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MELANOMA

Don't let sleeping cells lie

Melanomas are heterogenous tumours that are highly metastastic, but patients with this disease can be cured if they are treated at an early stage before tumour cells colonize distant organs. Therefore, keeping the growth of primary tumours and metastases under control is one possible route to successful therapy. Two papers from the groups of Meenhard Herlyn and Jean-Pierre Abastado help us to understand how this can be achieved.

The histone demethylase JARID1B is highly expressed by a small proportion of melanoma cells. Herlyn and collaborators observed a correlation between the expression of JARID1B and slow proliferation. Furthermore, melanoma cells expressing enhanced green fluorescent protein (EGFP) under the control of the *JARID1B* promoter showed increased survival in sphere-forming assays, which favour the outgrowth of melanoma stem cells. Knocking down the expression of JARID1B resulted in rapid proliferation, but an inability to form spheres *in vitro* owing to a lack of continued proliferation. However, when melanoma cells were transplanted into mice, both $EGFP^+$ and $EGFP^-$ cells showed the same ability to initiate tumour formation. Interestingly, loss of JARID1B resulted in a reduction in the number of melanoma cell metastases in the lung, leading the authors to conclude that JARID1B might not be necessary for tumour initiation but is probably required for tumour progression and the initial formation of metastases. Further experiments showed that the Notch pathway might cooperate with JARID1B in mediating melanoma progression.

The suppression of early metastatic growth was also investigated by Jean-Pierre Abastado and collaborators in a mouse model of spontaneously arising melanoma. By comparing the genome of the different tumours that had developed in the same mouse, they found that the gene expression profiles were similar, but specific for each mouse, meaning that most lesions corresponded to metastases but not independent primary melanomas. These findings also imply that the metastases had arisen early during the development of the primary melanoma. The use of dopachrome tautomerase — an enzyme expressed only in melanocytes and melanomas — as a tumour cell marker, revealed the presence of tumour cells in visceral organs as soon as 3 weeks after birth. However, metastases were not detectable until 1.5 years of age, suggesting a mechanism of tumour dormancy. To further characterize this finding, the authors depleted the mice of $CD8^+$ T cells. Mice developed overt metastases only 2 months later. Interestingly, the number of cycling melanoma cells was much higher in $CD8^+$ T cell-depleted mice, indicating that the expansion of disseminated melanoma cells is initially suppressed by the immune system.

These two papers support two possible routes for the treatment of melanoma: the targeting of slow cycling populations of melanoma cells, which are likely to be important for the survival of disseminated cells, and the boosting of the immune response to target these cells.

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ORIGINAL RESEARCH PAPERS Roesch, A. *et al.* A temporarily distinct subpopulation of slow-cycling melanoma cells is required for continuous tumor growth. *Cell* **141**, 583–594 (2010) | Eyles, J. Tumor cells disseminate early, but immunosurveilance limits metastatic outgrowth, in a mouse model of melanoma. *J. Clin Invest.* **120**, 2030–2039 (2010)

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