en iyi şekilde yararlanmak için, tüm deneylerin farklı araştırma grupları arasında tekrarlanabilirliğe izin verecek şekilde, kontrollü ve standart yöntemlerle yapılması çok önemlidir.

Gelecekte, fizyolojik mikro ortamda birden fazla nöral hücre tipini ve vaskülarizasyon tekniğinin gelişmesiyle birlikte kan-beyin bariyeri penetrasyonunu da içerebilen sitosistemlerle, tedavi araştırmaları yapmak mümkün olacaktır.

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