KANSER METABOLİZMASI

13. BÖLÜM

Ayşe Kutluhan DOĞAN[1]

GİRİŞ

Kanserler, hücrelerin normal doku gelişiminin haricinde meydana gelen proliferasyonlarla sonuçlanan mutasyonlar kazandığı hastalıklardır. Bu somatik mutasyonlar, çevrelesel etkileşimlerle hücre dönüşümüne sebep olurlar. Bu çevre; genetik, yaşam tarzı, diyet, fizyoloji, immün sistemin durumu ve tümör hücrelerinin mikro ortamı gibi çok sayıda faktör tarafından belirlenir ancak bunlarla sınırlı değildir. Genler ve çevre arasındaki bu etkileşimin bağlantı noktasında da **hücresel metabolizma** bulunur.

Metabolizma, enzimlerin aracılık ettiği birbirine bağlı bir dizi kimyasal reaksiyonu içerir. Diyet ile makro besinler olarak alınan karbonhidratlar, yağlar ve proteinler, hücresel düzeyde glukoz, lipitler ve amino asitler olarak alınır ve daha sonra metabolik ağı oluşturan bir dizi birbirine bağlı kimyasal reaksiyonla dönüştürülürler. Bu besinler elektron açısından zengin indirgenmiş formlarında saklanır ve katabolizma olarak bilinen süreç boyunca oksitlenir. Bu oksidatif süreçlerde elektronların serbest bırakılması ile, yaşamın devamını sürdürebilmek için gereken enerji üretilir. Metabolizma ayrıca katabolizmanın ara maddelerinin yapısal bileşenlere ya da protein, nükleik asit, hücre membranı yapımında kullanılan malzemelere dönüştürülmesine de izin verir. Buna **anabolizma** veya **anabolik metabolizma** denir. Metabolizma, proteinler ve nükleik asitlerle doğrudan reaksiyona giren ve onların aktivitesini değiştiren moleküller üreterek hücresel mekanizmanın diğer unsurlarıyla doğrudan iletişim kurabilir.

Kontrolsüz proliferasyonu sürdürebilmek için, bütün bu metabolik fonksiyonlara adapte olabilme yeteneği malignitenin herbir aşamasının yaygın özelliğidir. Gerçekten de, farklı metabolik gereksinimler anoikiz, invazyon ve metastaz gibi kanserle ilişkili her süreçte kendini gösterir. Bu metabolik programlama, hem farklı metabolik süreçleri yönlendiren onkojenik sinyallerden hem de doku vaskülaritesi ve serum besin içeriği gibi çevresel faktörlerden ileri gelir. Metabolizma, diyet ve egzersiz gibi yaşam tarzı tarafından da manipüle edilebilir. Bu nedenle kanserin önlenmesi ve tedavisinde metabolizmadan yararlanmak çok önemli bir yoldur.

Bu bölümde, metabolik yeniden programlamanın temelleri ve kanser hücrelerinde adaptasyon tartışılmaktadır. Hem bu değişmiş metabolizmaya yol açan ilkeler hem de sonuçta ortaya çıkan özel gereksinimler ana hatlarıyla belirtilmektedir.

WARBURG ETKİSİ

Yeterli oksijen bulunan koşullarda, terminal olarak farklılaşmış hücreler genellikle glikozu üç enzimatik yol aracılığıyla metabolize eder; **glikoliz, trikarboksilik asit (TCA) döngüsü** ve **elektron taşıma zinciri (ETC)** [1,2].

Tam oksidasyonda; bir glikoz molekülünden sonuçta 36 enerji depolayan molekül adenozin 5′-trifosfat (ATP) ve indirgenmiş nikotinamid adenin dinükleotid (NADH) [1,2] gibi enerji açısından zengin bileşikler elde edilir. Bu süreçler bölümlere ayrılmıştır: sitozolde glikoliz, mitokondride TCA döngüsü ve ETC.

[1] SBÜ Yedikule Göğüs Hastalıkları ve Göğüs Cerrahisi Hastanesi Radyasyon Onkolojisi ORCID iD: 0000-0003-2613-9855

miktarlarda glikoza ihtiyaç duyar ve birçok kanser hücresiyle aynı derecede Warburg etkisine maruz kalır[12]. Yetersiz glikoz, T hücresi inaktivasyonuna veya ölümüne yol açabilir[129,130]. Gerçekten de, tümör mikro ortamında bulunan immünosupresyonun çoğu, T hücrelerinin yeterli besinleri elde edememesine atfedilir[131]. Ek olarak, tümör hücreleri, Efektör T hücrelerinde hücre ölümüne neden olan triptofan katabolizmasını aktive etmek için indolamin 2′3′-dioksijenazı (IDO) upregüle eder[132]. Besin stresine ek olarak, oksijen miktarı da T hücre fonksiyonunu etkilemede önemli bir rol oynar. Hipoksinin neden olduğu HIF aktivasyonu, immün aktiviteyi baskılayan PD-1 ve CTLA4'ü transkripsiyonel olarak upregüle eder[133,134]. HIF ayrıca, immun aktiviteyi azaltan T regulatuar hücrelerin (Tregs) ekspresyonunu destekler[135]. Bu nedenle, T hücreleri tümör baskılayıcı veya tümörü teşvik edici olabilir[136].

T hücrelerinin ex vivo ve in vivo uyarılmasına odaklanan immünoterapi tümörlerin yönetimi için umut verici bir yoldur.

SONUÇ

Kanser metabolizmasına olan ilgi artışı bu hücrelerdeki metabolik yolaklarının hücresel otonom değişikliklerine yönelik olsa da, şimdilerde bu tümör hücrelerini etkileyen mikroçevreleri, dokusal orjinleri, germ hücresi genetikleri, karaciğer fizyolojisi, mikrobiyom, diyet ve egzersiz dahil birçok unsuru içeren çevreleriyle olan etkileşimlerinin önemi çok daha iyi anlaşılmaktadır. Bu faktörlerdeki çeşitliliğin tümörlerdeki metabolik yolları nasıl etkileyebileceği çalışmaların ana konusu olacak gibi görünmektedir.

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