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Editorial

Sphingolipid Activity in Oxidative Stress Response and Tumor Immunity

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Editorial

Sphingolipids have become recognized as highly bioactive lipids with critical impacts on essential cellular functions and systemic host responses [1]. Especially the central molecules of this family, ceramide with its metabolites sphingosine and Sphingosine-1-Phosphate (S1P) exert key controls in the regulation of cell survival/death and immune surveillance [2,3]. Exposure of cancer cells to stress-causing agents or treatments, for instance Photodynamic Therapy (PDT) up regulates the expression of enzymes controlling de novo synthesis of sphingolipids and results in an increase in tumor levels of ceramide, its precursor dihydroceramide as well as S1P [2,4-6]. Moreover, adjuvant treatment with agents that prompt increases in cellular levels of key sphingolipids was demonstrated as effective in increasing the cure rates of PDT-treated tumors [5,6].

Oxidative stress involving Endoplasmic Reticulum (ER) such as inflicted by PDT has recently raised a particular interest in immunology research because of the relevance of ER stress response to the induction of Immunogenic Cell Death (ICD) [7]. In case when the Unfolded Protein Response (UPR), orchestrated in an attempt of re-establishing local homeostasis is unsuccessful in resolving the insult, selected signal transduction pathways become activated securing the transition from adaptive to lethal phase of ER stress response [8]. This is accompanied by the abundant expression of various Damage-Associated Molecular Patterns (DAMPs) due to the induction of their trafficking from the ER to cellular surface and extracellular space enabling them to drive inflammatory/immune responses. One of the prototypic DAMPs is the ER protein calreticulin [9]. However, ER is also the site of biosynthesis of sphingolipids and it was shown recently that the key members, ceramide, S1P and sphingosine become exposed on the surface and/or released from PDT-treated tumor cells acquiring the capacity to act as DAMPs [10-11]. Secretion of S1P from cells is a well-established phenomenon [12]. As a lipophilic molecule, ceramide is arguably not released as a free entity but possibly in membrane fragments shed from damaged cells or secreted in exosomes [11]. The sphingolipids ceramide and S1P were found expressed on cell surface in PDT dose-dependent manner and were detected as early as 15 minutes post treatment [10]. They were shown to have a capacity to influence immune cells in their microenvironment, including activating inflammasome (sphingosine) and NFκB signaling in macrophages [10,11,13].

Macrophages and other immune cells are richly endowed with receptors that can recognize DAMP signaling mediated by sphingolipids; these extend from specific receptors like those dedicated for S1P to pattern recognition receptors including Toll-like receptors and NOD-Like Receptor Pyrin Domain-Containing 3 (NPLR3). Macrophages normally contain much higher levels of ceramide and S1P than cancer cells. Incubated in presence of PDT-treated tumor cells or supernatants from their culture, macrophages were found to elevate considerably their levels of ceramide and S1P [11]. This observation suggests that sphingolipid-mediated DAMP signaling could not only be detected but also further amplified in these immune sentinels for optimal propagation of danger signals.

The approach to increasing tumor cure-rates of certain cancer therapies by adjuvant application of sphingolipid metabolism-modulating agents is attracting attention by the revealed prospects of two pronged action: boosting dihydroceramide/ceramide-mediated mitochondrial apoptosis plus lethal autophagy and potentiating antitumor immune responses by stepping-up sphingolipid DAMP signaling. Interestingly, and similarly to the DAMP calreticulin, the latter may be more dominant for therapy outcome as suggested by the lack of benefit with tumors growing in immunocompromised hosts [14]. There are indications that blocking ceramide conversion into sphingosine may result in a repression of the activity of both lymphoid and myeloid immunoregulatory populations that hinder immune rejection of tumors (Korbelik, unpublished findings). Therefore, a number of indicators have emerged recently warranting the benefits of dedicated investigation on how to exploit sphingolipid metabolism modulation for potentiating the development of antitumor immunity instigated by established cancer treatment modalities.

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