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New aspects of sphingosine-1-phosphate in inflammation, cancer progression, and metastasis

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Sphingosine 1-phosphate (S1P) is a pleiotropic bioactive sphingolipid metabolite that regulates numerous processes important for inflammation and cancer. S1P is generated intracellularly by two sphingosine kinases (SphK1, SphK2) and is exported out of cells by Spinster 2 (Spns2) to exert its effects through activation of five specific cell surface S1PRs in autocrine or paracrine manners. In this lecture, I will focus on several new roles of SphKs and Spns2 in regulation of immune cell trafficking, cancer progression, and pulmonary metastasis. I will highlight critical roles for circulating S1P produced by tumors and the SphKs/S1P/S1PR axis in obesity-promoted inflammation, metastatic niche formation and breast cancer metastasis. I will also summarize the role of Spns2 in autoimmune diseases and metastatic pulmonary colonization. In addition, I will discuss recent studies demonstrating that SphK1 is recruited to sphingosine-enriched endocytic vesicles and that phosphorylation of sphingosine to S1P by SphK1 is involved in endocytic membrane trafficking and autophagy and in the crosstalk between endocytosis, autophagy, and apoptosis. Collectively, our work suggests that targeting Spns2 and/or SphKs/S1P/S1PR axis would be a useful therapeutic for several human diseases including metastatic cancers.

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