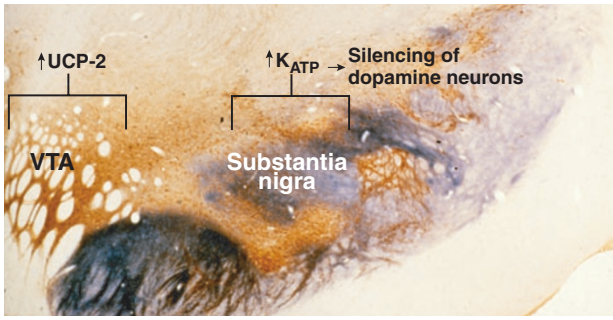

Figure 1 In Parkinson disease, only certain dopamine neurons in adjacent regions of the midbrain are lost; Liss *et al.* report a potential explanation. High expression of K_{ATP} channels in the dopamine neurons of the substantia nigra may trigger preferential cell death. On the other hand, lower expression of this channel and higher expression of the uncoupling protein UCP-2 in dopamine neurons of the ventral tegmental area (VTA) may block neuron loss.

lives or dies. The work may also open the door for new therapeutic strategies aimed at slowing the progression of Parkinson disease.

If K_{ATP} channels govern differential vulnerability of dopamine neurons in Parkinson disease, it would provide a mechanism for the coupling of metabolic disturbances in dopamine neurons with functional effects on membrane potential and cell firing. The K_{ATP} channel, however, is downstream of the metabolic perturbations. Accordingly, the pathological process involving dopamine neurons must occur before K_{ATP} channel–induced silencing of dopamine neurons. Therefore, it is likely that K_{ATP} channels are not the sole mediators of degeneration in dopamine neurons.

Interestingly, Liss *et al.* noted that ventral tegmental area dopamine neurons express higher levels of uncoupling protein UCP-2 than do vulnerable substantia nigra neurons, and mild mitochondrial uncoupling decreases K_{ATP} channel function. This suggests that UCP-2 may be upstream of K_{ATP} in determining vulnerability of dopamine neurons (**Fig. 1**). Another recent study reported that UCP-2 knockout mice show increased MPTP-induced neuronal death[8].

A major question now is how K_{ATP} channel–mediated silencing of dopamine neurons triggers cell death. This finding runs counter to prevailing notions that neurodegeneration is associated with hyper- rather than hypoexcitability. One could envision that K_{ATP}-induced silencing of dopamine neuron activity ultimately works through a series of interconnected brain regions, which may also underlie the therapeutic effects of deep brain stimulation in Parkinson disease. Alternatively, decreased membrane excitability and firing rate of dopamine neurons may disrupt autaptic trophic support (self-produced growth factors). Regardless of the downstream mechanism, the work of Liss *et al.* suggests that neuronal silence may not always be golden.

Individuals with Parkinson disease also have an impaired insulin response to glucose[9]. Sulfonylurea drugs, which are used to treat type II diabetes, block K_{ATP} channels. The findings of Liss *et al.* suggest that such drugs may be useful in the treatment of Parkinson disease and may reduce the risk, or slow the progression, of the illness. We are unaware of any epidemiological studies that report an association between Sur1 or Kir6.2 and Parkinson disease; such a study is warranted.

Clinical trials in parkinsonism with tolbutamide—a sulfonylurea drug—conducted before the modern era of therapies for Parkinson disease were inconclusive[10]. The data hinted, however, that this drug may be effective in less severely affected individuals with Parkinson disease. If dopamine neurons have not yet degenerated, perhaps K_{ATP} channel antagonists could slow disease progression.

The work of Liss *et al.* provides sorely needed new targets for slowing the progressive loss of dopamine neurons in Parkinson disease. Perhaps the new targets will allow us to reach a point where all dopamine neurons are left behind.

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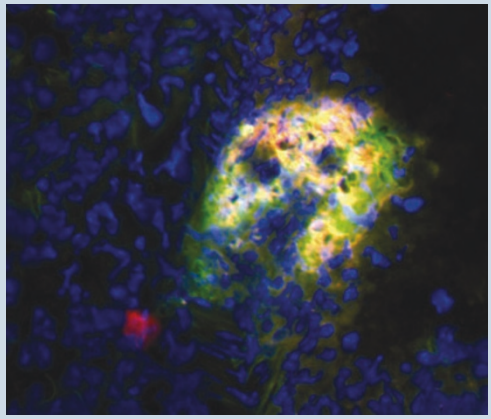
Envoys of metastasis



Bone marrow cells lodged throughout the body seed the development of metastases in mice, report Rosandra Kaplan and colleagues (*Nature* **438**, 820–827). What's more, blocking a signal from the marrow cells can prevent the migration of metastatic cells to these locations.

The researchers first observed that bone marrow cells clustered at pre-metastatic locations before the arrival of tumor cells. These progenitor bone marrow cells were identified using markers typical of such cells. The cells also expressed vascular endothelial growth factor receptor-1 (VEGFR1), which seemed to be necessary for migration of metastatic cells. Shown is one such cluster of marrow cells (VEGFR1 in red, GFP-labeled marrow cell in green and DNA in blue).

It is unclear what causes the bone marrow cells to cluster in the first place. But in mice with tumors, expression of a protein that sticks to bone marrow cells, fibronectin, was somehow increased at organs that conventionally host metastatic tumors.

To show the involvement of VEGFR1, the researchers grew tumor cells in the presence of VEGFR1-expressing cells; as a result, the tumor cells adhered more strongly and divided more rapidly. VEGFR1 cells isolated from pre-metastatic clusters secreted growth factors, which may attract circulating tumor cells.

Finally, antibodies that blocked VEGFR1 completely prevented metastases in animals with established tumors. To date VEGF inhibitors have been used in clinical trials with the aim of thwarting angiogenesis and tumor blood supply. The findings suggest that they might be of use to block metastasis.

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