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Mitochondria Give Cells a Tan

The discovery of melanogenin [1], a small molecule that induces pigmentation in melanocytes, has led to identification of a mitochondrial protein as target. The finding is relevant therapeutically, and argues for how chemical biology can be used to elucidate organelle-specific functions.

Organelles are not normally considered as direct targets of small molecules, and chemical biology efforts usually do not intend to elucidate how specific organelles influence cellular function. However, when several small molecules and physiological stimuli point to an unexpected role of a particular organelle in a biochemical pathway, it is important that the involvement of the organelle in the resulting phenotype be brought into focus. In this context, it is appropriate to highlight the article authored by Snyder and colleagues in the present issue of Chemistry & Biology as an independent line of evidence pointing to a role for mitochondria in melanogenesis (Figure 1).

Melanogenesis is the process through which the pigment melanin is synthesized in melanocytes. Understanding melanogenesis is therapeutically relevant for treating skin pigmentation disorders such as vitiligo [2] (a condition in which large patches of skin loose pigment). Chemical agents that promote melanocyte pigmentation could also serve as differentiation-inducing agents for the treatment of melanoma a deadly skin cancer [3]. The cause of vitiligo is not known [2], although abnormal regulation of melanocyte apoptosis has been considered as an explanation [4].

In the article by Snyder and colleagues [1], a combinatorial library of triazine derivatives, all possessing a linker tag [5], was screened in a cell-based assay for compounds inducing pigmentation in an unpigmented, melanocyte-derived cell line. Several compounds were identified to be active at inducing melanin pigment formation. Prominent among these was one referred to as melanogenin. Target identification was facilitated by the direct incorporation of the linker tag into the structure of the screened molecules. This led to the discovery of prohibitin as a target of melanogenin. Reducing prohibitin mRNA levels with siRNAs inhibited the effects of melanogenin and other stimuli on pigment induction, suggesting a role for prohibitin in the melanogenesis pathway.

Most importantly, prohibitin was found to localize to melanocyte mitochondria, an observation that could easily escape attention. However, three previous lines of work make prohibitin's involvement in melanogenesis and localization to mitochondria an important discovery. First, UV irradiation is the physiologically relevant inducer of pigment production in melanocytes [6–9]. In non-melanocytes, UV irradiation influences mitochondrial function, including downstream apoptotic signaling pathways [10]. Second, IBMX, a phosphodiesterase inhibitor, is an inducer of melanin production [9], albeit not as potent as melanogenin. By elevating cAMP, IBMX activates protein kinase A signaling, which can also interact with mitochondrial signal transduction pathways [11–13]. Third, a variety of inhibitors of the mitochondrial FO/F1 ATPase were previously found to induce pigmentation in melanocytes, further pointing to a role for mitochondrial signal transduction in the induction of melanin production [14].

How do mitochondria regulate melanin production? In melanocytes, pigment production is a specific adaptation associated with protection against sunlight. In melanocytes, UV irradiation and IBMX—as well as mel-

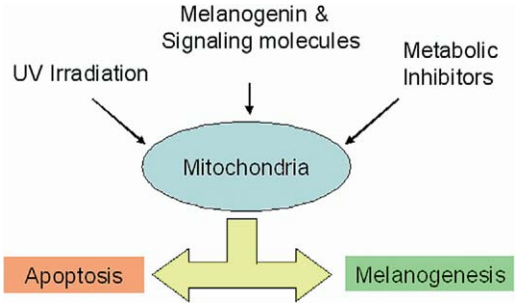

Figure 1. Mitochondrial Responses to Stimuli

In melanocytes, noxious insults such as ultraviolet radiation, metabolic inhibitors, and small molecules such as isobutylmethylxanthine (IBMX) and melanogenin induce a protective, melanin synthesis response. Many independent lines of evidence now suggest an important signaling role for mitochondria in the induction of melanin synthesis.

anogenin—may influence stress response pathways, which can alter the levels of tyrosinase, a key enzyme in the melanin biosynthesis pathway [13–17]. Because in non-melanocytes UV irradiation can induce apoptosis through activation of the mitochondrial permeability transition, it is tempting to speculate that in melanocytes part of the mitochondrial UV-response pathway has been co-opted as a signal to upregulate the production of protective pigments. Prohibitin itself may be one of the key signaling mediators of this signaling role in response to UV light. As reported by Snyder and colleagues, neither IBMX nor melanogenin are able to induce melanin production when prohibitin expression is silenced.

These observations make one marvel at the many cellular functions associated with mitochondria. We expect mitochondria to be involved in metabolism, energy production, and redox balance. More recently, we have come to expect mitochondria to be involved in apoptosis signaling, calcium signaling, and insulin signaling and glucose regulation. So, if we find that mitochondria are involved in melanogenesis, perhaps we should not be too surprised. Indeed, every protein encoded by the genome is localized to some cellular organelle or subcompartment. In as much as we discover new protein functions with phenotypic cell-based assays and small-molecule screens, we are actually discovering novel functions of the organelles in which these proteins are localized.

In conclusion, identification of prohibitin as a target of melanogenin serves as an example for how chemical biology can provide important insights into the function of organelles in living cells. With the advent of organelle-targeted chemical libraries [18, 19] and the development of quantitative structure-localization relationship studies [19, 20], chemical biologists are taking direct steps toward facilitating the large-scale elucidation of organelle-specific functions. In the meantime, relating the phenotypic response of the cells to small molecules to the localization of the small molecules' targets can be viewed as a reasonable starting point for formulating a hypothesis about how organelles are involved in different phenotypic responses.

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