NEURO-ONCOLOGY

New drug blocks brain metastasis

Silibinin blocks brain metastasis in humans and mice, according to a new study published in *Nature Medicine*. Investigators found that silibinin stops reactive astrocytes from making the brain microenvironment amenable to tumour growth.

Brain metastasis is a common complication in patients with systemic cancer and is associated with a poor prognosis. Surgery and radiotherapy are the only treatments currently available for the majority of individuals with brain metastases and novel approaches are sorely needed.

Investigators previously identified silibinin, a compound derived from milk thistle seeds, as a potential anti-metastasis agent, but they did not understand its mechanism of action. Evidence has suggested that the compound impairs activation of signal transducer and activator of transcription 3 (STAT3). In the new study, researchers led by Manuel Valiente investigated whether this activity of silibinin mediates its anti-metastatic effect.

The team discovered that STAT3 enables reactive astrocytes to establish an environment that supports metastasis. The STAT3-expressing astrocytes interfered with immune responses to the tumour and promoted cell growth. However, silibinin bound to STAT3 in astrocytes and blocked this pro-metastatic effect.

Administration of silibinin in a mouse model of brain metastasis decreased STAT3 signalling and reduced metastasis burden in these animals compared with that in untreated mice. Encouraged by the safety and efficacy of the drug in mice, the team set up a small clinical study in humans. Compassionate use of silibinin was granted for 18 patients with lung cancer and secondary brain metastases.

Silibinin reduced brain metastasis by at least 30% in 75% of the patients and eliminated metastasis in 20% of patients. The treatment extended the average survival time of the patients to 15.5 months compared with an average of 4.0 months in patients with brain metastasis who received only standard treatment at the same institution.

> “Silibinin reduced brain metastasis by at least 30% in 75% of the patients and eliminated metastasis in 20% of patients”

“We find it very exciting that we can target metastasis — even established macrometastases — by targeting a component of the microenvironment,” comments Valiente. Clinical trials in large patient cohorts are now needed to confirm the findings of this study.

The team are also investigating whether this drug could be used in combination with new immune checkpoint inhibitors. Silibinin could alleviate immunosuppression caused by reactive astrocytes, which would enable the immunotherapies to have a beneficial effect in a greater number of people.

Charlotte Ridler

ORIGINAL ARTICLE Priego, N. et al. STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis. *Nat. Med.* https://doi.org/10.1038/s41591-018-0044-4 (2018)

NEUROINFLAMMATION

Microglia show sex-specific gene expression profiles

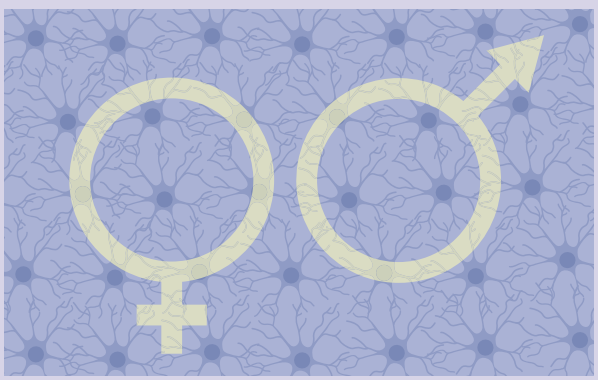
Microglia in the adult mouse brain have sex-specific transcriptomic signatures that remain stable even after transplantation of the cells into a brain of the opposite sex, new research published in *Cell Reports* reveals. These findings could help to explain sex differences in neurological disease susceptibility and outcomes.

“What prompted us to compare the microglial transcriptome of males and females was the fact that microglial activity appears to be relevant for neurodegeneration, and that several neurodegenerative diseases have a sex-related prevalence,” explains study leader Adriana Maggi. “For example, Parkinson disease is more prevalent in males than in females, whereas the opposite is true for Alzheimer disease.”

Through the use of RNA sequencing, the researchers identified 546 genes that showed differential levels of expression between microglia from male and female mice. The male microglial transcriptome showed enrichment for genes associated with inflammation, suggesting that male microglia tend to adopt a more inflammatory phenotype than their female counterparts.

Phenotypic differences between male and female microglia have previously been attributed to the effects of sex hormones. However, Maggi and colleagues found that ovariectomy, which dramatically reduces the levels of circulating oestrogen, did not substantially alter the patterns of microglial gene expression in the brains of adult female mice.

> “The male microglial transcriptome showed enrichment for genes associated with inflammation”



Credit: Lara Crow/Macmillan Publishers Limited

The sex-specific transcriptomic signatures were maintained when microglia were transplanted into the brains of mice of the opposite sex. In addition, transplantation of female microglia into the brains of male mice mitigated the progression of cerebral ischaemia, suggesting a role for sex-specific microglial characteristics in determining the impact of brain insults.

“We would now like to know when microglia differentiate into the male and female phenotypes,” says Maggi. “We also need to understand whether this sexual differentiation has any relevance to disorders that are more prevalent in males or females, and whether sex hormones have any role in microglial ageing.”

Heather Wood

ORIGINAL ARTICLE Villa, A. et al. Sex-specific features of microglia from adult mice. *Cell Rep.* **23**, 3510–3511 (2018)