Bench to Bedside

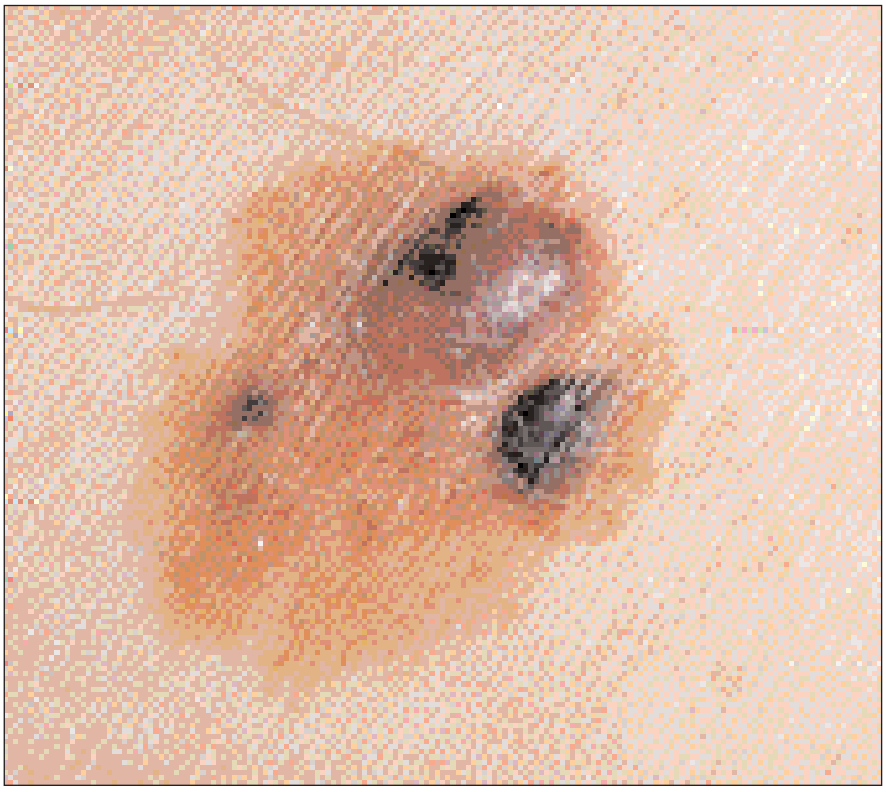
Do environmental toxins cause Parkinson's disease?

It has been hypothesized that exposure to environmental toxins plays an important role in the etiology of Parkinson's disease (*Cell Tissue Res* 2004; 318:225-41). In support of this association, fruit flies that lack a gene linked to the disease have been shown to be sensitive to the herbicide paraquat and the insecticide rotenone.

Parkinson's disease, the second most common age-related neurodegenerative disorder, occurs in both sporadic and inherited forms. The sporadic forms of Parkinson's disease have been associated with exposure to environmental toxins, which are thought to cause oxidative damage to the brain; the inherited forms are linked to gene mutations (*Cell Tissue Res* 2004;318: 225-41). One such mutation occurs in the human gene *DJ1*, which the fruit fly *Drosophila* also possesses in 2 separate versions, *DJ1A* and *DJ1B*.

Marc Meulener and colleagues recently created fruit flies lacking both forms of the *DJ1* gene in an attempt to better understand their function. The flies, which otherwise were normal, were found to be 10-fold more sensitive to paraquat and rotenone and had increased rates of death after exposure (*Curr Biol* 2005;15:1572–7). In a complementary study, Fiona Menzies and colleagues found that overexpression of *DJ1A* in fruit flies can protect dopaminergic neurons — whose loss occurs in Parkinson's disease — from paraquat exposure (*Curr Biol* 2005;15: 1578–82).

Together, these results suggest that the *Drosophila DJ1* genes play a role in protecting dopaminergic neurons from oxidative stress, which, in turn, may be caused by agricultural chemicals like paraquat. If the results extend to human *DJ1*, they provide a link between sporadic and inherited forms of Parkinson's disease and point to *DJ1* as a therapeutic target.



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Melanocytes may possess an inherent ability to metastasize.

Why is melanoma so malignant?

Melanoma is a particularly aggressive form of malignant disease that routinely metastasizes unless detected early. The reasons why melanoma is so adept at metastasizing, when other forms of malignant disease are not, are now beginning to be understood.

The metastatic propensity of melanoma may be the result of particular mutations that occur during development, or it may be that melanocytes are simply intrinsically predisposed to becoming malignant. Research by Piyush Gupta and colleagues points to the second option — melanocytes possess an inherent ability to quickly metastasize (*Nat Genet* 2005;doi:10.1038/ng1634).

Gupta and colleagues introduced an identical set of cancer-causing genes into human fibroblasts and melanocytes and injected the resulting tumour cells into mice. They found that tumours from the fibroblast cancer cells didn't spread, whereas the melanoma cells spread extensively, which suggests that something inherent to the melanocytes was leading to the metastatic behaviour.

Dermal melanocytes originate from migratory embryonic cells of the neural crest. These cells are built to migrate, and Gupta and colleagues linked this ability to a gene called *Slug*, which also controls the expression of numerous other genes. Indeed, the deletion of *Slug* from melanoma cells left them unable to metastasize.

Although Gupta and colleagues' results do not reveal whether the *Slug* gene is alone responsible for melanoma metastasis, their research suggests the potential importance of melanocyte-specific factors in malignancy and broadens our understanding of the pathogenesis of this often lethal cancer.
— Compiled by David Secko, Vancouver

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