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Review Article

Revisiting the sphingolipid rheostat: Evolving concepts in cancer therapy

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Introduction

Nearly two decades have passed since it was first proposed that regulation of the interconvertible sphingolipid metabolites, ceramide and sphingosine-1-phosphate (S1P), and their opposing signaling pathways are major determinants of cell fate, a concept referred to as the "sphingolipid rheostat". Since then, many reports have substantiated the role of the sphingolipid rheostat in cell fate determination and in the initiation, progression, and drug sensitivity of cancer. Thus, modulation of the rheostat has emerged as a focus for treatment strategies to battle cancer. S1P regulates numerous processes important for cancer including proliferation, transformation, angiogenesis, metastasis, survival, and drug resistance. Ceramide on the other hand has been linked to cell growth arrest and cell death. With the increased understanding of sphingolipid metabolism and signaling, as well as the present focus on therapies designed to modulate the levels of sphingolipids in cancer, it is an appropriate time to re-examine the sphingolipid rheostat concept and determine how it fits within the current knowledge of sphingolipid signaling in cancer.

Sphingolipid metabolism

Sphingolipids are essential constituents of all eukaryotic membranes. They contain a sphingoid base, a fatty amino alcohol of typically 18 carbons, in mammalian cells called sphingosine. *De novo* synthesis of the sphingoid base begins with the condensation of palmitate and serine catalyzed by serine palmitoyl transferase, leading to the formation of dihydrosphingosine (sphinganine), which is then amino-acylated with a chain of 14–32 carbons to form various dihydroceramide species by a family of six (dihydro) ceramide synthases. Dihydroceramides are desaturated to form ceramides and complex sphingolipids, such as glycosphingolipids and sphingomyelin that are built by linking different head groups to the primary hydroxyl group of ceramides. During catabolism, both basal and signal-mediated, these head groups are hydrolyzed, re-generating ceramide. Ceramide is a bioactive lipid in its own right, and can be deacylated by ceramidases to yield sphingosine. Sphingosine, which is not an intermediate in the *de novo* biosynthetic pathway, is also a bioactive molecule and can be phosphorylated by sphingosine kinase (SphK) type 1 and 2 to sphingosine-1-phosphate (S1P), again a potent signaling molecule. S1P can be irreversibly degraded by S1P lyase (SPL) or dephosphorylated to sphingosine, which can then be re-acylated back to ceramide. It is the rapid, compartment-specific interconversion of these three metabolites with distinct effects on cell fate that forms the biochemical basis of the so-called "sphingolipid rheostat".

The sphingolipid rheostat

In 1996, the term "sphingolipid rheostat" was proposed [1] to tie together several seminal findings demonstrating the capacity of S1P and ceramide to differentially regulate cell growth and survival by modulation of opposing signaling pathways [1–3]. This was based on the discoveries that elevation of ceramide induces cell growth arrest and apoptosis [3], whereas S1P production is required for optimal cell proliferation induced by growth factors [4] and suppresses ceramide-mediated apoptosis [1]. Insight that the "sphingolipid rheostat" coordinately regulates the levels of these sphingolipid metabolites to control cell fate emerged from inhibition of SphK leading to decreased S1P and elevated ceramide, and subsequent cell death (Fig. 1). Thus, the sphingolipid rheostat appeared to be a sensing mechanism for cells to regulate their fate in part through the interconversion between S1P and ceramide.

In the years since, efforts have been made to elucidate the molecular mechanisms and signaling pathways by which these

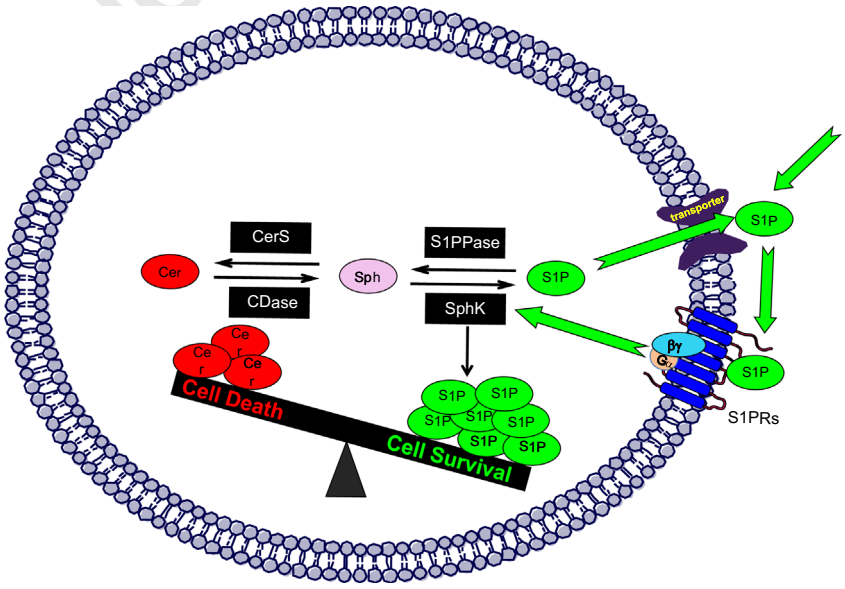

Fig. 1 – The updated sphingolipid rheostat. This schematic cartoon shows important enzymes that regulate the levels of S1P and ceramide and includes "inside-out" signaling by the S1P/S1PR1 axis that can influence actions of the sphingolipid rheostat. CerS, ceramide synthase; CDase, ceramidase; S1PPase, S1P phosphatase; S1PRs, S1P receptors.

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