PROTEİNLERİN POSTTRANSLASYONEL MODİFİKASYONLARI

Sistematik Anlatım ve
Hastalıklarla İlişkileri

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Proteinlerin Posttranslasyonel Modifikasyonları

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ÖNSÖZ

DNA'daki bilginin fonksiyonel ürünü olan proteinler, hücre içinde ve metabolizmasında neredeyse bütün biyokimyasal reaksiyonları katalizleyen yapısal ve fonksiyonel makromoleküllerdir. Ancak vücudumuzda genlerden çok daha fazla çeşitlilikte protein bulunmaktadır. Hiç kuşku yok ki proteinlerdeki bu çeşitliliği arttıran mekanizmaların en başında postranslasyonel modifikasyonlar gelir. Bu nedenle postranslasyonel modifikasyonların gün geçtikçe artan çeşitliliği biyokimya ve moleküler biyolojinin en hararetli konularından biridir.

Proteinlerin olgunlaşmasını ve işlevselliğini sağlayan postranslasyonel modifikasyonlar ister gen anlatımı ve epigenetik regülasyonlar, ister hücre içi metabolik süreçler ve hücre dışı etkenlere tepki olsun, bütün bu canlılık fonksiyonları ve bu fonksiyonların spatial ve zamansal regülasyonları oldukça kompleks bir ağ gibi birbirleri ile dinamik bir şekilde ilişkilidir. Bu kompleks yapının mimari olan protein modifikasyonlarının büyük bir kısmı açıklanmayı beklemektedir.

Halihazırda birçok proteinin fizyolojik fonksiyonu tam netlik kazanmamışken, birçok genetik hastalığın dışa vurumu yine protein ve modifikasyonlarının hatalı, eksik veya aşırı bir şekilde gerçekleşmesi ile sonuçlanır. Ayrıca oksidatif veya metabolik stres gibi çeşitli stres faktörleriyle tetiklenen birçok hastalık postranslasyonel modifikasyonlarla doğrudan ilişkilidir. Bu bağlamda postranslasyonel modifikasyonların etkileri ve fizyolojik karşılıklarını belirlemek hastalıkların patofizyolojisini anlamak ve modern tıpta, hastalık tespitinde, yeni ilaç türleri geliştirmede ve doku mühendisliğinde daha da devrim yaratacak yeni fırsatlar sağlayacaktır.

Tahminen 200.000'den fazla protein modifikasyonu 700 farklı grup altında sınıflandırılmış olmakla birlikte bu konu hakkında bildiklerimizi özetleme girişimi bu kitabı yazmaya motive eden bir fikir oldu. Kitabın hazırlık aşamasında karşılaşılan en büyük sorun, anlatımı bir sınıflandırma anlayışıyla düzenleme ihtiyacıyla ortaya çıkmaktadır. Çünkü birçok modifikasyon bulunduğu sınıflandırma içinde istisnai durumları ile kesin bir dil kullanımını engellemektedir. Bu değişenleri de hesaba katarak anlatılan bu çalışmada 40'tan fazla modifikasyon mekanizmaları ile beraber modifikasyonların fizikokimyasal özellikleri, varsa tercih ettiği protein üzerindeki fonksiyonel etkileri, her bir modifikasyonun düzensizliğinde gelişen patolojik olaylar, en güncel literatürler ışığında örneklenerek derlenmiştir.

Kitap anlaşılır bir sadelikte hazırlanmış içerikte, moleküler biyoloji ve biyokimya alanında çalışan akademisyenlere, temel tıp bilimleri ve eczacılık alanında çalışan bütün profesyonellere fayda sağlayacağı düşüncesindeyim.

Dr. Nadir Gül

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Ich widme dieses Buch,
welches ich mit großer Freude geschrieben habe,
meinen geliebten Kindern Lara und Levent.

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İÇİNDEKİLER

1. PROTEİNLER

Adı Yunanca, önde duran, birincil anlamına gelen 'proteios' kelimesinden türeyen proteinler, genlerde kodlanmış bilginin fonksiyonel karşılığı olan makromoleküllerdir (Hartley, 1951). Yapısal olarak en karmaşık ve işlevsel olarak en sofistike moleküller olarak bilinen bu makromoleküler canlılık faaliyetleri için gerekli olan bütün hücresel faaliyetlerde görev alırlar.

Proteinlerin yapı taşı olan amino asitler, genler ile aktarılan çeşit ve dizilimleri ile proteinlerin fizikokimyasal özelliklerini ve henüz sentezlenirken onların katlanmasını, stabilitesini belirlerler. Bu durum milyonlarca yıl süren evrimsel süreçte proteinleri kazandıkları aktiviteler için gerekli olan, prostetik grupların veya kofaktörlerin yanısıra proteinin hücre içindeki lokalizasyonunun, fonksiyonun ve hatta ömrünü belirleyecek olan modifikasyonların hassas ayarlarıdır.

Biyokimyasal olarak değişik büyüklüklerde ve şekillerde gelişen proteinler iki şekille tasvir edilirler.

Globüler proteinler: tipik olarak sferik yapıya sahip suda çözülebilir proteinlerdir. Düzensiz amino asit sekansları ile oluşan bu yapılar; sıcaklık ve pH'a karşı göreceli olarak hassastırlar.

Fibröz proteinler: hücrenin şeklini vermek üzere uzun ve ince bir yapısal forma sahip olan bu proteinler sıklıkla tekrarlayan amino asit sekansları içerirler. Sıcaklık ve pH'a karşı göreceli olarak daha dayanıklıdırlar ve suda çözünmezler.

Globüler ve fibröz yapıların bu keskin farklılıkları proteinlerin hücresel işlevlerini de dizayn etmektedir bu bağlamda proteinler işlevlerine göre 7 ana grup altında değerlendirilir.

- Mekanik destek olan yapısal proteinler
- Metabolizma için elzem molekülleri depolayan proteinler
- Oksijen gibi molekülleri taşıyan transport proteinleri
- Mekanik ve hareketlilik sağlayan kontraktil proteinler
- Büyüme ve farklılaşmayı sağlayan hormonal proteinler

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