Brain Metastases: Mechanisms and Therapeutics

Abstract:
Specific molecular mechanisms allowing primary cancer cells to metastasise into the brain are now understood. The resultant secondary cancers have a range of negative consequences for patients. Treating these secondary cancers alongside the primary cancer holds the most promise for future therapy.

Introduction:
- Brain Metastases (BM) are secondary cancers that have spread to the brain from an organ with a primary cancer.
- They affect around a third of adults with primary cancer. BM also account for around 70% of all brain tumours in adults (1).
- The prognosis for a patient diagnosed with BM is bleak, and surgery and radiotherapy have to date comprised the traditional treatment strategy.
- In many cases surgery is not possible due to the location of the legion, and radiotherapy does not show enough success.
- Current figures estimate the average survival length for a patient diagnosed with BM as being between 6-9 months (1), highlighting the desperate need for new and more effective therapy.
- The aim of this project was to identify how the mechanisms for improving the therapeutic provision for patients with BM may be harnessed and used to therapeutically target both primary and secondary cancer cells.
- Further, could this project identify areas of poor understanding or clinical efficacy and put forward novel mechanisms for improving the therapeutic provision for patients with BM?

Main Findings:
Mechanism of Metastasis: Epithelial-mesenchymal transition (EMT) - loss of proteins that mediate cell-cell junctions, e.g. claudin, occludin and E-cadherin - caused by changes in gene expression mediated by the EMT-associated transcription factors TWIST, SNAIL and ZEB and Wnt/β-catenin signalling pathway (2). The actin and microtubule components of the cytoskeleton undergo rearrangement which alters the cell shape. Cells can then overturn the blood brain barrier (BBB) and gain access to brain tissue by expressing metastasis progression genes – e.g. Angiopoeitin-like-4, a glycoprotein that can dissociate cell-cell junctions of endothelial cells in the BBB (2).
Neuropathology: The effect of BM on brain function is highly diverse between patients, and greatly depends on the location of the lesion within the brain. Legions in the forebrain affect personality and mood; whilst legions in the midbrain can affect movement, balance, vision and can induce some psychiatric symptoms. Legions at the hindbrain generally cause nausea and severe headaches (3). There is no definitive set of symptoms for a patient with BM, as the brain controls so many higher perceptual functions. What is clear, however, is that patients’ quality of life is severely affected through physical symptoms, psychiatric symptoms, or both.

Treatments – the future?
Agents that target both CNS and non-CNS tumours are the most useful. Systemic therapy involves delivery of chemotherapeutic agents with activity against primary cancer cell type – e.g. Capecitabine in Breast Cancer BM. One issue with systemic therapy is the poor accumulation of the agents into the brain tissue where the legions are located. The presence of the BBB prevents many agents from crossing into the brain, but efflux transporters further contribute to the clearance of agents (4). It may be possible, however, to use inhibitors of these transporters to decrease the efflux of the agents; leading to an increase in the concentration reaching the brain legions to exert their anticancer activities.

Conclusion:
The molecular mechanisms behind BM manifestation and progression hold the key to providing more effective therapies for patients who desperately require it. Novel treatment strategies based upon systemic therapy are likely to be the area of most interest for future research.

Key References:

Acknowledgements:
Dr Aysha Divan, SMCB, Faculty of Biological Sciences, University of Leeds.

Name Kurt Rushworth
Supervisor Dr Aysha Divan
Poster 60