Bölüm 1

MİTOKONDRİYAL KATLANMAMIŞ PROTEİN YANITI VE KANSER

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GİRİŞ

Kanser hücreleri kontrolsüz bir şekilde çoğaldıkça, aynı zamanda kendileri için de dezavantaj oluşturacak bir dizi olumsuzluğun ortaya çıkmasına neden olur. Bu nedenle kanser hücreleri, kendilerinin neden olduğu olumsuzluklara karşı kendilerini koruyacak ve/veya daha az etkileyecek savunma sistemlerine ihtiyaç duyarlar (1). Özellikle mitokondriler, kanserin farklı aşamalarında büyümeye ve hayatta kalmaya katkı sağlar (2). Ancak mitokondriler aynı zamanda genetik değişikliklere uğrar ve bozulmuş bir elektron taşıma zinciri oluşturur. Bu da aşırı miktarda mitokondriyal reaktif oksijen türleri (mtROS) üretilmesine neden olur (3, 4). Normal koşullarda ve hastalığın erken evrelerinde, mitokondriler hücresel büyüme ve hayatta kalma için faydalı olan ılımlı düzeylerde mtROS üretirler. Ancak mitokondriyal bozukluklar arttıkça, mtROS seviyeleri tolere edilebilir eşiği aşabilir ve tümör hücreleri için ölümcül hale gelebilir (5, 6). mtROS, mitokondriyal katlanmamış proteinlerin açığa çıkmasını ve bir araya gelmesini teşvik ederek, mitokondrileri giderek daha kırılgan ve işlevsiz hale getirir (3, 7). Mitokondriyal katlanmamış protein yanıtı (mtUPR), *C. elegans* ve memeli sistemlerinde gözlemlenen bir mitokondriyal stres yanıtıdır (8, 9). Kanserde mitokondriyal bütünlüğü koruyarak ve tümör büyümesini teşvik ederek önemli bir destek sistem olarak görev yapar (10). mtUPR, mtROS' un zararlı etkilerini hafifletmek için bir dizi şaperon ve proteazı harekete geçirir. Artan kanıtlar, mtUPR genlerinin *C. elegans* ve memeliler arasında korunduğunu göstermektedir (11).

Bu bölümde mtUPR' nin tümör büyümesi ve ilerlemesini desteklemede mitokondrilerin işlevsel bozukluğunu önleme yeteneği ele alınmaktadır. mtUPR' nin mitokondriyal sağlığı koruma yeteneği incelenerek, mtUPR bileşenlerinin bireysel işlevleri, klinik sonuçlarla olan ilişkileri ve tümörü teşvik edici rolleri

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yüksek derecede bağımlı olduğunu açıkça göstermektedir (153, 154). Bu nedenle, prostat kanseri gibi agresif ve dirençli kanserlere karşı yeni terapiler geliştirmek için önemli bir hedef olduğu söylenebilir.Formun Üstü

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