A thematic review series: lipid modifications of proteins

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More than a dozen years ago, Dr. Patrick Casey wrote a review for the *Journal of Lipid Research* (*JLR*) on a fledgling area of lipid biology: the biochemistry and enzymology of protein prenylation (1). His article and others on the same topic (2) stimulated interest in the posttranslational modification of proteins with lipids. During the past decade, there have been many advances in understanding lipid modifications of proteins, spanning not only enzymology and biochemistry, but also genetic and pharmacologic studies linking lipid modifications to the pathogenesis and treatment of human disease. Accordingly, I thought that it was a good time for *JLR* to consider a thematic review series on lipid modifications. I was pleased to be able to recruit several leaders in this field to write reviews on topics of their choosing. I am confident that the upcoming reviews will be a useful resource for lipid biologists and will stimulate interest in this area of research.

I will lead off the series, along with two colleagues, Dr. Loren Fong (University of California, Los Angeles) and Dr. Susan Michaelis (Johns Hopkins University). The focus of our review will be the posttranslational processing of farnesylated protein in mammalian cells, prelamin A. Prelamin A normally undergoes multistep processing to yield lamin A, a structural protein of the nuclear lamina. Prelamin A terminates with a CAAX motif, which triggers farnesylation of a C-terminal cysteine (the C of the CAAX motif), endoproteolytic release of the last three amino acids (AAX), and methylation of the newly exposed farnesylcysteine. After these modifications, prelamin A is actually cleaved a second time, clipping off an additional 15 residues from the C terminus (including the farnesylcysteine methyl ester) and releasing mature lamin A. This second cleavage step is carried out by a membrane protease of the endoplasmic reticulum, ZMPSTE24. In the absence of ZMPSTE24, farnesyl-prelamin A accumulates in cells, causing misshapen cell nuclei and disease phenotypes resembling those in progeroid syndromes. The finding that Hutchinson-Gilford progeria syndrome is caused by an accumulation of a mutant form of farnesyl-prelamin A has focused even more interest on this topic. Recently, we suggested that the farnesylation of prelamin A could be crucial for disease pathogenesis, in that a key cellular phenotype of these disorders, misshapen nuclei, can be ameliorated by inhibitors of protein farnesylation.

Dr. Robert Bishop (Schering-Plough Research Institute) will review the current status of farnesyltransferase inhibitors (FTIs). Inhibitors of protein farnesyltransferase were initially developed to fight cancer, with the expectation that these drugs would block the prenylation of mutationally activated forms of Ras, preventing their ability to be targeted to the plasma membrane. Further studies, however, revealed that both K-Ras and N-Ras are alternatively prenylated by geranylgeranyltransferase type I in the setting of FTI treatment. Geranylgeranylated forms of Ras retain the ability to associate with the plasma membrane and participate in signal transduction pathways that contribute to cellular transformation. In spite of the alternative prenylation pathway, however, FTIs are effective at inhibiting the growth of a wide variety of human tumor cells in vitro, suggesting that the antitumor activity of FTIs may be dependent on blocking the farnesylation of proteins other than the Ras family. FTIs also inhibit the growth of a wide range of human tumor xenograft models and have been shown to sensitize these tumor models to various chemotherapeutics, most notably taxanes. Several FTIs have entered human clinical trials and have displayed activity in certain clinical settings, both alone and in combination regimens. Dr. Bishop’s review will summarize the basic biology of FTIs, the antitumor activity of FTIs in preclinical models, and the current status of the human clinical trials.

Dr. Michel Gelb (University of Washington) will review the possibility that FTIs might be effective agents in fighting parasitic diseases. Dr. Gelb and colleagues have shown that the pathogenic parasites *Trypanosoma cruzi*, *Trypanosoma cruzi*, *Leishmania major*, and *Plasmodium falciparum* express protein farnesyltransferase, and have gone on to identify FTIs that inhibit parasite growth at subnanomolar concentrations and kill parasites at low nanomolar levels.

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Experimental studies indicate that protein farnesyltransferase could be an ideal target for new antiparasitic drugs.

Dr. Miguel Seabra (Imperial College, London) will review the geranylgeranylation of the Rab proteins, which are critical for vesicular transport within cells. Like the Ras family of proteins, small GTPases of the Rab family must associate with cellular membranes for activity, and this membrane attachment is mediated by posttranslational modification with a geranylgeranyl lipid. The cellular machinery for Rabs is quite specialized, involving both Rab geranylgeranyltransferase (RGGT) and a Rab binding protein, Rab escort protein (REP). Recent advances in the biochemistry and structure of RGGT and REP will be reviewed, along with the topic of the targeting of Rab proteins to different organelles. Dr. Seabra will also discuss genetic diseases resulting from defects in the Rab prenylation machinery. A retinal degenerative disease, choroideremia, results from a loss-of-function mutation in REP-1, and a mouse Hermansky-Pudlak syndrome model, guncemal, is caused by a mutation in the α-subunit of RGGT. Both diseases appear to be caused by selective defects in Rab function.

Dr. Lorena Beese (Duke University) will review the structural biology of protein farnesyltransferase and protein geranylgeranyltransferase type I. Her laboratory has crystallized both enzymes and solved their structures, identifying the binding pockets for enzyme substrates and facilitating the understanding of a unique mechanism of action for these enzymes. The structures have clarified the specificities of the two enzymes for farnesyl diphosphate and geranylgeranyl diphosphate and have defined how the enzymes are blocked by specific inhibitor drugs.

Dr. Mark Philips (New York University) will write a review on the targeting of isoprenylated proteins to membrane surfaces. In his review, he will discuss the importance of prenylation itself and of the “postisoprenylation” modifications (i.e., proteolytic release of the AAX, carboxyl methylation, and palmitoylation) in the subcellular trafficking of the Ras and Rho family of GTPases. The special importance of carboxyl methylation for the proper targeting of farnesylated proteins will be explored. Also, the intracellular locations of these enzymatic modifications will be discussed, along with the mechanisms for the trafficking of prenylated proteins to the plasma membrane. Finally, the implications of posttranslational processing for Ras signaling will be discussed.

Dr. Robert Deschenes (Medical College of Wisconsin) and Dr. Maurine Linder (Washington University, St. Louis) will review protein palmitoylation. Palmitoylation is a post-translational modification in which a 16-carbon fatty acid is added to a cysteine via a thioester linkage. This reversible modification facilitates protein–membrane interactions and subcellular trafficking of proteins. Even though the posttranslational modification of proteins by palmitoylation was identified 30 years ago, the enzymes that catalyze this reaction were only identified recently. Two protein palmitoyltransferases, one for Ras and the other for a casein kinase, were revealed by genetic screens in yeast. Both contain a related sequence motif referred to as the DHHC-CRD (Asp-His-His-Cys-cysteine rich domain). The residues of the DHHC-CRD are required for palmitoyltransferase activity and therefore serve as a signature for this class of protein acyltransferases (PATs). The review will discuss the genetic and biochemical evidence that DHHC-CRD proteins are PATs and examine the evolutionary relationships for this large family of proteins.

The final installment of the thematic review series will be written by Dr. Sandy Hofmann (University of Texas Southwestern). She will review the removal of lipid modifications in lysosomes. Palmitoylated proteins are degraded by a lysosomal palmitoylcysteine hydrolase, palmitoyl protein thioesterase (PPT1). The enzyme is a classical lipase, with a canonical lipase structure and well-defined fatty acid and peptide binding sites. Prenylated cysteines are metabolized by a prenylcysteine lyase that has a unique mechanism, functioning as an unusual flavin dinucleotide-dependent thioether oxidase that produces free cysteine, an isoprenoid aldehyde, and hydrogen peroxide. Prenylcysteine lyase is also located within lysosomes. Deficiency in PPT1 causes a neurodegenerative disorder of children, infantile neuronal ceroid lipofuscinosis.

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