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Review Article

Neutral Sphingomyelinase and Breast Cancer Research

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Our understanding of the functions of neutral sphingomyelinase (N-SMase) signaling has advanced over the past decade. In this review, we focus on the roles and regulation of N-SMase 1, N-SMase 2, N-SMase 3, an enzyme that generates the bioactive lipid ceramide through the hydrolysis of the membrane lipid sphingomyelin. A large body of work has now implicated N-SMase 2 in a diverse set of cellular functions, physiological processes, and disease pathologies. We focus on different aspects of this enzyme's regulation from transcriptional, post-translational, and biochemical. Furthermore, we expected N-SMase involvement in cellular processes including inflammatory signaling, cell growth, apoptosis, and tumor necrosis factor which in turn play important roles in pathologies such as cancer metastasis, variable disease, and other organ system disorders. Lastly, we examine avenues where targeted N-SMase inhibition may be clinically beneficial in disease scenarios. **(J Menopausal Med 2015;21:24-27)**

Key Words: Breast neoplasms, Sphingomyelin phosphodiesterase, Tumor necrosis factor-alpha

Introduction

Sphingomyelin hydrolysis is catalyzed by a class of enzymes referred to as sphingomyelinases (SMases) to generate ceramide. Ceramide and sphingolipid metabolites are well-established regulators of many important cellular signaling pathways and are implicated in human health and disease.[1] SMases are classified based on their pH optima of activity into acid, neutral, and alkaline subtypes. Of the four different mammalian neutral SMases that have been identified; neutral SMase 1 (N-SMase 1), N-SMase 2, N-SMase 3, Mitochondrial-Associated Neutral SMase (MA-N-SMase) appears to be the predominant N-SMase in cellular systems, physiologies, and pathologies.[2,3] Breast cancer is still the most common type of cancer in women and Gail model (risk measurements) thought prediction increase role.[4] Surgical resection method is the best way for a correct diagnosis but recently, in surgery incisions and shorter time of more precise lesions, scars and could result from reduced recommend the future of mammotome.[5] According to a recent study, breast cancer characteristics of Korean postmenopausal women have a high incidence is also higher hormone receptor-positive rate of breast cancer.[6] Breast cancer patients are not recommended hormone therapy. Because it is hormone therapy increases of the risk and affect the existing not expected to not diagnosis another breast cancer.[7]

This review will focus on the roles and regulation of this enzyme emphasizing recent findings implicating N-SMase in disease processes.

Classification of Neutral SMase

1. N-SMase 1

N-SMase 1 was the first discover mammalian N-SMase

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based on sequence homology to bacterial SMases. It is not activated by phospholipids.[8] N-SMase 1 activity on sphingomyelin *in vitro*, overexpression in cells does not affect sphingomyelin metabolism.[8,9] The role of N-SMase 1 in sphingolipid metabolism is unclear. Although a function for N-SMase 1 is not apparent, With regards to N-SMase 1, this may be particularly relevant given the different subcellular localizations of endogenous and overexpressed proteins.

2. N-SMase 2

N-SMase 2 is to be known to study mammalian N-SMase and has emerged as a key mediator of cellular stress-induced generation of ceramide. Several characterizations have identified a number of mechanisms for activation and regulation of N-SMase 2. These studies provide a base to investigate other N-SMase isoforms, as well as potential areas and modes for therapeutic intervention.

3. N-SMase 3

Human N-SMase 3 was be come to in 2006,[10] relatively little work has been reported since regarding further biochemical and functional characterization. The peptide sequence only matches 7 of the 11 residues in the identified human protein and bovine homolog.[11] The question if the original purified bovine and identified human proteins correspond to the same protein. N-SMase 3 shares no sequence homology with any N-SMases or any other characterized type of enzyme catalytic domain. The region comprising the catalytic domain is yet to be identified. A C-terminal transmembrane helix is predicted to embed N-SMase 3 in the membrane.[10]

Two conflicting reports have characterized N-SMase 3 activity. In the original identification, N-SMase 3 activity is reported to occur at neutral pH and require Mg^{2+} or Mn^{2+}.[10] The observed activity was slightly enhanced, approximately two-fold, by the phospholipid. In a later study, MCF-7 cells transiently and stably overexpressing N-SMase 3 did not have significant N-SMase activity over vector controls.[11] We suppose to future studies will determine the underlying reasons behind this major discrepancy. N-SMase 3 suggested that may activity a role in tumor necrosis factor-α (TNF-α) mediated signaling.[10,12] However, another report found that N-SMase 2 was the primary N-SMase activated by TNF-α in MCF-7 cells.[11,13,14]

4. MA-N-SMase

MA-N-SMase is the most recently identified mammalian N-SMase being discovered in 2010[15] by sequence homology with N-SMase 2 and a zebrafish mitochondrial N-SMase.[16] The subcellular localization of overexpressed MA-N-SMase protein varied with cell type, showing strong or partial co-localization with mitochondrial markers, in addition to co-localization with endoplasmic reticulum markers.[15] Present in mitochondria providing a putative mechanism for activation and/or regulation of MA-N-SMase activity *in vivo*.[15] MA-N-SMase is little known about beyond basic properties. However, the identification of a mammalian mitochondrial N-SMase presents another potential endogenous mechanism, in addition to action of ceramide synthesis, for mitochondrial ceramide generation. This is exciting considering the numerous studies linking ceramide to mitochondrial activation of apoptosis.[17] Another potential role for MA-N-SMase is in fertilization. Activation of an unidentified SMase during fertilization was inferred by a corresponding decrease in sphingomyelin and increase in ceramide levels.[18]

Neutral SMase Inhibitor

Many subtypes N-SMase about N-SMase 2 have only inhibitor, GW4869 and variety inhibitor.[19,20] GW4869 has been widely used as a tool to identify and confirm N-SMase 2-specific functions.[1] GW4869 is inference thought to inhibit N-SMase 2 by interfering with APL activation,[19] but this pathway still not become known to inhibitor.

Mechanism of Pathway Action

1. Response to TNF-α

TNF-α triggers the activation of the sphingomyelin-ceramide pathway through stimulation of SMases.[21] TNF-α pathway is induced by the hydrolysis of sphingomyelin to ceramide, which is considered as a putative bioactive

sphingolipid in cell signaling.[22] TNF-α has been reported to activate acidic and N-SMases 2 and 3.[10,21,23] Activation of N-SMases in response to the cytokine TNF-α was initially observed in the HL-60 cell line (leukemia cell line). The TNF-α receptor-1 (TNFR-1), ordinarily known to the p55 receptor.[24-27] It is pathway a distinct region of the p55 receptor was found to mediate the increase in N-SMase activity and was the neutral N-SMase activation domain (NSAD).[24] Factor associated with N-SMase (FAN-SMase) that influences N-SMase activity in response to TNF-α .[24,25] Indeed, overexpression of a dominant-negative form of FAN-SMase alters TNF-α induced N-SMase 3 activation in MCF-7 (human breast cancer cell line) cells.[10] In addition to the elucidation of the molecular partners, other investigations have focused on cellular factors that influence TNF-α activation of N-SMase 2. Reported that the levels of glutathione, which can inhibit neutral SMase activity, are critical for TNF-α activation. Functionally, the activation of N-SMase 2 has implications in the inflammatory response of TNF-α . HeLa cells were known that N-SMase 2 acts on the PI3K/Akt pathway to activate endothelial nitric oxide synthase (eNOS). This suggests that N-SMase 2-derived ceramide can have bioactive action by itself in response to TNF-α or can be metabolized into other lipids to induce differential responses.

2. N-SMase: apoptosis

Recent findings have demonstrated a functional regulation of N-SMase 2 in response to lung insults and in certain lung diseases. Initially, reported that H_2O_2 stimulation and reactive oxygen species (ROS) formation activates N-SMase 2 to mediate apoptosis in human airway epithelium, while glutathione pretreatment prevents apoptosis.

N-SMase and Breast Cancer

Recent studies are interested in N-SMase about related with of cancer. However, gynecologic diseases related research has been studied a little, among the rest active in the research of breast cancer. Hormone-dependent growth has been observed in some human cancers including breast cancer.

N-SMase enzyme activity and ceramide level regulate of breast cancer cell line (MCF-7, MDA-MB-231 cells). In agreement with the study N-SMase 2 is known that functions as an N-SMase that N-SMase 2 of over expression caused decrease in cell growth in MCF-7 breast cancer cells.[23]

Conclusion

In summary, recently, reported N-SMase related with cell signal and immune response about many studies and research proceed. TNF-α and apoptosis pathway, cell responsive involvement and associated with various diseases. Nowadays, cancer research or research processing of breast cancer has been known slightly studying furthermore in front of various gynecological disease relative thinking.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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