

## Protein prenyltransferases

Sebastian Maurer-Stroh, Stefan Washietl and Frank Eisenhaber

Address: Research Institute of Molecular Pathology, Dr Bohr-Gasse 7, A-1030 Vienna, Austria.

Correspondence: Sebastian Maurer-Stroh. E-mail: stroh@imp.univie.ac.at

Published: 1 April 2003

*Genome Biology* 2003, **4**:212

The electronic version of this article is the complete one and can be found online at <http://genomebiology.com/2003/4/4/212>

© 2003 BioMed Central Ltd

### Summary

Three different protein prenyltransferases (farnesyltransferase and geranylgeranyltransferases I and II) catalyze the attachment of prenyl lipid anchors 15 or 20 carbons long to the carboxyl termini of a variety of eukaryotic proteins. Farnesyltransferase and geranylgeranyltransferase I both recognize a 'Ca<sub>1</sub>a<sub>2</sub>X' motif on their protein substrates; geranylgeranyltransferase II recognizes a different, non-CaaX motif. Each enzyme has two subunits. The genes encoding CaaX protein prenyltransferases are considerably longer than those encoding non-CaaX subunits, as a result of longer introns. Alternative splice forms are predicted to occur, but the extent to which each splice form is translated and the functions of the different resulting isoforms remain to be established. Farnesyltransferase-inhibitor drugs have been developed as anti-cancer agents and may also be able to treat several other diseases. The effects of these inhibitors are complicated, however, by the overlapping substrate specificities of geranylgeranyltransferase I and farnesyltransferase.

### Gene organization and evolutionary history

#### Gene organization

Protein prenylation is the posttranslational attachment of either a farnesyl group or a geranylgeranyl group via a thioether linkage (-C-S-C-) to a cysteine at or near the carboxyl terminus of the protein. Farnesyl and geranylgeranyl groups are polyisoprenes, unsaturated hydrocarbons with a multiple of five carbons; the chain is 15 carbons long in the farnesyl moiety and 20 carbons long in the geranylgeranyl moiety (see Table 1). There are three different protein prenyltransferases in humans: farnesyltransferase (FT) and geranylgeranyltransferase 1 (GGT1) share the same motif (the CaaX box) around the cysteine in their substrates, and are thus called CaaX prenyltransferases, whereas geranylgeranyltransferase 2 (GGT2, also called Rab geranylgeranyltransferase) recognizes a different motif and is thus called a non-CaaX prenyltransferase [1]. Each protein consists of two subunits,  $\alpha$  and  $\beta$ ; the  $\alpha$  subunit of FT and GGT1 is encoded by the same gene, *FNTA* (see Table 1).

The genomic organization of the human genes that encode protein prenyltransferases is shown in Figure 1 (available

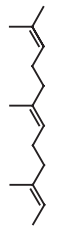
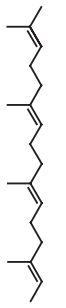
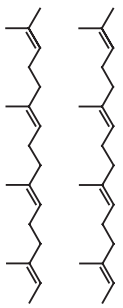
with the complete version of this article, online). It is interesting to note that the genes encoding both subunits of non-CaaX prenyltransferases are much smaller (about 6-9 kilobases, kb) than those of the CaaX prenyltransferases (about 30-76 kb). The number of exons in the two types of genes are similar; the differences in gene size therefore result from differing intron lengths.

Automatic comparisons of data from expressed sequence tags (ESTs) with genes (for example using the program Acembly, for which the results are available from the NCBI AceView server [2]) shows that all the human protein prenyltransferase genes have multiple alternative splice variants. The extent of translation of the various predicted transcripts and the structures and functions of the resulting proteins remain to be established experimentally; some of the predicted transcripts may be derived from missplicing rather than being real splice variants.

#### Evolutionary history

Protein prenyltransferases are currently known only in eukaryotes, but they are widespread, being found in vertebrates,

**Table 1****Features of human protein prenyltransferases**

	Farnesyltransferase (FT)	Geranylgeranyltransferase I (GGT1)	Geranylgeranyltransferase II (GGT2 or RabGGT)
Gene name ( $\alpha$ subunit)	<i>FNTA</i>	<i>FNTA</i>	<i>RABGGTA</i>
Gene name ( $\beta$ subunit)	<i>FNTB</i>	<i>PGGT1B</i>	<i>RABGGTB</i>
Substrate motif	Carboxy-terminal $-Ca_1a_2X$ box*	Carboxy-terminal $-Ca_1a_2X$ box*	Carboxy-terminal motif such as $-CC$ , $-CXC$ , $-CCX$ , $-CCXX$ , $-CCXXX$ , or $-CXXX$ †
Lipid anchor	 Farnesyl	 Geranylgeranyl	 Geranylgeranyl (one or two moieties per substrate)

\*C, cysteine;  $a_1$ , and  $a_2$  are amino acids that are preferably aliphatic; the identity of  $a_1$  is more flexible than  $a_2$ . X can be C, S, Q, A, M, T, H, V, N, F, G, or I for FT, or L, F, I, V, or M for GGT1 (in decreasing order of affinity). †Requires an escort protein such as REPI.

insects, nematodes, plants, fungi and protozoa, including several parasites. The chromosomal locations and number of exons from protein prenyltransferase genes in the major eukaryotic model organisms are shown in Table 2 (available with the complete version of this article, online). The  $\alpha$  and  $\beta$  subunits have different folds, so are unlikely to have arisen from a common ancestor. Molecular phylogenetic analysis shows that orthologous proteins in different species are more closely related to each other than to their paralogs in the same species; the relationships between the  $\beta$  subunits are not fully clear. As well as the known genes, processed pseudogenes resulting from retrotransposition events have been found in the human and mouse genomes [3,4].

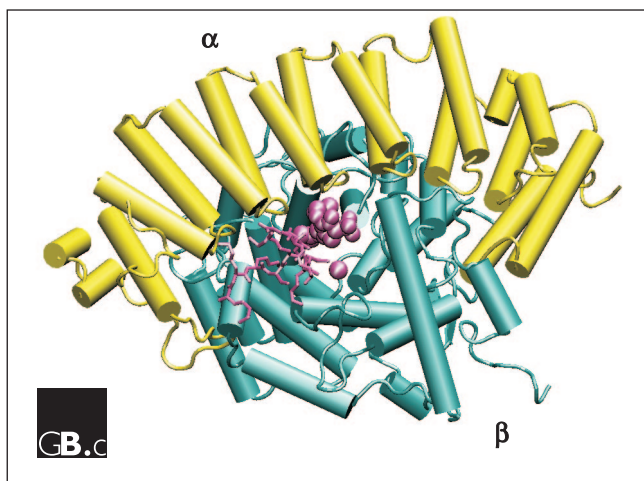
The  $\alpha$  subunits of protein prenyltransferases consist of tetratricopeptide repeats and are part of the tetratricopeptide repeat superfamily [5], which also includes functionally diverse proteins involved in transcription, co-chaperoning, protein transport, cell-cycle control and phosphorylation. Although evolution of repeat proteins is difficult to analyze and interpret, Zhang and Grishin [6] have deduced convincingly that the *FNTA* and *RABGGTA* genes originated from a common ancestor that already contained multiple tetratricopeptide repeats rather than having independently amplified the number of motifs as the families diverged over time.

The  $\beta$  subunits of protein prenyltransferases are part of a superfamily of prenyltransferases [7]; other members of the

superfamily catalyze different reactions involving polyisoprenes [10-12]. Further details on the prenyltransferase superfamily, including Figure 2, a superposition of the structures of bacterial squalene-hopene cyclase [16] and the  $\beta$  subunit of rat FT [17], are available with the complete version of this article, online.

### Characteristic structural features

The CaaX prenyltransferases FT and GGT1 and the non-CaaX prenyltransferase GGT2 share the same heterodimeric structure [1] (Figure 3). In the  $\alpha$  subunits of both types of protein prenyltransferases, seven tetratricopeptide repeats are formed by pairs of helices (helices 2 to 15) that are stabilized by conserved intercalating residues. The  $\alpha$  subunits of GGT2 in mammals and plants also have an immunoglobulin-like domain between the fifth and sixth tetratricopeptide repeat, as well as leucine-rich repeats at the carboxyl terminus. The functions of these additional domains in GGT2 are as yet undefined, but they are apparently not directly involved in the interaction with substrates and Rab escort proteins (see below) [18,19]. The tetratricopeptide repeats of the  $\alpha$  subunit form a right-handed superhelix, which embraces the  $(\alpha-\alpha)_6$  barrel of the  $\beta$  subunit [20]. The  $\beta$  subunits include most of the substrate- and lipid-binding pockets [20] and their tight association with the respective  $\alpha$  subunits is required for proper function [21]. Compared with FT, GGT2 has a

**Figure 3**

The complete structure of rat FT (PDB identifier 1D8D [70]). The spheres in the center represent the farnesyl-pyrophosphate and  $Zn^{2+}$ , and the amino acids in stick representation are the CaaX motif of the protein substrate. The molecular representation was created using VMD [69].

larger hydrophobic pocket in the  $\beta$  subunit to accommodate the longer lipid [22].

It is difficult to estimate the effect of alternative splicing on the structure of protein prenyltransferases. We would expect that the integrity of the structure of the  $\beta$  subunits would be more sensitive to non-terminal truncations than are the  $\alpha$  subunits, because the modular structure of the tetratricopeptide repeat motifs in the  $\alpha$  subunits would allow truncations and additions without severe consequences for the hydrophobic packing of the structure. Details of the enzymatic mechanism of protein prenyltransferases are available with the complete version of this article, online.

### Localization and function

The results of systematic oligonucleotide microarray experiments catalogued in the human gene-expression index database [33,34] show that protein prenyltransferases are expressed in a variety of tissues. Both CaaX prenyltransferases seem to be active (that is, their  $\alpha$  and  $\beta$  subunits are coexpressed) in a range of tissues, and the non-CaaX prenyltransferase subunits are also expressed in several more tissues. It should be noted, however, that many of the expression levels listed [33,34] are close to the detection threshold and could therefore result from cross-hybridization between close homologs rather than true expression. Interestingly, the  $\alpha$  subunits also appear to be expressed in tissues that lack expression of the corresponding  $\beta$  subunits; this suggests that single subunits, or isoforms of them, might have additional, prenylation-independent functions in the cell.

As the  $\alpha$  subunit of CaaX prenyltransferases is shared between FT and GGT1, its expression must be higher than that of each  $\beta$  subunit if it is to form 1:1 complexes with the  $\beta$  subunits of both enzymes. These higher expression levels seem to be transcriptionally regulated by different promoters; in order to produce recombinant CaaX prenyltransferases in the laboratory, it is thus necessary to downregulate expression of the  $\alpha$  subunits when coexpressing with  $\beta$  subunits [35].

Lipid anchors are common posttranslational modifications that can direct the subcellular localization of proteins. Other lipid modifications, such as myristoylation [36-38], palmitoylation [39,40] and glycosylphosphatidylinositol (GPI) anchors [41,42], are mainly important for attachment of the protein to membranes, but lipid modification by protein prenyltransferases seems to have a more complex role: the farnesyl and geranylgeranyl moieties attached to the substrates are directly involved in protein-protein interactions as well as in protein-membrane interactions [43]. The importance of protein prenyltransferases is illustrated by the involvement of their substrates in critical cellular pathways and diseases [44].

### Substrates and functions of CaaX prenyltransferases

Typical substrates that are farnesylated by FT include many members of the Ras superfamily of small GTPases (H-Ras, K-Ras, N-Ras, Ras2, Rap2, RhoB (which is also geranylgeranylated), RhoE, Rheb, TC10, and TC21), as well as the nuclear lamina proteins lamin A and B, the kinetochore proteins CENP-E and CENP-F, fungal mating factors, cGMP phosphodiesterase  $\alpha$ ,  $\gamma$  subunit variants of G proteins, DnaJ heat-shock protein homologs, rhodopsin kinase, the peroxisomal membrane proteins Pex19 and PxF and paralectin (a neural protein suggested to be involved in membrane dynamics). GGT1 preferentially geranylgeranylates some of the other small GTPases (such as Rac1, Rac2, RalA, Rap1A, Rap1B, RhoA, and RhoB (which is also farnesylated, as noted above), RhoC, Cdc42, Rab8 (which is also geranylgeranylated by GGT2), Rab11, and Rab13, as well as some  $\gamma$ -subunit variants of G proteins, cGMP phosphodiesterase  $\beta$  and the plant calmodulin CaM53. Typically, prenylation by CaaX protein prenyltransferases is accompanied by further posttranslational processing, most often involving cleavage of the carboxy-terminal tripeptide ( $-a_1a_2X$ ) followed by carboxymethylation of the carboxyl terminus [45-47]. Palmitoylation is another modification that sometimes takes place after prenylation [48].

Because several prenylated substrates are involved in diseases, inhibition of protein prenyltransferases has great potential for medical applications. A boom in the field was triggered by the finding that inhibition of FT in mice that have tumors derived from H-Ras-transformed cells leads to tumor regression, while the inhibitor has no adverse effect on the organism [49]. This led to successful completion of clinical phase I trials of farnesyl transferase inhibitors

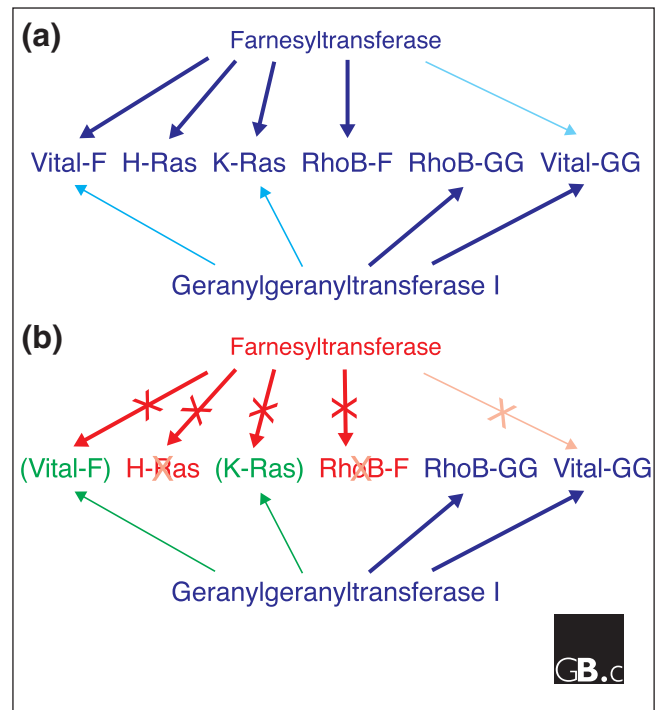
(FTIs), but in phase II trials the efficacy of the inhibitors towards a broad spectrum of different cancer cells (such as K-Ras-transformed cells) was far below the high expectations that arose from the phase I trials. Surprisingly, however, beneficial effects were found for other, non-neoplastic diseases; for example, diabetic retinopathy and macular degeneration [50]. The unexpected physiological effects of FT inhibition are partly due to a striking cross-specificity between the two CaaX prenyltransferases: both FT and GGT1 can use either farnesyl-pyrophosphate or GGPP to a certain extent to transfer lipids to several of each others' substrates as well as their own [51,52], and several substrates can be either farnesylated or geranylgeranylated. The substrates probably compete *in vivo* for the enzymes loaded with the preferred polyprenyl-pyrophosphate, and the type of modification that is added depends on the relative affinity of the substrates for the enzymes.

In cancer cells, FTIs are known to affect growth in soft agar (anchorage-independent growth), cell-cycle progression at the G1-S phase and the G2-M phase checkpoints, the morphology of the cytoskeleton (formation of actin stress fibers) and induction of apoptosis. The substrate proteins that have been suggested to be involved in these effects include H-Ras [49], Rheb [53], CENP-E [54] and RhoB [55]; FTI effects are reviewed in more detail elsewhere [56]. The effects of FT inhibition in cells transformed with H-Ras differ from those on cells transformed with K-Ras. This difference has been attributed to the ability of GGT1 to alternatively prenylate some proteins, through the cross-specificity mentioned above, including K-Ras but not H-Ras (see Figure 4). RhoB can be both farnesylated and geranylgeranylated; Prendergast and colleagues [57] have suggested that the different levels of farnesylated and geranylgeranylated RhoB in FTI-treated cells compared with untreated cells could contribute to the observed effects of FTIs.

### Substrates and functions of non-CaaX prenyltransferases

The main substrates for prenylation by GGT2 are the Rab family of proteins, the largest group of small GTPases in the Ras superfamily. There are at least 60 different Rabs in humans [58]. They interact with the Rab escort protein REP, which is required for the prenylation of Rabs by GGT2 [30], and are involved in the docking of transport vesicles to their specific target membranes [59].

As with CaaX protein prenyltransferases, deficiencies in prenylation by non-CaaX protein prenyltransferases are relevant to diseases [59,60]. A mutation inactivating a start codon of the major transcript of the  $\alpha$  subunit of GGT2 is one of the many mutations involved in the recessively inherited Hermansky-Pudlak syndrome and related disorders [61,62], in which platelet synthesis, platelet organelle function and pigmentation are affected. X-linked choroideremia (CHM) results in retinal degeneration, with symptoms starting from



**Figure 4**

Differential prenylation of substrates of CaaX protein prenyltransferases (a) under normal conditions and (b) in the presence of a FT inhibitor. Substrates are shown in the middle of each panel, with the two enzymes above and below. 'Vital-F' and 'Vital-GG' represent all the proteins for which farnesylation (Vital-F) or geranylgeranylation (Vital-GG) are essential; RhoB-GG represents geranylgeranylated RhoB and RhoB-F represents farnesylated RhoB. Thick arrow, normal prenylation activity; thin arrow, reduced prenylation activity through cross-specificity of the non-preferred enzyme; arrows with crosses, blocked prenylation activity during inhibition of FT; brackets, substituting prenylation activity by GGT1 during inhibition of FT.

night blindness in young people and progressing over decades until vision is completely lost [63]. It is caused by loss-of-function mutations in the *CHM* gene, which encodes Rab escort protein 1 (REP1) [64]. Loss-of function mutations in the *Rab27a* gene cause Griscelli syndrome, whose symptoms are similar to Hermansky-Pudlak syndrome and other diseases associated with insufficient Rab prenylation [60].

### Frontiers

There are several issues that merit further study in the regulation of protein prenyltransferases. Firstly, it is not clear how the concomitant transcription of the two subunits from two different chromosomes is regulated or where and how the subunits meet to build up functional prenyltransferases. Secondly, given that there are multiple splice variants, it is likely that additional variants of subunits will be found to have distinct functions or regulatory roles; an example is a variant of the FT/GGT1  $\alpha$  subunit that has been reported to be directly involved in signaling by transforming growth factor  $\beta$  and

activin [65]. Interpretation of results in areas ranging from molecular biology to clinical trials must take into account possible isoforms with varying functions or altered interactions to avoid erroneous conclusions. A third issue is the striking differences in gene size and intron length between the two types of protein prenyltransferases, discussed in more detail in the complete version of this article, online.

Finally, more research is also needed on the effects of FTIs. After the rush to develop inhibitors, basic research is now needed as well as clinical trials in order to improve the understanding of the basic processes involved [66]. For example, it cannot be ruled out that some effects of FTIs are not a direct consequence of inhibiting prenylation but are instead due to cross-reactivity with proteins from completely different pathways. It is tempting to speculate that one of the proteins that are evolutionarily related to the protein prenyltransferases (such as other prenyltransferases) could be affected by FTIs; the selectivity of existing FTIs, which do not inhibit even the much more closely related GGTs, makes this scenario most unlikely, however. The next task is to identify clearly the proteins whose altered prenylation causes the observed effects of FT inhibition. Given the multiplicity and heterogeneity of these effects, it is clear that they cannot be attributed to one single farnesylated protein that lacks a lipid modification because of FT inhibition; rather, alterations in the function of several proteins probably cause the observed effects, with variations depending on the cell type, disease and organism. Further research may eventually lead to FTIs being used successfully to treat cancers and other diseases.

## Acknowledgements

The authors are grateful for useful comments from Maria Novatchkova and Alexander Schleiffer as well as for continuous support from Boehringer Ingelheim. This project has been partly funded by the Fonds zur Förderung der wissenschaftlichen Forschung Österreichs (FWF grant P15037) and by the Austrian National Bank (OeNB).

## References

- Casey PJ, Seabra MC: **Protein prenyltransferases.** *J Biol Chem* 1996, **271**:5289-5292.
- AceView** [<http://www.humangenet.org>]
- Andres DA, Milatovich A, Ozcelik T, Wenzlau JM, Brown MS, Goldstein JL, Francke U: **cDNA cloning of the two subunits of human CAAX farnesyltransferase and chromosomal mapping of FNTA and FNTB loci and related sequences.** *Genomics* 1993, **18**:105-112.
- Dhawan P, Yang E, Kumar A, Mehta KD: **Genetic complexity of the human geranylgeranyltransferase I beta-subunit gene: a multigenic family of pseudogenes derived from mis-spliced transcripts.** *Gene* 1998, **210**:9-15.
- Blatch GL, Lassle M: **The tetratricopeptide repeat: a structural motif mediating protein-protein interactions.** *BioEssays* 1999, **21**:932-939.
- Zhang H, Grishin NV: **The alpha-subunit of protein prenyltransferases is a member of the tetratricopeptide repeat family.** *Protein Sci* 1999, **8**:1658-1667.
- Liang PH, Ko TP, Wang AH: **Structure, mechanism and function of prenyltransferases.** *Eur J Biochem* 2002, **269**:3339-3354.
- Altschul SF, Madden TL, Schaffer AA, Zhang J, Zhang Z, Miller W, Lipman DJ: **Gapped BLAST and PSI-BLAST: a new generation of protein database search programs.** *Nucleic Acids Res* 1997, **25**:3389-3402.
- Eddy SR: **Profile hidden Markov models.** *Bioinformatics* 1998, **14**:755-763.
- Wendt KU, Poralla K, Schulz GE: **Structure and function of a squalene cyclase.** *Science* 1997, **277**:1811-1815.
- Nes WD, Venkatramesh M: **Enzymology of phytosterol transformations.** *Crit Rev Biochem Mol Biol* 1999, **34**:81-93.
- Sturley SL: **Conservation of eukaryotic sterol homeostasis: new insights from studies in budding yeast.** *Biochim Biophys Acta* 2000, **1529**:155-163.
- Janowski BA, Willy PJ, Devi TR, Falck JR, Mangelsdorf DJ: **An oxysterol signalling pathway mediated by the nuclear receptor LXR alpha.** *Nature* 1996, **383**:728-731.
- Kim JH, Lee JN, Paik YK: **Cholesterol biosynthesis from lanosterol. A concerted role for Sp1 and NF-Y-binding sites for sterol-mediated regulation of rat 7-dehydrocholesterol reductase gene expression.** *J Biol Chem* 2001, **276**:18153-18160.
- Bateman A, Birney E, Durbin R, Eddy SR, Howe KL, Sonnhammer EL: **The Pfam protein families database.** *Nucleic Acids Res* 2000, **28**:263-266.
- Wendt KU, Lenhart A, Schulz GE: **The structure of the membrane protein squalene-hopene cyclase at 2.0 Å resolution.** *J Mol Biol* 1999, **286**:175-187.
- Long SB, Casey PJ, Beese LS: **The basis for K-Ras4B binding specificity to protein farnesyltransferase revealed by 2 Å resolution ternary complex structures.** *Structure Fold Des* 2000, **8**:209-222.
- Dursina B, Thoma NH, Sidorovitch V, Niculae A, Iakovenko A, Rak A, Albert S, Ceacareanu AC, Kolling R, Herrmann C, et al.: **Interaction of yeast Rab geranylgeranyl transferase with its protein and lipid substrates.** *Biochemistry* 2002, **41**:6805-6816.
- Pylypenko O, Rak A, Reents R, Niculae A, Sidorovitch V, Cioaca MD, Bessolitsyna E, Thoma NH, Waldmann H, Schlichting I, et al.: **Structure of rab escort protein-1 in complex with rab geranylgeranyltransferase.** *Mol Cell* 2003, **11**:483-494.
- Park HW, Boduluri SR, Moomaw JF, Casey PJ, Beese LS: **Crystal structure of protein farnesyltransferase at 2.25 angstrom resolution.** *Science* 1997, **275**:1800-1804.
- Andres DA, Goldstein JL, Ho YK, Brown MS: **Mutational analysis of alpha-subunit of protein farnesyltransferase. Evidence for a catalytic role.** *J Biol Chem* 1993, **268**:1383-1390.
- Zhang H, Seabra MC, Deisenhofer J: **Crystal structure of Rab geranylgeranyltransferase at 2.0 Å resolution.** *Structure Fold Des* 2000, **8**:241-251.
- Moores SL, Schaber MD, Mosser SD, Rands E, O'Hara MB, Garsky VM, Marshall MS, Pompliano DL, Gibbs JB: **Sequence dependence of protein isoprenylation.** *J Biol Chem* 1991, **266**:14603-14610.
- Caplin BE, Hettich LA, Marshall MS: **Substrate characterization of the *Saccharomyces cerevisiae* protein farnesyltransferase and type-I protein geranylgeranyltransferase.** *Biochim Biophys Acta* 1994, **1205**:39-48.
- Reiss Y, Goldstein JL, Seabra MC, Casey PJ, Brown MS: **Inhibition of purified p21ras farnesyl:protein transferase by Cys-AAx tetrapeptides.** *Cell* 1990, **62**:81-88.
- Yokoyama K, McGeady P, Gelb MH: **Mammalian protein geranylgeranyltransferase-I: substrate specificity, kinetic mechanism, metal requirements, and affinity labeling.** *Biochemistry* 1995, **34**:1344-1354.
- Saderholm MJ, Hightower KE, Fierke CA: **Role of metals in the reaction catalyzed by protein farnesyltransferase.** *Biochemistry* 2000, **39**:12398-12405.
- Long SB, Casey PJ, Beese LS: **Reaction path of protein farnesyltransferase at atomic resolution.** *Nature* 2002, **419**:645-650.
- Furfine ES, Leban JJ, Landavazo A, Moomaw JF, Casey PJ: **Protein farnesyltransferase: kinetics of farnesyl pyrophosphate binding and product release.** *Biochemistry* 1995, **34**:6857-6862.
- Alexandrov K, Simon I, Yurchenko V, Iakovenko A, Rostkova E, Scheidig AJ, Goody RS: **Characterization of the ternary complex between Rab7, REP-1 and Rab geranylgeranyl transferase.** *Eur J Biochem* 1999, **265**:160-170.
- Alexandrov K, Horiuchi H, Steele-Mortimer O, Seabra MC, Zerial M: **Rab escort protein-1 is a multifunctional protein that accompanies newly prenylated rab proteins to their target membranes.** *EMBO J* 1994, **13**:5262-5273.
- Benito-Moreno RM, Miaczynska M, Bauer BE, Schweyen RJ, Ragnini A: **Mrs6p, the yeast homologue of the mammalian**

- choroideraemia protein: immunological evidence for its function as the Ypt1p Rab escort protein.** *Curr Genet* 1994, **27**:23-25.
33. Haverty PM, Weng Z, Best NL, Auerbach KR, Hsiao LL, Jensen RV, Gullans SR: **HuGEIndex: a database with visualization tools for high-density oligonucleotide array data from normal human tissues.** *Nucleic Acids Res* 2002, **30**:214-217.
  34. **HuGE Index** [<http://hugeindex.org/>]
  35. Tsao KL, Waugh DS: **Balancing the production of two recombinant proteins in *Escherichia coli* by manipulating plasmid copy number: high-level expression of heterodimeric Ras farnesyltransferase.** *Protein Expr Purif* 1997, **11**:233-240.
  36. Gordon JI, Duronio RJ, Rudnick DA, Adams SP, Gokel GW: **Protein N-myristoylation.** *J Biol Chem* 1991, **266**:8647-8650.
  37. Maurer-Stroh S, Eisenhaber B, Eisenhaber F: **N-terminal N-myristoylation of proteins: refinement of the sequence motif and its taxon-specific differences.** *J Mol Biol* 2002, **317**:523-540.
  38. Maurer-Stroh S, Eisenhaber B, Eisenhaber F: **N-terminal N-myristoylation of proteins: prediction of substrate proteins from amino acid sequence.** *J Mol Biol* 2002, **317**:541-557.
  39. Morello JP, Bouvier M: **Palmitoylation: a post-translational modification that regulates signalling from G-protein coupled receptors.** *Biochem Cell Biol* 1996, **74**:449-457.
  40. Resh MD: **Fatty acylation of proteins: new insights into membrane targeting of myristoylated and palmitoylated proteins.** *Biochim Biophys Acta* 1999, **1451**:1-16.
  41. Chatterjee S, Mayor S: **The GPI-anchor and protein sorting.** *Cell Mol Life Sci* 2001, **58**:1969-1987.
  42. Eisenhaber B, Bork P, Eisenhaber F: **Post-translational GPI lipid anchor modification of proteins in kingdoms of life: analysis of protein sequence data from complete genomes.** *Protein Eng* 2001, **14**:17-25.
  43. Sinensky M: **Functional aspects of polyisoprenoid protein substituents: roles in protein-protein interaction and trafficking.** *Biochim Biophys Acta* 2000, **1529**:203-209.
  44. Sinensky M: **Recent advances in the study of prenylated proteins.** *Biochim Biophys Acta* 2000, **1484**:93-106.
  45. Trueblood CE, Boyartchuk VL, Picologlou EA, Rozema D, Poulter CD, Rine J: **The CaaX proteases, Afc1p and Rce1p, have overlapping but distinct substrate specificities.** *Mol Cell Biol* 2000, **20**:4381-4392.
  46. Pei J, Grishin NV: **Type II CAAX prenyl endopeptidases belong to a novel superfamily of putative membrane-bound metalloproteases.** *Trends Biochem Sci* 2001, **26**:275-277.
  47. Bergo MO, Leung GK, Ambroziak P, Otto JC, Casey PJ, Gomes AQ, Seabra MC, Young SG: **Isoprenylcysteine carboxyl methyltransferase deficiency in mice.** *J Biol Chem* 2001, **276**:5841-5845.
  48. Hancock JF, Magee AI, Childs JE, Marshall CJ: **All ras proteins are polyisoprenylated but only some are palmitoylated.** *Cell* 1989, **57**:1167-1177.
  49. Kohl NE, Omer CA, Conner MW, Anthony NJ, Davide JP, deSolms SJ, Giuliani EA, Gomez RP, Graham SL, Hamilton K, et al.: **Inhibition of farnesyltransferase induces regression of mammary and salivary carcinomas in ras transgenic mice.** *Nat Med* 1995, **1**:792-797.
  50. Prendergast GC, Rane N: **Farnesyltransferase inhibitors: mechanism and applications.** *Expert Opin Investig Drugs* 2001, **10**:2105-2116.
  51. Armstrong SA, Hannah VC, Goldstein JL, Brown MS: **CAAX geranylgeranyl transferase transfers farnesyl as efficiently as geranylgeranyl to RhoB.** *J Biol Chem* 1995, **270**:7864-7868.
  52. Yokoyama K, Zimmerman K, Scholten J, Gelb MH: **Differential prenyl pyrophosphate binding to mammalian protein geranylgeranyltransferase-I and protein farnesyltransferase and its consequence on the specificity of protein prenylation.** *J Biol Chem* 1997, **272**:3944-3952.
  53. Tamanoi F, Kato-Stankiewicz J, Jiang C, Machado I, Thapar N: **Farnesylated proteins and cell cycle progression.** *J Cell Biochem* 2001, **Suppl 37**:64-70.
  54. Ashar HR, James L, Gray K, Carr D, Black S, Armstrong L, Bishop WR, Kirschmeier P: **Farnesyl transferase inhibitors block the farnesylation of CENP-E and CENP-F and alter the association of CENP-E with the microtubules.** *J Biol Chem* 2000, **275**:30451-30457.
  55. Lebowitz PF, Casey PJ, Prendergast GC, Thissen JA: **Farnesyltransferase inhibitors alter the prenylation and growth-stimulating function of RhoB.** *J Biol Chem* 1997, **272**:15591-15594.
  56. Tamanoi F, Gau CL, Jiang C, Edamatsu H, Kato-Stankiewicz J: **Protein farnesylation in mammalian cells: effects of farnesyltransferase inhibitors on cancer cells.** *Cell Mol Life Sci* 2001, **58**:1636-1649.
  57. Prendergast GC: **Actin' up: RhoB in cancer and apoptosis.** *Nat Rev Cancer* 2001, **1**:162-168.
  58. Pereira-Leal JB, Seabra MC: **Evolution of the Rab family of small GTP-binding proteins.** *J Mol Biol* 2001, **313**:889-901.
  59. Seabra MC, Mules EH, Hume AN: **Rab GTPases, intracellular traffic and disease.** *Trends Mol Med* 2002, **8**:23-30.
  60. Pereira-Leal JB, Hume AN, Seabra MC: **Prenylation of Rab GTPases: molecular mechanisms and involvement in genetic disease.** *FEBS Lett* 2001, **498**:197-200.
  61. Huizing M, Anikster Y, Gahl WA: **Hermansky-Pudlak syndrome and related disorders of organelle formation.** *Traffic* 2000, **1**:823-835.
  62. Dettler JC, Zhang Q, Mules EH, Novak EK, Mishra VS, Li W, McMurtree EB, Tchernev VT, Wallace MR, Seabra MC, et al.: **Rab geranylgeranyl transferase alpha mutation in the gunmetal mouse reduces Rab prenylation and platelet synthesis.** *Proc Natl Acad Sci USA* 2000, **97**:4144-4149.
  63. Seabra MC: **New insights into the pathogenesis of choroideremia: a tale of two REPs.** *Ophthalmic Genet* 1996, **17**:43-46.
  64. van den Hurk JA, Schwartz M, van Bokhoven H, van de Pol TJ, Bogerd L, Pinckers AJ, Bleeker-Wagemakers EM, Pawlowitzki IH, Ruther K, Ropers HH, et al.: **Molecular basis of choroideremia (CHM): mutations involving the Rab escort protein-1 (REP-1) gene.** *Hum Mutat* 1997, **9**:110-117.
  65. Wang T, Danielson PD, Li BY, Shah PC, Kim SD, Donahoe PK: **The p21(RAS) farnesyltransferase alpha subunit in TGF-beta and activin signaling.** *Science* 1996, **271**:1120-1122.
  66. Cox AD, Der CJ: **Farnesyltransferase inhibitors: promises and realities.** *Curr Opin Pharmacol* 2002, **2**:388-393.
  67. **Homo sapiens genome view** [[http://www.ncbi.nlm.nih.gov/mapview/map\\_search.cgi?](http://www.ncbi.nlm.nih.gov/mapview/map_search.cgi?)]
  68. **Protein Data Bank: structure explorer - 3SQC** [<http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=3SQC>]
  69. **Visual Molecular Dynamics** [<http://www.ks.uiuc.edu/Research/vmd/>]
  70. **Protein Data Bank: structure explorer - 1D8D** [<http://www.rcsb.org/pdb/cgi/explore.cgi?pdbId=1D8D>]



## .reviews

The complete version of this article, available online at <http://genomebiology.com/2003/4/4/212>, includes the following additional information:

**Further details** of the prenyltransferase superfamily, the enzymatic mechanism of protein prenyltransferases, and the implications of differences in gene size between the two types of protein prenyltransferases.

**Figure 1**, showing the gene structures and chromosomal locations of human protein prenyltransferase subunit genes.

**Figure 2**, showing the structural relationship between protein prenyltransferase  $\beta$  subunits and squalene-hopene cyclases.

**Table 2**, showing the protein prenyltransferases found in model organisms.

Reference annotations.