When an enzyme is mentioned in the White House, even if only in the world of the popular television drama West Wing, it is clear that this enzyme has earned a wide reputation. So the statement of a female doctor attending the First Lady's dinner party indicating that sphingosine kinase controls "all signal pathways to cancer growth" suggests that this enzyme, and its product sphingosine-1-phosphate (SIP), have gained prominence in the scientific community. Why have sphingosine kinase and SIP entered the popular media? In other words, what is the evidence of their importance?

Sphingosine kinase is a component of the sphingolipid metabolic pathway (Fig 1). Sphingosine kinase phosphorylates sphingosine, formed by deacylation of ceramide, to yield SIP. In turn, ceramide is well known as a structural component of the skin, where ceramides help to form the epidermal water–permeability barrier. Indeed, the epidermis synthesizes some unique ceramides, such as omega-hydroxyceramides (Behne et al, 2000) and phytosphingosine-containing ceramides (Hamanaka et al, 2002). However, perhaps less well known to those in the dermatologic field is the role of ceramide as a lipid second messenger. A little over a decade ago, reports began to surface concerning the ability of certain cytokines and other signals to activate a sphingomyelinase activity that hydrolyzes sphingomyelin to form ceramide and phosphorylcholine (reviewed in Kolesnick, 2002). In addition, using synthetic analogs to mimic the effects of sphingomyelinase-activating agents, these investigators demonstrated the ability of ceramide to function as a signaling molecule. A large number of subsequent studies have shown that ceramide can also be generated by a de novo pathway (Fig 1) and that ceramide functions mostly as an antiproliferative second messenger. Thus, increases in ceramide are often associated with growth arrest, differentiation, senescence and apoptosis, as has been shown in numerous cell types (reviewed in Kolesnick, 2002 and Hannun and Obeid, 2002), including keratinocytes (e.g., Bektas et al, 2000).

Consistent with the idea of ceramide as an antiproliferative signal, hyperproliferative cancer cells, which often evade the apoptosis usually triggered by ceramide-increasing agents, have been found to utilize multiple metabolic enzymes to decrease ceramide levels. For instance, multidrug-resistant cells express higher activities of the enzyme glucosylceramide synthase, which glycosylates the ceramide formed in response to chemotherapeutic agents to produce glucosylceramide and reduce ceramide levels (Fig 1 and reviewed in Hannun and Obeid, 2002). This enzyme also protects keratinocytes against ceramide-induced stress/apoptosis by converting ceramide to glucosylceramide (Uchida et al, 2002). Transformed cells have also been shown to exhibit increased activity of the enzyme, sphingomyelin synthase (Luberto and Hannun, 1998), which transfers the choline headgroup from phosphatidylcholine to ceramide to generate sphingomyelin and diacylglycerol (Fig 1). Other studies have indicated that provision of sphingolipids in the diet reduces tumor formation in mice treated with a carcinogen to induce the development of colon cancer and genetically predisposed to develop colon cancer (Vesper et al, 1999 and Schmelz et al, 2001). Sphingolipids can inhibit the development of skin carcinomas as well (Birt et al, 1998).

On the other hand, still other research has suggested that agents that increase ceramide can also trigger proliferative responses. For instance, mitogenic growth factors can activate ceramidase, which decylates ceramide to form sphingosine (reviewed in Spiegel et al, 1998). Sphingosine, in turn, can be phosphorylated by sphingosine kinase to yield sphingosine 1-phosphate. This lipid metabolite acts as a first messenger by binding to a family of GTP-binding protein-coupled receptors, the SIP receptors (formerly known as the endothelial differentiation gene, or EDG, receptors—see Chun et al, 2002), although other data also suggest possible intracellular sites of SIP action (reviewed in Spiegel et al, 1998). In most cell systems (but see below) SIP mediates proliferative cell responses and/or cell survival (reviewed in Spiegel et al, 1998). Thus, the combined activities of ceramidase and sphingosine kinase may account for the observation that some ceramide-elevating agents increase proliferation. Indeed, in human keratinocytes 1,25-dihydroxyvitamin D₃-stimulated sphingomyelinase activation does not lead to apoptosis because of the concomitant generation of SIP (Manggau et al, 2001). In addition, the activity of sphingosine kinase can be regulated by protein kinase C (reviewed in Spiegel et al, 1998), which may explain the finding that the ability of an agent to trigger apoptosis may depend on the activation status of diacylglycerol-activated protein kinase C. Thus, regulation of the interconversion of different pro- and antiapoptotic sphingolipid metabolites, as well as pathways of glycerolipid metabolism, may determine the ultimate cellular response to various agents.

On the other hand, in this issue of the Journal of Investigative Dermatology Vogler et al demonstrate that in keratinocytes (but not dermal fibroblasts) SIP functions as an antiproliferative, prodifferentiative signal. The mechanism underlying the opposite effect of SIP in keratinocytes versus dermal fibroblasts (as well as other cell types) is not known. This antiproliferative, prodifferentiative effect in keratinocytes also seems paradoxical based on their observation that SIP has the additional capacity to stimulate the migration of these cells. It can be speculated, however, that SIP released from platelets at sites of wounding, may stimulate healing and reepithelialization by recruiting keratinocytes to the site and inducing their differentiation to mature cells. Moreover, the mechanism by which SIP exerts its function is not entirely clear, since Vogler et al provide evidence of G-protein-coupled SIP receptors both in keratinocytes in vitro and in the epidermis, as well as possible intracellular actions of this lipid messenger. A component(s) of the sphingolipid pathway may also play a role in atopic dermatitis. Thus, Imokawa and colleagues have discovered increased levels of a novel sphingolipid-metabolizing

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**Paradoxical Effects of Sphingosine-1-Phosphate**

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enzyme only in atopic dermatitis patients, but not in normal controls or those with contact dermatitis or chronic eczema (Murata et al., 1996). This enzyme, glucosylceramide sphingomyelin deacylase, removes the acyl group from sphingomyelin (and glucosylceramide) to produce sphingosylphosphorylcholine (and glycosylated sphingosylphosphorylcholine) (Higuchi et al., 2000). Indeed, sphingosylphosphorylcholine (SPC) is up-regulated in the stratum corneum of atopic dermatitis patients (Okamoto et al., 2003). SPC, in turn, is thought to function as a ligand for G-protein-coupled SPC receptors, similar to the SIP receptors, and trigger cellular responses such as enhanced transglutaminase activity (Higuchi et al., 2001). In addition, SPC increases intercellular cellular adhesion molecule-1 (ICAM-1) expression on keratinocytes (Imokawa et al., 1999). Since ICAM-1 can recruit leukocytes from the circulation, this effect may contribute to the presence of activated immune cells in patients with atopic dermatitis. In addition, the loss of the sphingomyelin substrate from the epidermis of these patients might also contribute to another feature of the disease—reduced epidermal ceramide levels (see references cited in Murata et al., 1996), which may mediate, at least in part, the observed symptom of skin dryness. Whether this decrease in ceramide also alters a signaling pathway, in addition to its effects on the lipid permeability barrier, is not yet clear.

On the other hand, it is clear that metabolites of the sphingo- lipid pathway play an important role in epidermal physiology. Obviously, some of these sphingolipids function as structural components of the lipid permeability barrier. As shown in this issue, another member of this pathway, SIP functions as a signal to activate several G-protein-coupled SIP receptor subtypes, as well as possibly acting intracellularly. Another metabolite, SPC may also affect keratinocyte cellular responses, possibly through G-protein-coupled SIP-like receptors. Undoubtedly, an understanding of the interconversion of these lipid structural and signaling molecules is essential, and additional studies, like the one by Vogler et al. on the role and actions of sphingolipids in keratinocytes and in the epidermis are necessary.

REFERENCES


