BÖLÜM 6

CYP1B1'İN KARSİNOGENEZ VE TÜMÖR BİYOLOJİSİNDEKİ ROLÜ

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GİRİŞ

Sitokrom P450 1B1 (CYP1B1), çok sayıda endojen molekülün ve çevresel ksenobiyotiğin oksidatif metabolizmasından sorumlu, hem içeren monooksijenazlardan oluşan büyük bir grup olan sitokrom P450 süper ailesinin bir üyesidir. Klasik detoksifikasyon rolünün yanı sıra, CYP1B1, malign transformasyona katkıda bulunan önemli hücresel süreçlerdeki rolü nedeniyle giderek daha fazla ilgi görmektedir. Östrojen gibi hormonları metabolize ederek ve oksidatif DNA hasarına neden olabilen reaktif ara ürünler üreterek CYP1B1, metabolizma, genotoksik stres ve tümör başlangıcı arasında doğrudan bir biyokimyasal bağlantı kurar. Ayrıca, bu enzim hücre içi redoks homeostazını ve sinyal yollarını düzenleyerek hücre çoğalmasını, invazyonunu, anjiyogenezisini ve apoptoza direncini etkiler. Çeşitli solid tümörlerde CYP1B1'in anormal aşırı ekspresyonu, normal dokulardaki sınırlı varlığıyla birleşince, hem tanısal bir biyobelirteç hem de terapötik bir hedef olarak potansiyelini daha da vurgulamaktadır. Kemorezistansa, sağkalım sinyallemesine ve kanser kök hücre fenotiplerinin korunmasına katkısı, CYP1B1'in metabolik bir katalizörden daha fazlası olarak hareket ettiğini, onkojenik fenotipi şekillendirmede aktif bir katılımcı olduğunu göstermektedir.

Bu derlemenin amacı, CYP1B1'in kanser gelişimi ve ilerlemesindeki moleküler ve hücresel rollerine kapsamlı bir genel bakış sunmaktır. Biyokimyasal, genetik ve translasyonel çalışmalardan elde edilen kanıtları bir araya getirerek, bu çalışma CYP1B1'in hem metabolik bir enzim hem de tümör biyolojisinin bir düzenleyicisi olarak nasıl işlev gördüğünü açıklamayı amaçlamaktadır. Özellikle apoptoz

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kritik biyokimyasal işlevlerinden biri, bu hormonu reaktif katekol östrojenlere dönüştüren 17β-estradiolün 4-hidroksilasyonudur. Bu metabolitler, DNA'ya zarar veren ve mutasyonlara neden olan reaktif oksijen türleri üreterek redoks döngüsüne katılabilir ve böylece östrojen metabolizmasını doğrudan hormona bağlı kanserlerin başlangıcı ve ilerlemesiyle ilişkilendirebilir. Metabolik aktivitesine ek olarak, Wnt/β-katenin, PI3K/Akt ve uPA-uPAR gibi önemli onkojenik sinyal yollarını düzenleyerek tümör hücrelerinin hayatta kalmasını, göç etmesini ve kanser kök hücresi benzeri fenotiplerin korunmasını destekler. Çeşitli malignitelerde CYP1B1 ekspresyonunun artması, kötü prognoz ve terapötik dirençle tutarlı bir şekilde ilişkilendirilmiştir ve bu durum, hem bir biyobelirteç hem de tümör agresifliğinin işlevsel bir itici gücü olarak ikili yapısını vurgulamaktadır. Ölüm reseptörü yollarının baskılanması, anti-apoptotik gen ekspresyonunun artırılması ve redoks duyarlı sinyalleme kaskadlarının düzenlenmesi yoluyla CYP1B1, apoptozu etkili bir şekilde engeller ve terapötik stres altındaki malign hücrelere hayatta kalma avantajları sağlar.

Birlikte ele alındığında, CYP1B1 artık yalnızca bir detoksifikasyon enzimi olarak değil, tümör oluşumunun ve tedavi yanıtının kritik bir düzenleyicisi - kanser hücresi kalıcılığını desteklemek için metabolik ve sinyal ağlarını entegre eden bir "**apoptozis inhibitörü**" olarak görülmelidir. Tümörlerde normal dokulara kıyasla seçici aşırı ekspresyonu, CYP1B1'i hassas onkoloji için umut verici bir moleküler hedef haline getirmektedir. CYP1B1 inhibisyonunu araştıran gelecekteki çalışmalar, tümör metabolizmasını yeniden programlamak, apoptotik duyarlılığı geri kazandırmak ve ilaç direncini aşmak için yeni fırsatlar sunabilir ve nihayetinde kanser yönetimindeki tedavi stratejilerini yeniden tanımlayabilir.

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