CANCER

On the move

DOI:
10.1038/nrn2245

The highly invasive nature of cancerous cells is a key problem for the surgical removal of malignant gliomas. Therefore, the identification of factors that promote invasion is crucial for the development of effective treatment strategies. In a recent study published in *PLoS Biology*, Johnston *et al.* identified the neurotrophin receptor p75 (p75^{NTR}) as a likely mediator of glioma cell invasion.

The authors set out to identify genes that are differentially expressed in highly invasive versus non-invasive glioma cells by injecting green fluorescent protein (GFP)-expressing human glioma cells into the brain of immunocompromised mice. GFP-positive cells that migrated away from the resulting tumour cell mass were collected, expanded in culture and re-injected into mice to further select for highly invasive cells. Cells from the main tumor mass were also cultured, for comparative purposes. Microarray analysis of the highly invasive and non-invasive cell lines obtained using this protocol revealed significant differences in the expression of approximately 30 genes. The gene that encodes p75^{NTR} was one of the most overexpressed in the invasive cell populations and was chosen for further investigation. In neurons, p75^{NTR} is known to have roles in diverse functions, including axonal outgrowth, neuronal survival and cell death (depending on the cellular context). It has also been shown to promote tumorigenesis in other types of cancer, but has never before been implicated in brain tumours.

The culture medium of the established cell lines tested positive for neurotrophins, suggesting that p75^{NTR} could be activated by autocrine or paracrine signals *in vivo*. To assess whether the invasiveness of glioma cells depends on the expression and function of p75^{NTR}, the authors compared the migration and invasion of highly invasive and non-invasive cell lines in the presence of nerve growth factor (NGF), a p75^{NTR} ligand, using standard *in vitro* assays. NGF increased the invasion potential of only the p75^{NTR}-overexpressing, highly invasive cells, suggesting that p75^{NTR} mediates invasiveness, and that it does so in a neurotrophin-dependent manner.

Downregulation of p75^{NTR} by RNA interference significantly inhibited the migration and invasion of the highly invasive cells *in vitro* and also abolished their responsiveness to neurotrophins. By contrast, migration and invasion increased significantly in human glioma cells when p75^{NTR} was ectopically expressed. When these p75^{NTR}-overexpressing cells were injected into the brains of immunocompromised mice, highly infiltrative tumors resulted. Concordantly, cells that expressed mutant p75^{NTR} that can no longer bind neurotrophins produced tumours with well-defined borders when injected into the mice.

When the authors investigated the expression of p75^{NTR} in different brain-tumour samples, they detected it in 85 % of glioblastoma multiforme specimen. In culture, p75^{NTR}-positive cells from these specimens were more migratory than p75^{NTR}-negative cells.

These findings suggest that p75^{NTR} is a neurotrophin-dependent mediator of glioma invasion. Future studies will reveal the molecular mechanism of p75^{NTR} function in the invasive process, and it might be possible to exploit this knowledge for therapeutic purposes.

Claudia Wiedemann

ORIGINAL RESEARCH PAPER
Johnston, A. L. M. *et al.* The p75 neurotrophin receptor is a central regulator of glioma invasion. *PLoS Biol.* **5**, 1723–1737 (2007)