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MicroReview

Control of fatty acid desaturation: a mechanism conserved from bacteria to humans

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Summary

Unsaturated fatty acids (UFAs) have profound effects on the fluidity and function of biological membranes. Microorganisms, plants and animals regulate the synthesis of UFAs during changing environmental conditions as well as in response to nutrients. UFAs homeostasis in many organisms is achieved by feedback regulation of fatty acid desaturase gene transcription through signalling pathways that are governed by sensors embedded in cellular membranes. Here, we review recently discovered components of the regulatory machinery governing the transcription of fatty acid desaturases in bacteria, yeasts and animals that indicate an ancient role of transmembrane signalling mechanisms and integrate membrane composition with lipid biosynthesis.

Introduction

cis-Unsaturated fatty acids (UFAs) have crucial roles in membrane biology and signalling processes in organisms ranging from bacteria to humans. The relative UFA content of cellular phospholipids exerts a major influence on the physical properties of most biological membranes. UFAs have a much lower transition temperature than saturated fatty acids because the steric hindrance imparted by the rigid kink of the *cis*-double bond results in much poorer packing of the acyl chains. Thus, UFAs are key molecules in the regulation of cellular membrane fluidity. In addition to their structural role, UFAs have recently been recognized as signalling molecules involved in several essential cellular processes, such as cell differentiation and DNA replication (for recent reviews see Heird and Lapillonne, 2005; Mansilla and de Mendoza, 2005). Alterations in UFA biosynthesis have been implicated in various disease states, including cardiovascular disease, obesity, non-insulin-dependent diabetes mellitus, hypertension, neurological diseases and cancer (Brenner, 2003; Nakamura and Nara, 2004; Sampath and Ntambi, 2005; Thijssen and Mensink, 2005). There are two major mechanisms by which living organisms synthesize UFAs: mostly of them use an oxygen-dependent fatty acid desaturation pathway, whereas many prokaryotes, including *Escherichia coli*, synthesize UFAs anaerobically (Mansilla *et al*., 2004). The fatty acyl desaturases, which introduce double bonds into fatty acyl chains, encompass a family of enzymes, representatives of which are found in all eukaryotes (Tocher *et al*., 1998; Pereira *et al*., 2003; Sperling *et al*., 2003), as well as some prokaryotes such as cyanobacteria, bacilli, mycobacteria and pseudomonads (Mansilla and de Mendoza, 2005; Cronan, 2006; Zhu *et al*., 2006). The reaction catalysed by these enzymes is an oxygen-dependent desaturation of the full-length fatty acid chain, either as an acyl-thioester or as a phospholipid fatty acid moiety, and requires a specific electron transport chain (Fig. 1).

Recent advances in the study of the regulation of fatty acyl desaturases from different organisms have revealed a conceptual convergence: (i) the physical properties of the membrane can activate a signal transduction pathway that controls the expression of their genes and (ii) UFAs, the product of desaturases, act as negative signalling molecules that turn the pathway off. Bacilli, yeast and mammalian regulatory pathways controlling the expression of fatty acid desaturases emerge as the best-understood model systems to postulate such conceptual convergence (Fig. 2). Even in these examples, the information is still fragmentary, and therefore we do not have a complete mechanistic picture of these pathways. Yet, the evident parallels allow certain generalizations to be drawn.

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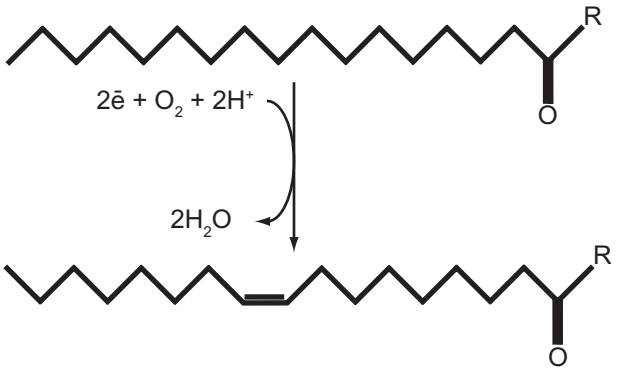

Fig. 1. Reactants and products of a representative fatty acid desaturase. This is a $2e^-$ and O_2-dependent dehydrogenation at an unactivated position of the fatty acid acyl chain, resulting in a *cis*-double bond formation. For acyl-CoA desaturases, R is CoA; for acyl lipid desaturase, R is a phospholipid.

In this review we summarize the current knowledge and recent advances in our understanding of how cells co-ordinate membrane fluidity homeostasis by end-product feedback regulation of desaturase gene transcription.

The DesK–DesR pathway of *Bacillus subtilis*

When poikilothermic organisms such as bacteria, plants and fish are exposed to suboptimal growth temperatures, their membrane lipids become more rigid, leading to subnormal functioning of cellular activities (Phadtare, 2004; Mansilla and de Mendoza, 2005; Al-Fageeh and Smales, 2006). Adaptation to such new conditions involves an increase in the proportion of UFAs in their membrane. The resulting increase in UFA content causes membrane lipid fluidity to return to its original state, or close to it, with concurrent restoration of normal cellular activity at the lower temperature (Mansilla *et al.*, 2004; Phadtare, 2004).

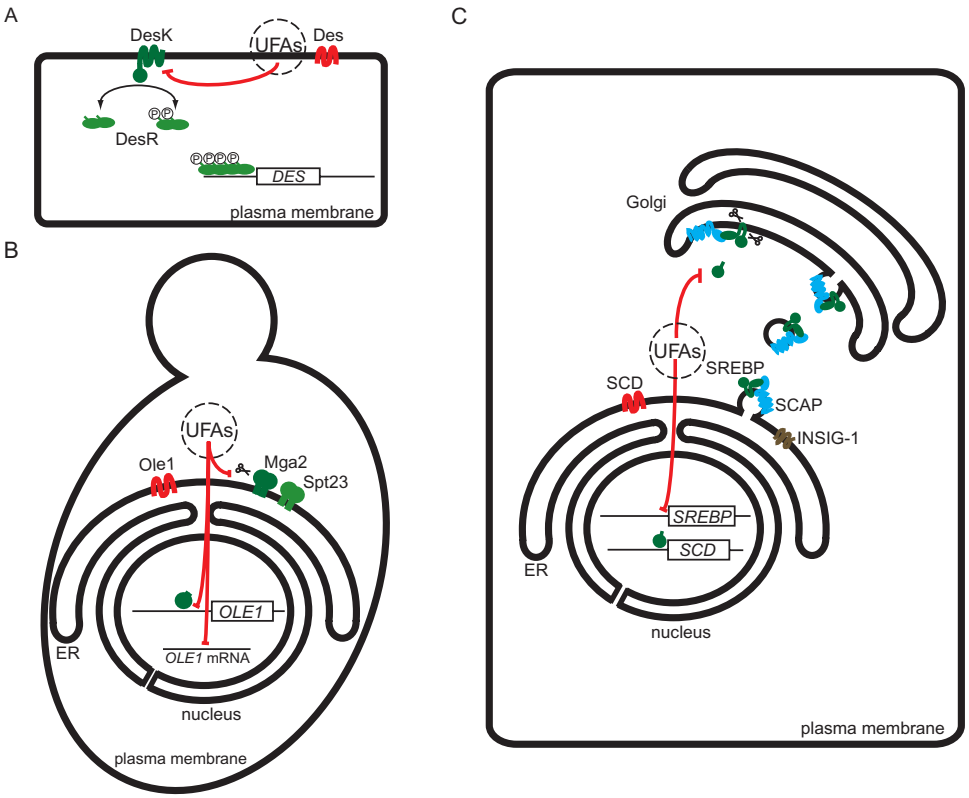

Fig. 2. Models for signal transduction pathways controlling fatty acid desaturation in different organisms.
A. In *B. subtilis* cells, the fluidity sensor DesK determines the phosphorylation state of the transcription factor DesR. The phosphorylated form of DesR leads to activation of the *des* gene and UFAs antagonize DesK kinase activity, presumably affecting the lipid environment of its TM domains.
B. Budding yeast desaturase gene expression requires proteolytic processing of either ER dormant transcription factors Mga2p or Spt23p. UFAs negatively downregulate *OLE1* expression at multiple levels, including intramembrane proteolytic processing repression.
C. In mammalian cells, regulated ER to Golgi trafficking and intramembrane proteolytic processing of SREBP-1 are required for desaturase gene expression. UFAs repress the generation of active soluble SREBP-1 protein as well as its gene transcription.

Bacillus subtilis has only one desaturase, Δ5 desaturase (Δ5D), encoded by the *des* gene (Aguilar *et al*., 1998; Altabe *et al*., 2003). The *B. subtilis* desaturase catalyses the introduction of a *cis*-double bond at the Δ5 position of existing saturated fatty acids in membrane phospholipids. *B. subtilis*, *des* gene transcription increases in response to decreased temperature (Aguilar *et al*., 1998; Kaan *et al*., 2002). A canonical two-component regulatory system comprising the histidine kinase DesK and the response regulator DesR regulates *des* expression (Aguilar *et al*., 2001). The sensor kinase DesK contains five transmembrane (TM) helices and a long cytoplasmic C-terminal tail, which harbours the kinase domain, DesKC. *In vitro* experiments show that DesKC undergoes autophosphorylation on the conserved His188 (Albanesi *et al*., 2004). The phosphorylated kinase then transfers the phosphate to the Asp54 of the dimeric effector DesR, leading to the stabilization of a DesR-P tetramer. This tetramer binds two adjacent, non-identical DesR-P binding sites within the *des* promoter, leading to recruitment of RNA polymerase and activation of *des* transcription (Cybulski *et al*., 2004). Genetic and biochemical evidence suggests that the balance of two antagonistic DesK activities determines the DesR phosphorylation state: a phosphate donor for DesR and a phosphatase activity for DesR-P (for a review, see Mansilla and de Mendoza, 2005). As the activity of DesR as a transcriptional activator is modulated by its phosphorylation state, the output of the DesK–DesR signal transduction pathway is determined by switches between kinase-biased and phosphatase-biased DesK activities. The balance between these activities would be regulated by changes in growth temperature that, in turn, dictates the fluidity of membrane lipids.

The *des* gene is tightly regulated during cold shock. While the *des* transcript is barely detectable at 37°C, its production is transiently induced upon a temperature downshift (Aguilar *et al*., 1999; Kaan *et al*., 2002). Induction of *des* occurs exclusively at the level of transcription in a promoter-dependent fashion and is not caused by stabilization of *des* mRNA, which was reported to be a major cause of the induction of cold-shock-inducible genes in bacteria (Aguilar *et al*., 1999; Gualerzi *et al*., 2003). Desaturation of fatty acids is indeed part of a homeostatic feedback loop, as shown by the fact that *des* transcription is not downregulated by prolonged incubation at low temperatures in the absence of UFAs synthesis, and by the fact that addition of UFAs to the culture medium of cells shifted from 37°C to 20°C specifically inhibits *des* transcription (Aguilar *et al*., 2001).

Experiments in which the proportion of membrane anteiso-branched fatty acids (a-BFAs) of *B. subtilis* was manipulated indicate that membrane fluidity, rather than growth temperature, controls *des* transcription (Cybulski *et al*., 2002). The a-BFAs, which are formed from isoleucine-derived ketoacids, decrease the transition temperature of *B. subtilis* membrane phospholipids and therefore are important to maintain the appropriate fluidity. Limiting the supply of isoleucine dramatically reduces the amount of a-BFAs of plasma membrane lipids, thereby allowing the order of membrane lipids of *B. subtilis* to be increased *in vivo* under isothermal conditions. Isoleucine depletion results in DesK/DesR-dependent activation of *des* transcription at constant temperature. Thus, *des* transcription is induced by the ability of DesK to sense a decrease in membrane fluidity generated either by a temperature downshift or by restricted availability of low-melting point fatty acids at the same temperature (Cybulski *et al*., 2002).

These findings raised a key question: how does DesK sense changes in membrane fluidity? One or more of the five TM helices in DesK could undergo a conformational change induced by a change in the physical state of the membrane lipid bilayer, and transmit this information to the cytoplasmic domain of DesK, thereby altering its activity (Aguilar *et al*., 2001). Direct support for the functional importance of the TM helices comes from studies of *B. subtilis* strains producing the soluble DesKC domain. In these strains, the *des* gene is constitutively expressed and its transcription is affected neither by growth temperature nor by the presence of UFAs (Albanesi *et al*., 2004). Therefore, the TM segments of DesK play an essential role in the end-product feedback regulation of *des* transcription.

The *OLE1* pathway of *Saccharomyces cerevisiae*

Like *B. subtilis*, *S. cerevisiae* possesses a single fatty acid desaturase, Ole1p, which introduces a double bound in the Δ9 position of fatty acids esterified to CoA (Stukey *et al*., 1989; Martin *et al*., 2002). Ole1p localizes into the endoplasmic reticulum (ER), where most of the lipid biosynthetic machinery resides. In this organelle, saturated C-16:0 (palmitic acid) and C-18:0 (stearic acid) acyl-CoA precursors are desaturated, yielding C-16:1 (palmitoleic acid) and C-18:1 (oleic acid) respectively, which are then distributed throughout the membranes of the cell systems and comprise more than 70% of the total fatty acids.

The *OLE1* gene is highly regulated in response to various environmental signals. Like the *B. subtilis des* gene, *OLE1* transcription is transiently activated at low temperature (Nakagawa *et al*., 2002). It is also induced under hypoxic conditions (Kwast *et al*., 1998). As the desaturation reaction utilizes oxygen as an electron acceptor *OLE1* induction under hypoxia might be a response to UFA depletion under such limiting substrate conditions (Nakagawa *et al*., 2001; Vasconcelles *et al*., 2001).

Two related homologous genes of the mammalian transcription factor NF-κB, *SPT23* and *MGA2*, are required for *OLE1* transcription. Disruption of either *SPT23* or *MGA2* has little effect on growth or UFA synthesis, whereas the simultaneous gene disruption results in synthetic auxotrophy for UFAs due to loss of *OLE1* mRNA (Zhang *et al*., 1999a). Spt23p and Mga2p are initially synthesized as inactive precursors that are anchored to the ER membrane via their single, C-terminal TM spans (Hoppe *et al*., 2000). An ubiquitin/proteasome-dependent process cleaves both precursors within their TM regions and the soluble N-terminal domains are transported into the nucleus to promote *OLE1* transcription (Hoppe *et al*., 2000; Hitchcock *et al*., 2001; Rape *et al*., 2001). Under optimal growth conditions, both *spt23*Δ and *mga2*Δ single mutants activate *OLE1* transcription to similar extents, indicating that each transcription factor by itself is sufficient for *OLE1* expression (Zhang *et al*., 1999a; Jiang *et al*., 2001). However, *MGA2* is essential, whereas *SPT23* is dispensable for *OLE1* transcriptional induction under both hypoxic and cold-shock conditions (Jiang *et al*., 2001; Nakagawa *et al*., 2002). In agreement with the preferential role of *MGA2* on *OLE1* transcriptional induction, Mga2p processing is induced during O_2 depletion (Jiang *et al*., 2002). Taken together, these results indicate that environmental signals that perturb membrane fluidity induce *OLE1* expression using a mechanism that involves proteolytic processing of TM domains of ER-anchored transcription factors.

Early work showed that fatty acid desaturation in yeasts is strongly inhibited by addition of UFAs to the growth media (Bossie and Martin, 1989). Furthermore, it was demonstrated that *OLE1* transcription is repressed by a variety of UFAs, the extent of inhibition increasing as the melting point of the added UFA declines (McDonough *et al*., 1992; Fujiwara *et al*., 1998). UFAs also increase *OLE1* mRNA destabilization by a mechanism that is independent of the nonsense-decay pathway, which requires the *OLE1* mRNA 5′ untranslated region and seems to be mediated by exosome mRNA degradation (Gonzalez and Martin, 1996; Vemula *et al*., 2003; Kandasamy *et al*., 2004).

Remarkably, Spt23p and Mga2p cleavage, and therefore generation of the competent transcription factors, are also affected by UFAs. Under normal growth conditions, UFA addition almost completely blocks Spt23p cleavage, whereas Mga2p processing seems to be mildly affected (Hoppe *et al*., 2000; Jiang *et al*., 2002). However, Mga2p cleavage, which is strongly induced by hypoxia, is counteracted by exposure of cells to UFAs (Jiang *et al*., 2002).

The synthesis of a soluble N-terminal fragment of Mga2p in an *spt23*Δ *mga2*Δ double mutant strain is sufficient to promote *OLE1* transcription, but expression of *OLE1* remains sensitive to inhibition by UFAs. This finding indicates that UFA-mediated repression of *OLE1* can also act downstream of Mga2p proteolytic cleavage (Chellappa *et al*., 2001). On the other hand, *OLE1* was also expressed but UFA-mediated repression was not observed when a soluble version of Spt23p was produced in the *spt23*Δ *mga2*Δ mutant strain, indicating that processing is the key step in Spt23p regulation by UFAs (Chellappa *et al*., 2001).

Regulation of proteolytic processing of Spt23p and Mga2p by UFAs and different environmental stresses that affect the physical state of cellular membrane lipids resembles the regulated intramembrane proteolysis (RIP) pathway (see below). The differences between Mga2p and Spt23p suggest that both proteins have evolved complementary, overlapping roles in the regulation of *OLE1*, and perhaps other genes that remain to be identified.

The sterol regulatory element-binding protein pathway of animal cells

Two distinct groups of fatty acid desaturases are present in mammals. One group comprises the stearoyl-CoA desaturase (SCD) and the other consists of Δ5D and Δ6 desaturase (Δ6D). SCD catalyses the biosynthesis of Δ9 monounsaturated fatty acids, while Δ6D and Δ5D are key enzymes in the synthesis of highly polyunsaturated fatty acids (PUFAs) (Nakamura and Nara, 2004; Ntambi and Miyazaki, 2004; Sampath and Ntambi, 2005).

Human and mice SCDs, which have a high degree of similarity to Ole1p, are the rate-limiting enzymes catalysing the biosynthesis of oleic acid from stearic acid in the ER (Ntambi and Miyazaki, 2004). Four isoforms of SCDs (SCD-1 to SCD-4) have been identified in mice (Miyazaki *et al*., 2004; Nakamura and Nara, 2004) and two (hSCD-1 and hSCD-5) in humans (Zhang *et al*., 1999b; Wang *et al*., 2005). *SCD-1* and *SCD-2* genes transcriptional regulation is inscribed in the widely spread signalling pathway known as RIP (Shimomura *et al*., 1998; Horton *et al*., 2002). The distinctive feature of RIP is that the cleavage of a protein within a membrane spanning helix releases a functional domain that is translocated to the nucleus, where it regulates transcription (for recent reviews, see Rawson, 2002; Ehrmann and Clausen, 2004). In the case of *SCD-1* and *SCD-2* transcriptional regulation, the TM proteins that are subject to RIP are the sterol regulatory element-binding proteins (SREBPs) (Tabor *et al*., 1999). SREBP-regulated cleavage is best understood for the control of cholesterol homeostasis. In the presence of sterols, SREBP and SREBP cleavage-activating protein (SCAP) form a complex that remains in the ER. Retention of the SREBP–SCAP complex in the ER requires interaction with INSIG-1 or -2. In the absence of sterols, SCAP undergoes a conformational change,

through its sterol-sensing domain (SSD), which detaches the SCAP–SREBP complex from INSIG-1/2. The SCAP–SREBP complex is then transported to the Golgi apparatus, where SREBP is proteolytically processed, releasing an active soluble domain. Processed SREBP travels to the nucleus and binds to sterol regulatory elements (SRE) to activate genes involved in the synthesis and uptake of cholesterol and fatty acids (Rawson, 2003; Goldstein *et al*., 2006). SREBPs have two isoforms, SREBP-1 and SREBP-2, which are transcribed from different genes. SREBP-1 has two subforms, SREBP-1a and SREBP-1c, which result from the use of two different promoters of the same gene and alternative splicing of the mRNAs (Yokoyama *et al*., 1993; Sato *et al*., 1994). SREBP-2 mainly activates the transcription of genes involved in cholesterol synthesis and uptake, whereas SREBP-1c targets genes for fatty acid synthesis, and SREBP-1a induces both (Horton *et al*., 2002). Transcription of both *SCD-1* and *SCD-2* genes is induced in response to sterol depletion and, conversely, diminished upon addition of excess sterols (Tabor *et al*., 1999). Detailed studies demonstrated that this sterol-mediated regulation of *SCD-1* and *SCD-2* is achieved through binding of processed SREBP-1a and nuclear factor Y to three conserved regions within the *SCD-1* and *SCD-2* promoters (Tabor *et al*., 1999).

It has long been recognized that a diet rich in UFAs decreases the production of SCDs (Sampath and Ntambi, 2005). On the other hand, several studies demonstrated that UFAs inhibit the cleavage of the precursor form of SREBP, resulting in decreased levels of nuclear SREBP and a concomitant reduction of SREBP target gene transcription (for a review, see Sampath and Ntambi, 2005). These finding were extended by Tabor *et al*. (1999), who found that PUFAs repress transcription of the murine *SCD-1* and *SCD-2* genes in a SREBP-dependent process. Hannah *et al*. (2001) provide a comprehensive analysis of the effects of various fatty acids on the levels of mRNA and protein for all three isoforms of SREBP in cultured human embryonic kidney (HEK-293) cells. Their results show that UFAs regulate both SREBP-1a and SREBP-1c but not SREBP-2. This regulatory role of UFAs is manifested in two different ways: first, *SREBP-1a* and *SREBP-1c* mRNA levels are markedly decreased by UFAs and, second, UFAs lowered the levels of the cleaved nuclear form of SREBP-1 (nSREBP-1), even in the absence of exogenous sterols (Hannah *et al*., 2001). The potency of UFAs increased with increasing chain length and degree of unsaturation. Oleate, linoleate (18:2), and arachidonate (20:4) were all effective, but the saturated fatty acids palmitate and stearate were not. When the level of mRNA for *SREBP-1a* was held constant through transfection, UFAs still reduced nSREBP-1. Moreover, UFAs did not have any effect on cells that were engineered to produce a truncated nuclear form of SREBP-1, suggesting that post-transcriptional repression is exerted at the level of the proteolytic processing of the SREBP-1 precursor (Hannah *et al*., 2001).

Recent advances have revealed that mammalian Δ5D and Δ6D desaturases share common regulatory mechanisms with those described for SCD desaturases (Nakamura and Nara, 2004). Most notably, SREBP1-c activates transcription of Δ5D and Δ6D and the production of these desaturases is also suppressed by PUFAs (Matsuzaka *et al*., 2002; Nakamura and Nara, 2002; 2004). Therefore, mammalian cells exert exquisite control over the three desaturases to maintain an appropriate composition of UFAs in their phospholipids.

Conclusions

Although the data reviewed here are incomplete, they clearly show that UFA synthesis catalysed by fatty acyl desaturases is co-ordinated by feedback regulation of transcription in organisms ranging from bacteria to human. These findings reveal mechanisms by which a conformational change in sensor proteins converts information about the physical properties of membranes into control of transcription of genes with end-products that ultimately alter the membrane composition.

The mechanisms described here have been selected through evolution to modify the biophysical properties of cellular membranes rapidly because they are well suited for a rapid and reversible activation of desaturase gene expression. The sensors controlling the production of the bacterial and mammalian desaturases receive their signals from the same environment in which the enzymes reside. Indeed, DesK is located in the plasma membrane, whereas SCAP resides in the ER membrane. Although a putative sensor that governs the cleavage of ER residents Mga2p and Spt23p has not yet been identified, it is most likely an ER protein.

A crucial unresolved problem relates to the mechanism of how regulatory circuits like the DesK–DesR and the OLE1 pathways are activated by an increase in the proportion of ordered lipids in response to environmental stresses. The TM helices of DesK seem to be essential to sense changes in membrane fluidity and for regulating the ratio of kinase activities to phosphatase activities of the C-cytoplasmic domain DesKC. Nevertheless, a detailed picture of the molecular mechanism of DesK TM signalling is still under development.

A still poorly understood scenario is that of the different roles of Mga2p and Spt23p in *OLE1* regulation. This division of labour between these two transcription factors suggests that the same signal transduction pathway has been adapted to integrate different signals at the ER membrane into different cellular responses. Identification

of new Mga2p- and Spt23p-regulated genes as well as the putative sensor that regulates the cleavage of these transcription factors represents a key step to a better understanding of *OLE1* regulation in yeasts.

The mechanisms by which UFAs repress SREBP-1 cleavage remain to be determined. It is not known if SCAP is involved in UFA-mediated SREBP-1 downregulation. An exciting possibility is that the SSD of SCAP might be a more general monitor of membrane lipid composition. If this is the case, inhibition of SREBP-1 processing might result from changes in the physical state of lipids, induced by UFAs in the local environment surrounding SCAP. UFAs act synergistically with sterols under certain circumstances (Seegmiller *et al*., 2002). As cholesterol induces a conformational change in SCAP and promotes interaction between SCAP and the INSIG proteins, the incorporation of UFAs into the ER membranes could enhance the binding of cholesterol to SCAP in same way.

The findings discussed here also raise several questions about how these regulatory circuits are down-tuned. Do UFAs become enriched around the TM helices of DesK? If this is the case, are UFAs preferentially synthesized around the sensor protein? What step in Spt23p and Mga2p ubiquitin-proteasome-mediated processing is inhibited by UFAs? Do UFAs affect INSIG–SCAP interactions or is another retention factor involved in UFA-mediated reduction of soluble SREBP-1 production? It will be interesting to pursue these questions to obtain a better understanding of the mechanisms by which cells maintain appropriate membrane fluidity. As shown by the examples discussed in this review, lessons from one system can quickly shed light onto others over vast evolutionary distances.

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