FEATURED NEW INVESTIGATOR

Sphingosine metabolism as a therapeutic target in cutaneous melanoma

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Melanoma is by far the most aggressive type of skin cancer with a poor prognosis in its advanced stages. Understanding the mechanisms involved in melanoma pathogenesis, response, and resistance to treatment has gained a lot of attention worldwide. Recently, the role of sphingolipid metabolism has been studied in cutaneous melanoma. Sphingolipids are bioactive lipid effector molecules involved in the regulation of various cellular signaling pathways such as inflammation, cancer cell proliferation, death, senescence, and metastasis. Recent studies suggest that sphingolipid metabolism impacts melanoma pathogenesis and is a potential therapeutic target. This review focuses on defining the role of sphingolipid metabolism in melanoma carcinogenesis, discussing sphingolipid-based therapeutic approaches, and highlighting the areas that require more extensive research. (Translational Research 2017;185:1–12)

Abbreviations: ALL = acute lymphocytic leukemia; Brms1 = breast cancer metastasis suppressor 1; CerS = ceramide synthase; CML = chronic myeloid leukemia; DES = desaturase enzyme; Drp1 = dynamin-related protein 1; ER = endoplasmic reticulum; GlcCer = glucosylceramide; GLUT1 = glucose transporter 1; PP1 = activating protein phosphatase 1; PP2A = protein phosphatise 2A; S1P = sphingosine 1 phosphate; S1PP = sphingosine-1-phosphate phosphatise; S1PR = sphingosine 1 phosphate receptor; SK1 = sphingosine-1-phosphate; SK2 = sphingosine kinases 2; SMase = sphingomyelinase; SMS = sphingomyelin synthase; SPT = serine palmitoyl CoA transferase

INTRODUCTION

According to the National Cancer Institute, the incidence of invasive melanoma in the United States was estimated to be about 73,870 cases in 2015 and one American dies of melanoma every hour.[1] Melanoma treatment depends on the stage of the cancer. Early lesions are often cured by surgical excision alone, whereas more advanced disease requires systemic therapy.[2] The 10-year overall survival rate for advanced melanoma is improving, but is still only 10%–15%.[3,4] One challenge in the field of melanoma is understanding the impact of the different metabolic pathways on melanoma pathogenesis. In particular, it is important to understand the role of the metabolism of cancer-related bioactive molecules in melanoma pathogenesis. This will help in developing novel therapeutic strategies that target the metabolism of such bioactive molecules.

Advances in sphingolipid research are continuously proving the impact of sphingolipid metabolism on cancer pathogenesis.[5] Sphingolipids are membrane lipids that

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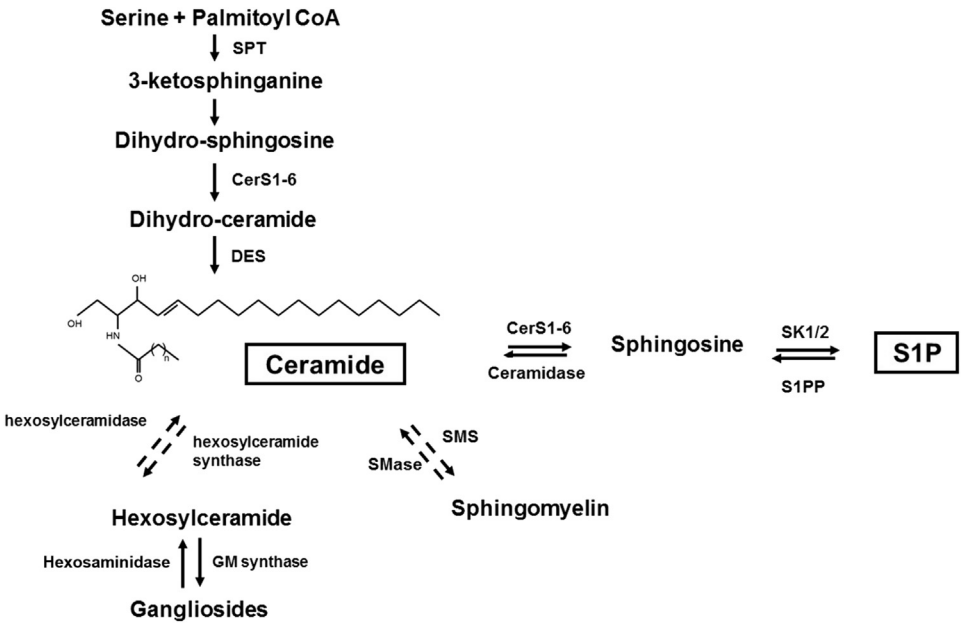

Fig 1. Metabolism of ceramide and S1P. Ceramide lies at the center of sphingolipid metabolism. De novo generation of ceramide requires the condensation of serine and palmitoyl CoA by the enzyme serine palmitoyl CoA transferase (SPT) to generate 3-ketosphinganine, which is then converted into dihydrosphingosine. Ceramide synthases (CerS1–6) generate dihydroceramide which get desaturated to ceramide by desaturase enzyme (DES). Ceramide can be converted to sphingosine-1-phosphate (S1P) via ceramidase followed by the action of sphingosine kinase 1 (SK1) or sphingosine kinases 2 (SK2). Ceramide can be generated back from S1P via sphingosine-1-phosphate phosphatase (S1PP). Ceramide can be generated from sphingomyelin via sphingomyelinase (SMase) and from glycosphingolipids via hexosylceramidase. Ceramide also serves as the precursor of sphingomyelin via sphingomyelin synthase (SMS) and gangliosides using several enzymes such as hexosylceramide synthase and GM synthase.

were discovered for their important functions in regulating membrane fluidity and subdomain structures. Indeed, sphingolipids have long been recognized as important structural components of the epidermis, securing the epidermal permeability barrier.[6] Recently, it was revealed that sphingolipids have signaling roles apart from their structural roles. In particular, several sphingolipid species were shown to act as bioactive signaling lipids in cancer cells. Ceramide is one of the most bioactive sphingolipids that plays a key role in many of the cellular functions including cell proliferation, death, migration, and senescence.[7] Ceramides account for 30%–40% of stratum corneum lipids.[8] Ceramide metabolism is intimately involved in cancer pathogenesis. Ceramide and its metabolites are not only involved in cancer initiation and progression, but also in the response of cancer cells to chemotherapeutic agents and radiation-induced cell death. Unlike ceramide, sphingosine-1-phosphate (S1P) is a tumor-promoting bioactive sphingolipid. The intricate balance between the levels of ceramide and S1P dictates whether a cancer cell undergoes proliferation or cell death. This is known as the ceramide-S1P rheostat and can be targeted by several approaches to sway the balance toward ceramide generation or inhibition of S1P synthesis, to result in cancer cell death. In this review article, we discuss the role of sphingolipid metabolism in the tumor pathogenesis of melanoma and the different potential therapeutic approaches that target sphingolipid metabolism.

METABOLISM OF BIOLOGICALLY ACTIVE SPHINGOLIPIDS: CERAMIDE AND S1P

Ceramide is composed of a sphingosine backbone esterified to a fatty acyl chain via an amide linkage.[5,7] The length of the fatty acyl chain conjugated to the sphingosine backbone characterizes the different species of ceramide. For instance, C_{18}-ceramide contains a fatty acyl chain with n = 18 carbons. Ceramide species range from C_{14}- to C_{26}- ceramides.[5]

Ceramide lies at the center of sphingolipid metabolism. It can serve as a precursor for more complex sphingolipids or as a product of the breakdown of other sphingolipids (Fig 1).[5] For example, ceramide acts as a precursor for the generation of glucosyl ceramides and as a product of the breakdown of sphingomyelin.[9]

De novo generation of ceramide involves the action of ceramide synthases 1–6 (CerS1–6). CerS1–6 catalyze the reaction of esterifying a fatty acyl CoA to