BÖLÜM 6

Gastrointestinal Sistem Kanserlerinin Gelişiminde Epigenetik Mekanizmalar

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Giriş

DNA metilasyonu, ökaryotik genomda en sık görülen kimyasal modifikasyonlardan biridir. Memelilerde bu süreç normal embriyonik gelişim için önemlidir. Gen ekspresyonunun düzenlenmesinde, X kromozomu inaktivasyonunda, genomik imprintingde, kromatin modifikasyonunda ve endojenik genlerin susturulmasında önemli rol oynar. Metilasyon, memeli DNA'sında gerçekleşen CG (sitozin-guanin CpG) dinükleotidlerinde bulunan sitozinlerde meydana gelir. Epigenetik, DNA dizisindeki değişikliklerden (yani mutasyonlar) kaynaklanmayan, gen ifadesindeki (diğer nükleer işlevler gibi) kararlı değişiklikleri düzenleyen moleküler olaylardır. Genom metilasyon modelindeki sapmalar, organizma yaşlanırken ve kanserojenezin erken evrelerinde, hatta klinik bir kanser teşhisi konmadan önce ortaya çıkabilir (1, 2).

Karsinojeneze, hücre içinde yaygın DNA metilasyon değişiklikleri eşlik eder. Memeli hücrelerinde bulunan ana form, ağırlıklı olarak CpG dinükleotidinde sitozinin karbon-5 pozisyonuna bir metil grubunun kovalent eklenmesi olan DNA metilasyonudur. Bu sitozin modifikasyon modeli, hücre bölünmesi yoluyla iletilebilir ve kanserde gen inaktivasyonuna katkıda bulunabilir (3). Bu değişiklikler, genellikle gen promotörlerini ve ilk ekzonları kapsayan çok sayıda 5'-sitozin-fosfat-guanin-3' (CpG) adasının fokal hipermetilasyonu ile global olarak hipometillenmiş bir genom ile karakterize edilir. Bu epigenetik değişikliklerin çoğu, tümörigenezin erken döneminde meydana gelir ve tümör tipi boyunca yaygındır. DNA metilasyon kanser biyobelirteçlerinin erken teşhis için iyi bir test kapsamında yalnızca bir veya birkaç lokusun hedeflenmesi gerektiğinden, bu tür testlerin yapımı da basittir. Bu özellikler, kanserle ilişkili DNA metilasyon değişikliklerini, güçlü yararlı klinikte

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Sonuç

DNA metilasyonu, biyolojik olarak anlamlı ve kanser araştırmalarının sıklıkla odak noktası olan önemli bir epigenetik değişikliktir. Genom çapında DNA metilasyonu, gastrointestinal malignitelerin metilasyon durumunu doğru analize etmek için yararlı bir ölçüdür. İlk tespitten tedaviye ve ardından izlemeye kadar olan hasta yolculuğunda, DNA metilasyon tahlillerinin klinik uygulamaya bilgi verebileceği birkaç nokta vardır. Cerrahi olarak çıkarılan tümör dokusu üzerindeki testler, tedavi direncinin işaretlerini, prognozu tahmin etmek veya tümörü moleküler olarak karakterize etmek, sınıflandırmak ve orijinini belirlemek için faydalıdır. Bu tür testler, halihazırda başarıyla yapılmış birkaç örnekle birlikte, popülasyon taramasında kullanılmaya uygun basit, ekonomik ve oldukça spesifik kanser tespit testlerinin geliştirilmesi için büyük umut vaat etmektedir.

Dolaşımdaki tümör DNA sıvı biyopsi analizleri kanseri yerinde izleme, tedaviye yanıtı izleme, minimal rezidüel hastalığı tespit etme ve kanser nüksü için erken bir biyobelirteç imkanı da sağlar. Tek genlerin bireysel katkısının hastalığın karmaşık biyolojisini yakalayamadığı açıkça görüldüğünden, DNA metilasyon paternlerinin yüksek oranda öngörücü kombinasyonlarının tanımlanmasında büyük çabalar sarf edilmiştir. Bu doğrultuda, çoklu biyobelirteç tiplerinin kombinasyonu tahmin gücünü destekleyebilir ve erken tanıyı mümkün kılabilir.

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