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Melanocytes: interface of cell biology and pathobiology with a focus on nitric oxide and cGMP signaling

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Human epidermal melanocytes represent a crucial protective barrier against UV irradiation and oxidative stress by generating the radical scavenging pigment melanin. Melanin is also known to act as a photosensitizer that generates active oxygen species upon UV irradiation, which may initiate hypopigmentary disorders (e.g., vitiligo) as well as UV-induced oncogene cell transformation. Finally, melanocytes *in vivo* are permanently targeted by environmental mechanical stimuli.

For human melanocytes, it has been shown that the nitric oxide (NO)-soluble guanylyl cyclase (sGC) pathway, through the activation of cGMP-dependent protein kinase, is involved in UVB-induced melanogenesis [1]. In previous studies we found that different guanylyl cyclase (GC) isoforms are responsible for cGMP synthesis in melanocytic cells. Normal human melanocytes and non-metastatic melanoma cell lines predominantly express sGC, which appears to be associated with melanogenesis, whereas absence of NO-sensitive GC, but upregulated activities of the membrane isoforms GC-A and GC-B were found in highly metastatic phenotypes [2]. We also showed that NO can induce perturbation of melanocyte-extracellular matrix interactions, which may contribute to loss of melanocytes or melanoma metastasis [3,4]. The NO effects appear to be modulated partly by cGMP [4].

In the frame of the current space exploration, we further have investigated the regulation of cGMP levels in melanocytes at altered gravity conditions. Our studies indicate that cultured melanocytes and non-metastatic melanoma cells respond to long-time exposure to hypergravity (up to 5 × g for 24 h) with an elevated cGMP efflux under conditions where phosphodiesterase (PDE)-mediated cGMP hydrolysis is inhibited or cGMP synthesis is induced, e.g., by NO [5]. Cyclic GMP efflux was inhibited in the presence of 1 μM trequinsin, a highly selective inhibitor of PDE5 and of transport by "multidrug resistance" proteins 4 and 5 (MRP4/5). Transport was further inhibited by probenecid, an inhibitor of endogenous non-selective transporters as well as of MRP4/5 and by cycloheximide as an inhibitor of *de novo* protein synthesis. It, therefore, can be suggested that the expression of endogenous non-selective cGMP transporters and/or MRP4/5 is increased under elevated acceleration in human melanocytes and non-metastatic melanoma cells. Similar results were found on mRNA levels. In contrast, elevated acceleration does not affect cGMP efflux in highly metastatic melanoma cells. We propose that altered gravity should be regarded as a possible factor that may induce signaling events in human melanocytes via cGMP that could be important for malignant transformation.

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