BÖLÜM 2

COVID-19 İMMÜNOLOJİSİ

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DOĞAL BAĞIŞIKLIK: SARS COV-2'YE KARŞI İLK SAVUNMA HATTI

SARS-CoV-2'nin hücreye girişi ve patern tanıma reseptörleri tarafından algılanması

SARS-CoV-2 (Ağır Akut Solunum Sendromu Koronavirüsü-2/Severe Acute Respiratory Syndrome-Coronavirus-2) *Coronaviridae* ailesi içerisinde Betakoronavirüs cinsinin bir üyesidir. SARS-CoV-2'de spike (S), membran (M), zarf (E) ve nükleokapsid (N) olmak üzere dört yapısal protein bulunmaktadır. S proteini viryon yüzeyindeki peplomerleri oluşturan Tip 1 glikoproteindir. E proteini hidrofobiktir ve M proteini sitoplazmik bir kuyruk ile kısa bir N terminal domaini içerir. Virüs ayrıca viral patogenezde çeşitli rollere sahip yardımcı proteinleri kodlayan birkaç açık okuma çerçevesi (ORF) üretir (1). Çoğu konak hücrenin enfeksiyonu için SARS-CoV-2 S proteini, ana hücresel reseptörü olan anjiyotensin dönüştürücü enzim 2'ye (ACE2) bağlanır. Ek olarak, konak hücrelerdeki bir serin proteaz olan TMPRSS2 (transmembran proteaz serin 2), S proteininin reseptör etkileşimleri ve hücreye giriş için önemlidir (2). Nöropilin-1, heparan sülfat proteoglikanları, C-tip lektinler veya furin gibi diğer konak proteinleri viral giriş için kofaktörler olarak etki edebilir (3). Hücrelere S proteininin bağlanmasının ardından viral ve konak membranları birleşebilir ve viral genomik RNA direkt olarak sitoplazmaya salınır. Alternatif olarak, bazı hücrelerde SARS-CoV-2 endozomlar içerisine alınır ve düşük pH ile tetiklenen katepsin aracılı bölünmenin ardından sitoplazma içerisine nükleokapsid girişini kolaylaştırmak için viral membranlar, endozomal membran ile birleşir (4). Sitoplazma içerisinde, SARS-CoV-2 genomik RNA'sı poliprotein (pp)1a ve pp1ab gibi iki büyük

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Makrofajlar, virüsleri doğrudan Toll benzeri reseptörler veya Fc reseptörleriyle immün kompleksler aracılı tespit edebilir. İmmün komplekslerin tanınması, makrofaj aktivasyonunu ve viral klirense katkıda bulunan efektör moleküllerin salınmasını tetikler. İmmün komplekslerin hızlı temizlenmesi, immün homeostaz ve inflamasyonun rezolüsyonu için kritik öneme sahiptir (169). Fc-reseptör sinyal aksında insanlar arasında önemli fonksiyonel heterojenite vardır. Son araştırmalar, şiddetli COVID-19'lu kişilerde fukoz kalıntısının yokluğu (afukozilasyon) ile karakterize edilen Fc alanlarının spesifik modifikasyonunu ortaya koymuştur. Afukozile edilmiş SARS-CoV-2 antikorlarının, COVID-19 sonrası sendromlu hastalarda aşırı inflamatuvar yanıta katkıda bulunması da olasıdır ve afukozile edilmiş IgG antikorlarının seviyelerinin ölçülmesi, COVID-19 sonrası sendrom riski taşıyan hastaların belirlenmesine yardımcı olabilir (170).

COVID-19 sonrası kalıcı semptomlara katkıda bulunabilecek bir başka immün düzensizlik yanıtı, virüs ortadan kaldırıldıktan sonra da devam eden kendi doku antijenlerine karşı zarar verici otoimmün bir yanıtın gelişmesidir. Parvovirüs B19, Epstein-Barr virüsü, Sitomegalovirüs, İnsan Herpes Virüsü-6, İnsan T Hücresi Lenfotropik Virüsü Tip 1, Hepatit A ve Hepatit C virüsü ve kızamıkçık virüsü dahil olmak üzere bir dizi viral enfeksiyondan sonra otoimmünitenin indüklenmesi söz konusudur (171). Önerilen mekanizmalar arasında moleküler benzerlik, self toleransın bozulması ve poliklonal aktivasyon yer alır. Otoantikorlara ek olarak, otoreaktif T hücrelerinin de doku hasarına ve post-COVID sendromuna katkıda bulunması mümkündür (172, 173).

Post-COVID sendromu olan hastalara anti-SARS-CoV-2 aşılarının uygulanmasıyla ilgili klinik semptomlarda iyileşme raporları, post-COVID sendromu olan hastalarda bir viral rezervuar olduğu yönünde kanı oluşturmuştur (140). Ayrıca, COVID-19'dan iyileşen hastalarda, bellek B hücre havuzu, enfeksiyondan altı ay sonra bile klonal dönüşüm göstermeye devam etmekte ve oluşturdukları antikorlar daha fazla somatik hipermutasyona, reseptör bağlanma alanı mutasyonlarına karşı dirence ve yüksek potansiyele sahiptir (104).

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