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Mini-review

Targeting the ceramide system in cancer

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ABSTRACT

Sphingolipids, in particular ceramide, have been described as important components of cellular signalling pathways. Ceramide can be produced via multiple mechanisms including through the hydrolysis of sphingomyelin by acid and neutral sphingomyelinase or by a *de novo* synthesis pathway. Recent studies have identified sphingomyelinases and ceramide synthases as important targets for γ-irradiation and chemotherapeutic drugs. Likewise, common cancer treatment modalities, such as γ-irradiation and many chemotherapeutic agents, induce cell death via the generation of ceramide. This suggests that the manipulation of ceramide production and metabolism could offer promising means for the enhancement of anti-tumor therapies. The focus of this mini-review will be to discuss contemporary evidence suggesting that ceramide forming pathways and ceramide itself are important targets for the treatment of tumors and the development of novel tumor treatment strategies.

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1. Generation of ceramide

Multiple pathways lead to the generation of ceramide (Fig. 1). The hydrolysis of sphingomyelin to ceramide is catalysed by acid, neutral and alkaline sphingomyelinases [1–3] that are named after the pH optimum of their activity. The *de novo* synthesis of ceramide starts at the endoplasmatic reticulum with the condensation of serine with palmitoyl-CoA resulting in 3-ketosphinganine, a step which is catalysed by the serine-palmitoyl transferase (for recent reviews see [4–6]). The 3-ketosphinganine reductase generates sphinganine from 3-ketosphinganine. Sphinganine is acylated to dihydroceramide, which is catalysed by sphinganine N-acyl-transferase, also named ceramide synthase. Finally, dihydroceramide is converted to ceramide by the activity of the dihydroceramide desaturase. At present, six different ceramide synthases [4,5] have been identified. Ceramide synthases selectively generate ceramides with distinct fatty-acid chain lengths [4,5], in particular CerS1 specifically generates C_{18}-ceramide, CerS2 predominantly generates very long chain ceramides (C_{24}-ceramide) and CerS5-6 mainly generate C_{16}-ceramide [7–10]. Ceramide can also be produced from sphingosine via retrograde activity of acid ceramidase [11], or by the hydrolysis of both complex glycosylated lipids [12] and ceramide-1-phosphate [13]. The present review will focus on the acid and neutral sphingomyelinases that hydrolyse sphingomyelin at a pH optimum of approximately 5.0 or 7.4, respectively.

The acid sphingomyelinase is synthesised from the *SMPD1* gene and can localise to different compartments of the cell through a process that appears to be determined by the glycosylation pattern of the enzyme [14,15]. These locations include lysosomes, the surface of the cell membrane and secretory lysosomes thus enabling the secretion of the enzyme from cells [1,14–17]. Deficiency of the acid sphingomyelinase results in the lysosomal storage disease, Niemann-Pick-type A [18].

Mammalian cells express several different neutral sphingomyelinases, which are limited to the cytoplasm, and localise to the endoplasmatic reticulum and/or mito-

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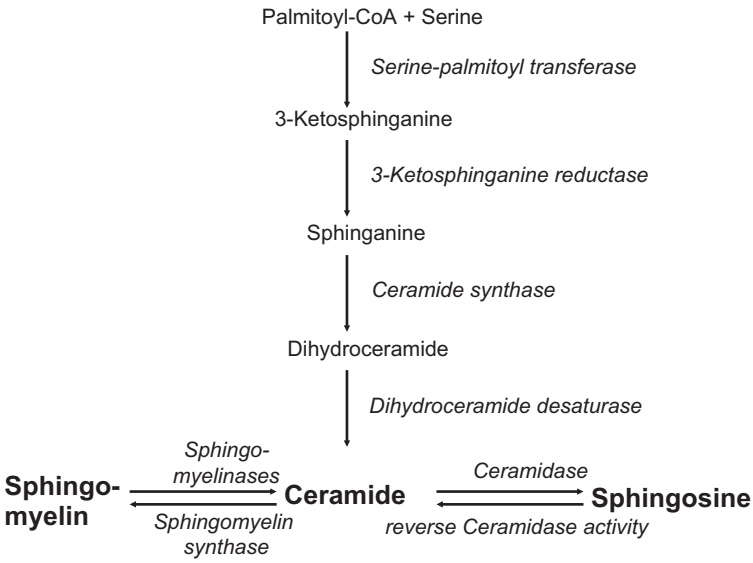

Fig. 1. Major pathways of ceramide generation. Ceramide can be *de novo* synthesised, released by the activity of sphingomyelinases or generated from sphingosine or glucosylceramides.

chondrial membranes [3,19–21]. NSMase1 is encoded by the *SMPD2* gene, but is most likely a lyso-platelet activating factor (PAF) phospholipase C *in vivo* [20,22]. NSMase2, encoded by the *SMPD3* gene, is located on human chromosome 16 and is a bona fide neutral sphingomyelinase [20,23]. Its deficiency results in osteogenesis and dentinogenesis imperfecta [23]. NSMase3 is encoded by *SMPD4* on human chromosome 2q21 and is regulated by cell stress [21,24].

The specific details regarding mechanisms of sphingomyelinase regulation still require definition. The activity of neutral sphingomyelinases appears to be controlled by the redox balance in the cell [25], however, no detailed molecular mechanisms are known. A recent study has indicated that the acid sphingomyelinase is partially cleaved after TNF-receptor stimulation, resulting in activation of the enzyme [26]. Activation of the TNF-receptor leads to rapid formation of endosomes containing both the receptor and caspase 7. These endosomes fuse with lysosomes, which contain acid sphingomyelinase, to form multivesicular bodies. This allows the acid sphingomyelinase to come into contact with caspase 7, which then cleaves the enzyme, rendering it active. A similar mechanism, i.e. the formation of multivesicular bodies might also result in phosphorylation of the acid sphingomyelinase at serine 508, which has also been shown to activate the enzyme [27]. In addition, certain stimuli result in exposure of the acid sphingomyelinase on the cell surface, and immunoprecipitation experiments have demonstrated that surface acid sphingomyelinase exists in its activated form [28]. This suggests the presence of an activation mechanism that is independent of caspases and protein kinase C (PKC) [E.G., unpublished observations]. One possible explanation for this finding is that surface acid sphingomyelinase is regulated by oxidation [29]. *In vitro* studies [29] indicated that oxidation of cysteine residue 629 results in the dimerisation and subsequent activation of the acid sphingomyelinase. It is unknown whether similar regulation occurs *in vivo*, although it has been shown that anti-oxidants and free radical scavengers prevent activation of the acid sphingomyelinase by DR5 or Cu^{2+} [29–32], thus suggesting a direct or indirect regulation of the acid sphingomyelinase by redox systems.

Several studies indicate a rapid translocation of the acid sphingomyelinase onto the extracellular leaflet of the cell membrane upon cellular stimulation by CD95 or stress stimuli [16,30,33,34]. It is probable that the acid sphingomyelinase resides in intracellular secretory lysosomes that are mobilised upon cell stimulation, fuse with the cell membrane and expose the enzyme [17]. Recent studies indicated that the translocation and fusion of these vesicles require and are mediated by syntaxin 4 [17].

2. Mechanisms of ceramide-mediated signalling

The plasma membrane is composed predominantly of phospholipids, glycosylated phospholipids, sphingolipids and cholesterol. Sphingolipids contain a ceramide moiety and appear to tightly associate with cholesterol. This interaction is mediated by hydrophilic interactions between the sphingolipid headgroups and the hydroxy group of cholesterol as well as hydrophobic van der Waals interactions between the ceramide moieties within sphingolipids and the sterol ring system [35–38]. These interactions result in the formation of small, distinct regions of the plasma membrane. These regions, termed rafts, [35] were recently visualised by STED microscopy [38]. Rafts, which are enriched in sphingolipids and cholesterol, exist in a liquid ordered status and thus spontaneously separate from other phospholipids in the cell membrane [35–38]. Their ability to separate themselves from other components of the plas-

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