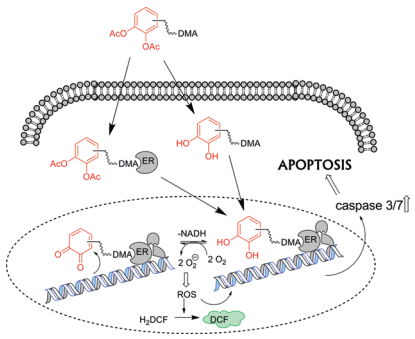
In this ISSUE

The Chemistry of Hormones

That estrogens are linked to cancer is well-established; the complex pathways that turn these important steroid hormones into carcinogens are not. Complicating the analysis is that both the hormonal and chemical properties of estrogens and their derivatives appear to contribute to cancer development, but distinguishing the effects of each is a formidable challenge. Peng *et al.* (DOI: 10.1021/cb9001848) describe the creation small molecule tools that enable analysis of the chemical component of estrogen activity without interference from its hormonal properties.

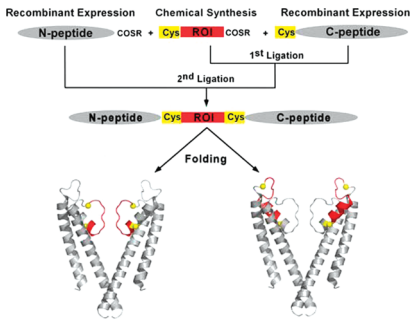
The reactive chemical moieties of two estrogen derivatives, which contain the functional groups capable of introducing oxidative DNA damage to the cell, were conjugated to a selective estrogen receptor modulator (SERM) that does not contain any form of estrogen. The compounds exhibited selective, increased cytotoxicity against cells expressing the estrogen receptor, suggesting that chemical damage inflicted on cells by estrogens is independent of their hormonal activity. Importantly, this discovery can be exploited in the design of agents that target estrogen-dependent cancer cells.



Channeling Semisynthetic Power

Powerful methods have been developed for investigating how protein structure affects function. Recombinant protein expression methods enable production of proteins of diverse size, structure, and function, while chemical synthesis techniques facilitate incorporation of nonnatural amino acids for more intricate exploration of structure—activity relationships. However, ion channels are one protein class that remains challenging to generate using either recombinant or synthetic methods alone, partly because of their large size and the extreme hydrophobicity of their membrane-spanning regions. Taking the best of both worlds, Komarov *et al.* (DOI: 10.1021/cb900210r) present a modular, semisynthetic approach for the generation of the potassium (K^+) channel KcsA.

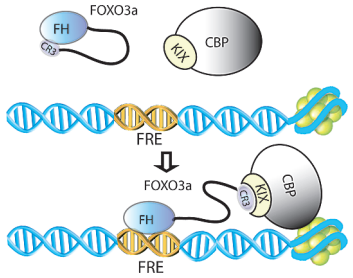
In the approach, the synthetic portion of the protein was limited to a region called the pore helix, which is involved in the gating process of the channel, while the rest of the protein was generated using recombinant methods. The pieces were subsequently ligated together to yield the full length channel. This approach, which should find general application in membrane protein production, enabled investigation into the function of a specific tryptophan residue in the pore helix.



Order in the Disordered

FOXO3a is a member of the forkhead box protein family of transcription factors that has been implicated in a range of cellular processes including cell differentiation, metabolism, cell-cycle arrest, and apoptosis. The well-characterized DNA-binding forkhead domain of FOXO3 contrasts with the remainder of the protein, which is thought to be made up of intrinsically disordered regions. Within these intrinsically disordered regions resides a transactivation domain called CR3, and CR3 recruits a transcription coactivator called CBP by binding to its KIX domain. However, the CR3 domain also interacts intramolecularly with the forkhead domain, and Wang *et al.* (DOI: 10.1021/cb900190u) now explore the purpose of this intramolecular interaction.

Using various nuclear magnetic resonance experiments, it was determined that the intramolecular interaction between the forkhead domain and CR3 prevents CR3 from binding to the KIX domain of CBP. However, when the forkhead domain binds to DNA, the CR3 domain becomes available to interact with KIX. The results suggest that the interplay between these domains plays a key role in the regulation of gene transcription activation.



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