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Direct Mechanisms in Cholesterol Modulation of Protein Function

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Preface

Cholesterol is a major lipid component of the plasma membrane where it constitutes up to ~50 mol% of the total membrane lipids. As such, it is not surprising that cholesterol effects on protein function have been historically attributed to its effect on the physical properties of lipid bilayers. First indications that cholesterol may bind directly to proteins started to emerge in the mid-1970s in studies on the eukaryotic sugar transport system [1], the Folch-Lees proteolipid protein, the major protein component of myelin [2], the Na^+/K^+-ATPase [3], and the band 3 protein that constitutes the main integral protein of the human erythrocyte membrane [4]. These studies opened a floodgate, and since then, cholesterol has been shown to play a direct role in the regulation of an ever-growing number of proteins.

In 1998, the first amino acid consensus sequence for cholesterol binding, the cholesterol recognition amino acid consensus (CRAC) motif, was proposed in the context of the peripheral-type benzodiazepine receptor, a transmembrane protein that mediates the translocation of cholesterol [5]. While the CRAC motif has been identified in multiple proteins since then, several other cholesterol binding motifs followed, and the characteristics of cholesterol-binding sites in proteins have continued to be defined.

The first structural evidence that cholesterol can bind directly to proteins emerged in mid-2002 with the determination of the structure of the cryptogein-cholesterol complex via X-ray crystallography at a 1.45 Å resolution [6]. Despite its small size, cryptogein, a fungal elicitor, displayed a large inner hydrophobic cavity that harbored the cholesterol molecule. The same year, a structure of the ligand-binding domain of the retinoic acid orphan receptor α was determined at 1.63 Å resolution in complex with cholesterol [7]. This was followed by a structure of the cholesterol-bound oxysterol-binding protein Osh4 at a 1.6 Å resolution in 2005 [8].

In 2007, a structure of the β2 adrenergic G-protein-coupled receptor was crystallized at a 2.4 Å resolution in complex with cholesterol [9]. In this structure, cholesterol mediated receptor-receptor interactions improving the stability of the receptor. This was another milestone in the quest to uncover the direct roles of cholesterol-protein interactions in protein function.

Over the course of several decades, numerous functional, structural, and computational studies have continued to shape our understanding of cholesterol-protein interactions, unraveling the growing number of roles that they play in cellular function. These range from cholesterol transport and storage to protein stability, folding, and localization. While many questions regarding the underlying molecular mechanisms remain unresolved, significant advances in our understanding of direct cholesterol-protein interactions have been made in recent years, and are the topic of this volume.

This is the second in a sequel of two volumes on the mechanisms of cholesterol modulation of protein function. The first volume (1115 in the Advances in Experimental Medicine and Biology Series) focused on sterol specificity as a means to distinguish between direct and indirect effects of cholesterol as well as on indirect mechanisms that impact protein function in response to variations in cholesterol level. The current volume complements the picture by focusing on protein targeting via direct interactions of the cholesterol molecule with sterol-sensing protein sites.

The first part of this volume introduces the reader to the general characteristics of cholesterol binding sites. This part starts with a survey of the different cholesterol-binding motifs that have been proposed over the years followed by an overview of the major classes of proteins that bind steroids and the insights gained from their study using X-ray crystallography. It then continues to two studies that utilize the growing number of structures of cholesterol-bound proteins available in the Protein Data Bank to present new insights into the molecular and structural characteristics of cholesterol-binding sites. The second part of this volume delves into more specific cases of cholesterol binding to G-protein-coupled receptors, ion channels, and cholesterol transporters that have been studied using combinations of experimental and computational approaches.

The editors are grateful to all the authors who contributed to this project aimed at portraying the intricate interactions between a variety of proteins and cholesterol. The editors are also thankful to senior mentors, collaborators, and colleagues for stimulating discussions, and for fostering a supportive environment for the completion of this diverse collection of contributions to the field.

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