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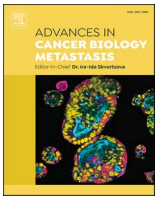

Unraveling cancer metastasis for more efficient therapeutic approaches

Despite the great progress made in elucidating the molecular properties and treatment of cancer, understanding the molecular mechanisms of invasive and metastatic tumour spread remains elusive. Approximately 90 % of cancer patients die from the development of metastases [1]. A comprehensive understanding of the molecular mechanisms of invasion and metastatic spread is crucial for the development of effective therapeutic strategies to prevent cancer spread. This special issue focuses on basic, translational and clinical research into the characteristics and mechanisms of aggressive cancer cells and their microenvironment that drive tumour invasion and metastatic spread.

The heterogeneity of tumours has hampered the development of effective cancer treatments. The interplay between different intrinsic molecular factors needs to be investigated and addressed to improve tumour response to treatment. An example of this interplay are steroid hormones-receptors and melanoma-associated antigens (MAGEs), which are separately involved in therapy resistance but whose interactions are poorly understood, as investigated in the study by Tavčar Kunstič and co-workers [2].

The heterogeneity of tumours is a consequence of the dynamic tumour ecosystem, the so-called tumour microenvironment, which consists of cancer cells and non-cancerous stromal and immune cells and supports cancer metastasis. New insights into the microenvironment of metastatic ovarian cancer are provided by the study by Vos et al. in patients with epithelial ovarian cancer, which indicates that invasive solitary cancer cells are present in the peritoneum and attach to the perivascular microenvironment. Their solitary nature and lack of proliferation indicate a dormant state that is unlikely to be affected by chemotherapy [3]. Lactate, the product of glycolysis of tumour cells, is extensively studied in the context of tumour metabolites and their effects on the tumour microenvironment, such as evasion of the tumour immune system. The review by Sharma et al. presents and discusses the study of lactate in cancer biology research and therapeutic interventions against cancer [4]. Hypoxic conditions are characteristic of tumours and a study by Menon and co-workers identified hypoxia-related signalling pathways that have prognostic value for patients with thyroid cancer [5].

Non-coding RNAs are key regulators of cancer progression and have been found to be involved in metastasis of various aggressive cancers. In the review by Anil and co-workers, the studies on the functional role of long non-coding RNAs in pancreatic cancer and their diagnostic and prognostic potential are reviewed and addressed [6]. Li and co-workers provide evidence for the role of miRNA-203b in suppressing ovarian cancer invasion and metastatic colonisation and promising miRNA delivery for suppressing metastatic spread in the peritoneum [7].

The properties of epithelial-mesenchymal transition (EMT) at the invasive front of tumours allow cancer cells to migrate and invade surrounding tissues and distant organs. In the special issue, Oliverira and co-workers report on the involvement of kinin receptors in the EMT of glioblastoma cells, which enables the spread of cancer cells in the brain [8].

In addition to understanding the molecular mechanisms of cancer invasion and spread, the development of clinically relevant cancer models is crucial to mimic conditions in patients and test new therapeutic approaches to prevent drug failure in clinical trials. Zavbi's report provides an overview of current cancer models and the direction in which they should be developed to mimic the complex tumour microenvironment and patient-specific genetic background [9].

The growing knowledge of the molecular mechanisms of metastasis offers opportunities to improve clinical outcomes in cancer patients. New therapeutic interventions targeting the vulnerability of metastatic cancer cells and the protective tumour microenvironment are currently being tested, including immunotherapy and immune checkpoint inhibitors.

In the study by Zevnik et al., personalised combined immunotherapy of melanoma patients proved to be effective in inhibiting the spread of metastases. In the case report, a patient with metastatic melanoma with CDKN2A and BRAF mutations received postoperative therapy with the PD-1 inhibitor nivolumab in combination with the CTLA-4 inhibitor ipilimumab, which prolonged recurrence-free survival in this patient group [10]. Immunotherapy has significantly improved clinical outcomes in metastatic cancers such as melanoma. However, activation of the immune system can lead to serious immune-related side effects in patients, which can significantly affect their quality of life. A case report by Zovko and co-workers reported that a rare neurological immune-related side effect, limbic encephalitis, developed in a patient with metastatic melanoma following immunotherapy with a PD-1 checkpoint inhibitor [11].

Cannabinoids and their analogues are currently being investigated for their role in fighting cancer, in addition to their established use in clinics for palliative treatments. Ko and co-workers investigated the effect of synthetic cannabinoids on the growth of aggressive pancreatic and oral cavity cancer cells and showed interesting results that cannabinoids can target therapy-resistant cancer cells with stem-like properties [12]. Similarly, Dobovišek and co-workers have shown that cannabidiol reduces the viability of breast cancer cell lines and the addition of cannabidiol to the chemotherapeutic agent tamoxifen had an additive negative effect on cell viability in estrogen receptor-positive breast cancer cell lines [13]. These studies underly the urgent need to explore the anti-cancer effects of cannabinoids to understand their role in cancer progression and their interference with current treatments.

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These studies emphasise the urgent need to investigate the anti-cancer effects of cannabinoids to understand their role in cancer progression and their interference with current treatments.

Overall, the current special issue provides an overview of promising topics in cancer metastasis research and addresses clinical challenges in the treatment of cancer metastases. We are convinced that it will be an interesting read for both basic and clinical researchers in the field of cancer research.

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