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CELL SIGNALLING

Melanoma melanosomes shape the stromal niche

Melanocytes are specialized epidermal cells that produce the skin pigment melanin and transfer this pigment to adjacent keratinocytes via tissue-specific vesicles termed 'melanosomes'. Melanoma cells derived from melanocytes retain the ability to produce and secrete melanosomes. Now, Carmit Levy and colleagues have uncovered a novel mechanism by which melanoma melanosomes contribute to phenotypic changes in cancer-associated fibroblasts (CAFs), thereby creating a stromal niche that might support tumour progression.

Levy explains: "last year we reported the discovery of a micro-environmental trigger for melanoma metastasis. While working on this project, we examined human melanoma specimens and found that, surprisingly, the dermis of patients with melanoma *in situ* has different characteristics to the normal skin dermis". In particular, immunohistochemical staining revealed that melanoma *in situ* is associated with accumulation of fibroblasts within the dermis, despite confinement of tumour cells to the basal epidermis. "We were curious to discover the implications of this observation: that is, whether any of the early changes to the dermis contribute to melanoma pathogenesis."

Further analysis of the stained patient specimens revealed that some fibroblasts express the melanoma marker HMB-45, which the researchers hypothesized might reflect transfer of material via melanosomes. This hypothesis was supported by findings from staining for GPNMB, a melanosome marker, and cell-culture experiments. The researchers subsequently demonstrated that the uptake of melanoma melanosomes potentiates fibroblast proliferation and motility, with corresponding increases in the expression of genes involved in these processes, as well as proinflammatory genes. Moreover, melanosome-treated fibroblasts demonstrated properties of CAFs, promoting the aggressiveness of melanoma cells in both *in vitro* and *in vivo* models.

A melanoma-associated microRNA, miR-211, was demonstrated to be transferred via melanosomes to fibroblasts, recapitulating many of the phenotypic and gene-expression changes induced by melanoma melanosomes. Notably, inhibition of p38 in melanoma cells decreased secretion of both melanosomes and miR-211, and melanosomes from such cells had decreased capacity to induce a 'CAF' phenotype. A key target of miR-211 in the fibroblasts was mRNA encoding the tumour suppressor IGFR2, downregulation of which increases MAPK signalling downstream of IGF2/IGFR1. Indeed, inhibition of the MAPK pathway in fibroblasts abolished the effects of melanosomes and miR-211.

These findings suggest that melanoma cells shape the stromal niche early in the disease by manipulating dermal fibroblasts. Of note, progression of melanoma *in situ* involves invasion into the dermal layer, which is a prerequisite for tumour-cell interaction with blood vessels and, thus, metastasis. "Blocking the release of the melanoma-cell melanosomes might inhibit the early dermal changes that contribute to this process, and could, therefore, open novel therapeutic avenues for the prevention of melanoma metastasis," Levy opines. "Moreover, the characteristics of melanosomes released into the dermis could potentially be used as a new diagnostic marker for aggressive melanoma." She concludes, "our observations reveal a new aspect of cancer progression, and will hopefully lead to a new era of cancer diagnosis and prevention."

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