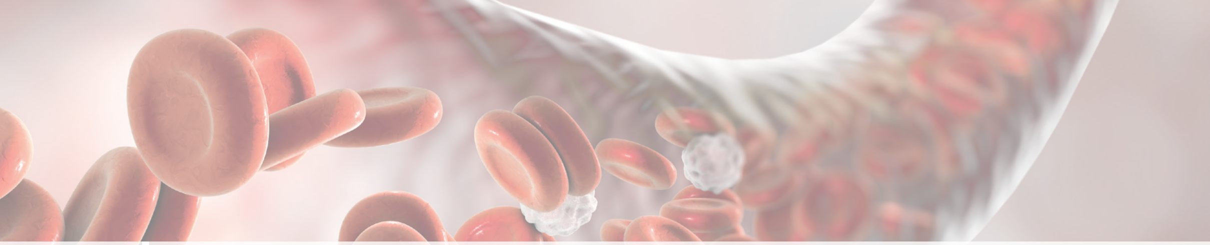

3. Bölüm

İSKEMİ VE REPERFÜZYONUN TEMEL MOLEKÜLER MEKANİZMALARI

Orhan CANBOLAT[1]

3.1. Özet

Beyin, kalp, karaciğer, böbrek ve ince bağırsaklar gibi organlarda birçok patolojik duruma bağlı olarak ortaya çıkan iskemi ve reperfüzyon (İ/R) tablosu birçok moleküler sistemi indükleyerek hücresel hasara ve organların fonksiyon kaybına yol açabilmektedir. İ/R süreçlerinde en temel problemler; hücre veya organel membranlarının geçirgenliğinde ve fonksiyonlarında bozulma, organellerin hasara uğramasına bağlı olarak ortaya çıkan hücresel fonksiyonların geri döndürülememesi ve bu süreçlere bağlı olarak ortaya çıkan moleküler mekanizmaların hücresel hasara yolaçması olarak tanımlanabilir. İ/R'da ortaya çıkan hücresel problemler hasara sebep olan patolojilerin şekli, tutulan organın farklılığı, İ/R'un süresi gibi birçok faktöre bağlı olabilir. İ/R hasarı için birçok moleküler mekanizma tanımlanmış olmasına rağmen ortaya çıkan moleküler patolojilerin temelinde hücre için gerekli olan temel moleküllerin, oksijenin sağlanamaması ve ATP sentezinin bozulması veya yıkımının artışı yatmaktadır. İ/R süreçlerinde yer alan temel moleküler mekanizmalar içerisinde; Ksantin oksidaz (KO), nikotinamid adenin dinükleotid (NADH) oksidaz, myeloperoksidaz (MPO) ve nitrik oksit sentaz (NOS) enzim aktivitelerinde artış, Mitokondri ve Endoplazmik Retikulum (ER)'da meydana çıkan metabolik değişiklikler, aktive edilmiş kupffer hücrelerinden ve nötröfillerden reaktif oksijen türleri (ROS), sitokinlerin salınımı, nötröfillerin endotel adezyonu ve lensositlerin aktivasyonu önem taşımakta-

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mektedir (254,255). Bununla birlikte, otofajinin, özellikle iskemik süre uzamışsa, İ/R'da hala zararlı bir rol oynayabileceği belirtilmelidir. Bu nedenle, otofaji aslında bir hücre ölümü sürecinden ziyade bir hücre hayatta kalma mekanizmasıdır. Bununla birlikte, kontrolsüz otofaji sonuçta hücrenin ölümüne yol açacaktır ve İ/R hasarına katkıda bulunabilir. Atg proteinleri ve light-chain 1(LC-1) arasındaki etkileşim, otofagozomların oluşumunu teşvik eder. Otofagozomlar, otofajiyi tetiklemek için lizozomla birleşir. Morfolojik olarak otofaji, işlenecek hücre bölmesi çevresinde bir izolasyon zarının veya fagoforun genişlemesi ile başlar (256,257). Membran daha sonra veziküler otofagozomu oluşturmak için bileşenleri tamamen sarar, bu daha sonra bir lizozomla birleşir bu oluşum, vps34, vps15 ve Beclin 1 (BECN 1) adı verilen bir sınıf III PI3K'dan oluşan başka bir kompleks tarafından daha da kolaylaştırılır. Otofagozomun lizozoma füzyonuna küçük GTPaz Rab7 ve lizozomal membran proteini lysosome-associated membrane protein 2 (LAMP2) aracılık eder (256-258). Hem iskemi hem de reperfüzyonun, otofagozom-lizozom füzyonu için önemli olan LAMP 2'de düşüşe yol açtığını göstermektedir. Reperfüzyonla indüklenen ROS ayrıca otofagozom oluşumunu uyaran, ancak otofaji-lizozom mekanizmasının transkripsiyonel inhibisyonuna neden olan artan BECN 1 bolluğunu tetikler. Bunlar birlikte, otofagozom klirensinde belirgin bozulmaya ve sonuçta ortaya çıkan otofagozom birikimine ve hasarlı hücresel bileşenlerin uzaklaştırılmasına neden olur (259). İ/R sürecinde otofaji konusu daha fazla araştırılması gereken konular içerisindedir.

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