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Inflammatory Reactions in Microenvironments, Leading to Melanomagenesis

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Abstract

Malignant melanoma is resistant to various therapies, while its incidence has been dramatically increasing. Among various factors, sun exposure, particularly ultra violet (UV) irradiation is considered to induce melanomas. Gangliosides have been markers of neuro-ectoderm-derived cancers like malignant melanomas and gliomas, but they also play crucial roles in their malignant properties. GD3 regulates cell signalling transduced through membrane microdomains. Chronic inflammatory reactions toward noxious stimuli cause cumbersome diseases such as cancers and degeneration, and glycosylation is involved in those processes. Here, melanocytes did not respond to UVB, while keratinocytes responded to UVB by secreting various cytokines such as TNFα and IL-6. Furthermore, these cytokines induced expression of melanoma-associated ganglioside GD3 on melanocytes. Expression of GD3 does not necessarily induce melanomas, but may form microenvironments for the generation of melanomas after long-term continuation. Consequently, combination of DNA mutagenesis and chronic inflammatory reaction seems to be critical for the melanomagenesis. Thus, 1. Mechanisms for the induction of GD3 synthase gene by inflammatory cytokines. 2. Meaning of GD3 expression in melanocytes. 3. Linkage between GD3 expression in melanocytes and melanomagenesis. 4. Prevention of UV exposure, are proposed as urgent issues to be solved in the near future.

Keywords: Malignant melanoma; Gangliosides; Inflammatory cytokines

Introduction

Malignant melanoma is a refractory cancer resistant to various therapies such as chemotherapy [1] and radiation even when combined with BRAF inhibitors [2]. Incidence of melanoma has been dramatically increasing, i.e. the lifetime risk of melanoma in 1935 was one in 1500 persons and one in 75 persons in 2000 in US [3,4]. Although primary causes of melanomas are not known, various inducing factors have been reported [4]. Above all, sun exposure plays a primary and supporting role in most melanomas [4]. In sunlight, ultra violet (UV) irradiation is an environmental carcinogen, and has been considered to induce melanomas *via* DNA damaging, carcinogenic, inflammatory, and immunosuppressive properties [5]. This is now broadly noticed by not only medical researchers but also by environmental scientists [6], since destruction of stratospheric ozone levels is considered to increase chance of UV exposure of people [7].

Sialic acid-containing glycosphingolipids, gangliosides have been considered to be markers of neuro-ectoderm-derived cancers such as malignant melanomas and gliomas [8]. Majority of melanomas specifically express ganglioside GD3 on the cell surface [9-12], thereby being a target of antibody therapy [13]. Ganglioside GD2 and GM2 have been also considered to be melanoma-associated antigens [14,15]. Recently, however, these melanoma-associated gangliosides have been reported to play crucial roles in the malignant properties of melanomas based on the sugar-remodeling experiments [16]. For example, ganglioside GD3 enhances tyrosine phosphorylation of p130Cas, focal adhesion kinase, and paxillin upon stimulation with growth factors [16,17]. GD3 expression also increased phosphorylation levels of Src family kinase, Yes [18], and altered intracellular localization of integrins, leading to increased cell proliferation, invasion and adhesion to extracellular matrices [19]. Thus, gangliosides are involved in the regulation of cell signaling transduced through membrane microdomains, such as lipid rafts, detergent-insoluble glycolipid rafts or glycolipid-enriched microdomain/rafts [20,21].

Recently, many studies suggest that chronic inflammatory reactions toward intrinsic and extrinsic noxious stimuli cause more cumbersome diseases such as malignant transformation and degeneration of tissues, and glycosylation is involved in those processes [22]. For example, GM3-only mice lacking GM2/GD2 synthase and GD3 synthase undergo severe inflammatory reactions and subsequent neurodegeneration [23]. Knockout mice of either one gene also exhibited inflammatory reactions with less intensity [24]. Another example is knockout mice of A4glnt1 lacking α1,4-N-acetylglucosaminyltransferase 1 gene [25]. The mutant mice are deficient of a unique O-glycan structure expressed in deep layer of stomach membrane, and showed increased secretion of various inflammatory cytokines and growth factors, and subsequent occurrence of gastric adenocarcinomas (Figure 1) [25].

Here, what we are most interested in is that melanocytes did not respond to UVB exposure in terms of cytokine production and secretion [26], although they might undergo DNA damage by UVB. Consequently, keratinocytes responded to UVB exposure by secreting various cytokines such as TNFα, IL-6, IL-1β, and IL-8 etc. Furthermore, the fact that these cytokines secreted from UV-irradiated keratinocytes induced expression of melanoma-associated ganglioside GD3 on melanocytes [26]. Culture supernatants from those keratinocytes also suppressed GM1/GD1b synthase gene in melanocytes, that is now considered to be rather a suppressive antigen

in the regulation of cancer properties [27,28]. Although expression of GD3 on melanocytes does not necessarily induce malignant transformation to melanomas, it may form microenvironments for the generation of melanomas. This kind of inflammatory environments around melanocytes might induce transformation of them after long-term continuation. Consequently, combination of DNA mutagenesis and chronic inflammatory reaction seems to be critical for the carcinogenic events (Figure 2).

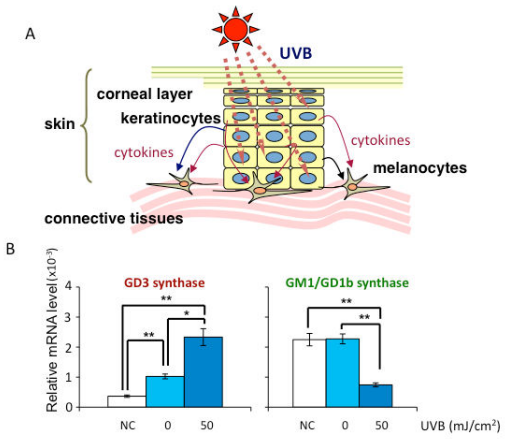

Figure 1. UVB irradiation modulates inflammatory environments in skin. A). A scheme to show paracrine stimulation of melanocytes to induce ganglioside GD3. B). Induction of GD3 synthase gene and suppression of GM1/GD1b synthase in melanocytes as measured by qRT-PCR. Melanocytes were cultured for 2 days with the supernatant of HaCat cells that had been exposed to repeated UV irradiation, and gene expression was analyzed by qRT-PCR [26]. Cells cultured with fresh medium were used as controls (NC).

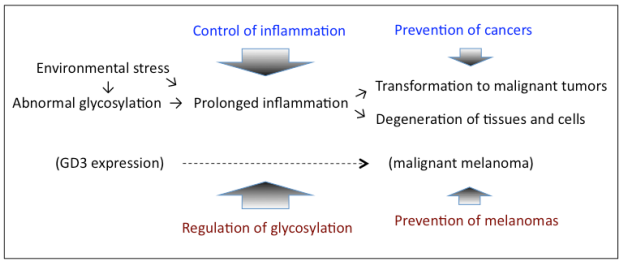

Figure 2. Chronic inflammation results in malignant cancer or degeneration. Environmental stresses such as UVB irradiation bring about changes in glycolipid expression based on inflammatory microenvironments. Processes for prolonged inflammation leading to melanomagenesis should be clarified. How to control inflammatory reactions and probably how to regulate glycosylation might be pivotal as indicated.

UV irradiation is currently considered to induce p53-mediated up-regulation of proopiomelanocortin (POMC) in keratinocytes, leading to generation of α-MSH and β-endorphin. Since α-MSH is considered to promote pigment production *via* cAMP in melanocytes, cross-talk between inflammatory cytokine-derived signals and α-MSH signals seems to be of quite interest.

Thus, next issues to be solved are as follows:

- Mechanisms for the induction of GD3 synthase gene by inflammatory cytokines secreted from adjacent keratinocytes.
- Clarification of meaning of the induction of GD3 expression in melanocytes by inflammatory cytokines.
- Linkage between GD3 expression in melanocytes and melanomagenesis, i.e. how GD3 expression is involved in the transformation of melanocytes to melanomas.
- Lessons drawn from the results of this paper, leading to the prevention of the disease.

Why only GD3 is induced and no other gangiosides? Transcriptional regulation of ST8SIA1 (GD3 synthase) as well as epigenetic regulation of the gene needs to be investigated. GD3 has been known to be expressed on immature cells such as neuronal stem cells and also in activated cells such as activated T lymphocytes [29]. GD3 has been also considered to be associated with apoptosis by FAS/FAS-ligand interaction [30]. Comparison of features between GD3-positive and GD3-negative melanocytes should be important, and would provide insights into this question. At this moment, GD3 expression is considered to reflect activation, de-differentiation, or adaptation to inflammatory environments. As described above, UV irradiation has multiple effects on the skin, including DNA changes, induction of reactive oxygen species, modulation of cutaneous immune system, and production of growth factors [31]. Generally, all these processes bring about inflammatory responses, promoting melanocyte survival and immunoevasion [31,32].

Conclusion

How GD3 expression upon UVB exposure leads melanocytes to transformation seems to be most esoteric question. Probably we need to consider general effects of long-term exposure of melanocytes to inflammatory cytokines and activation of related transcription factors on qualitative changes of cells [33]. As for preventive strategies of skin cancers, reduction of DNA photodamage by protection from the sun seems most efficient [34]. In order to regulate chronic inflammatory condition, aspirin and other non-steroidal anti-inflammatory drugs might be considered as chemoprevention agents [35].

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