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Cancer Horizons

CECOG educational illustrations: the blood–brain barrier and its relevance for targeted cancer therapies and immuno-oncology

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ABSTRACT

The blood–brain barrier (BBB) protects the central nervous system (CNS) from potentially harmful substances and molecules by limiting their influx from the blood stream into the brain parenchyma. Understanding the structure and functioning of the BBB is of major importance for the development of effective medical treatments for primary and secondary

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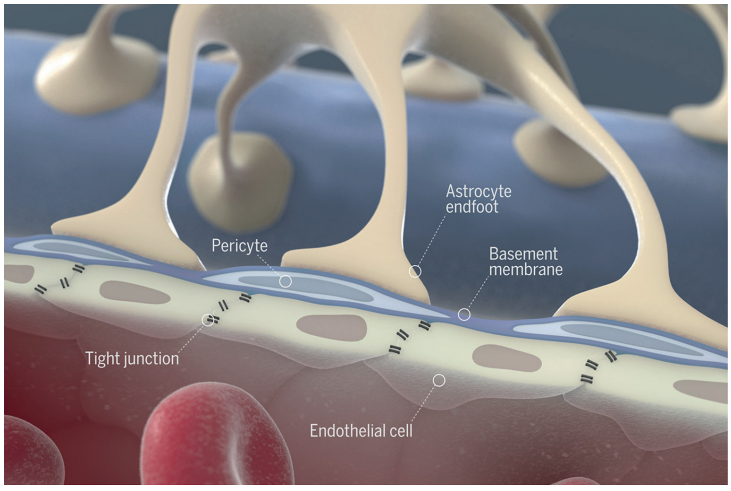

Figure 1 Blood–brain barrier constituents.

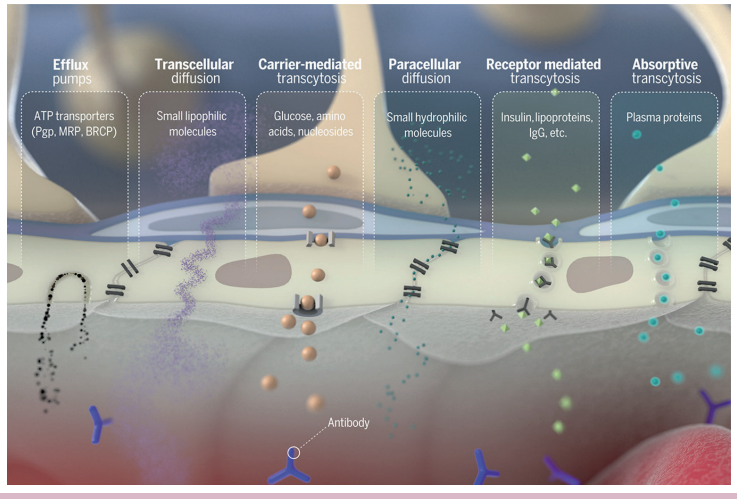

Figure 2 Transport routes across the intact blood–brain barrier.

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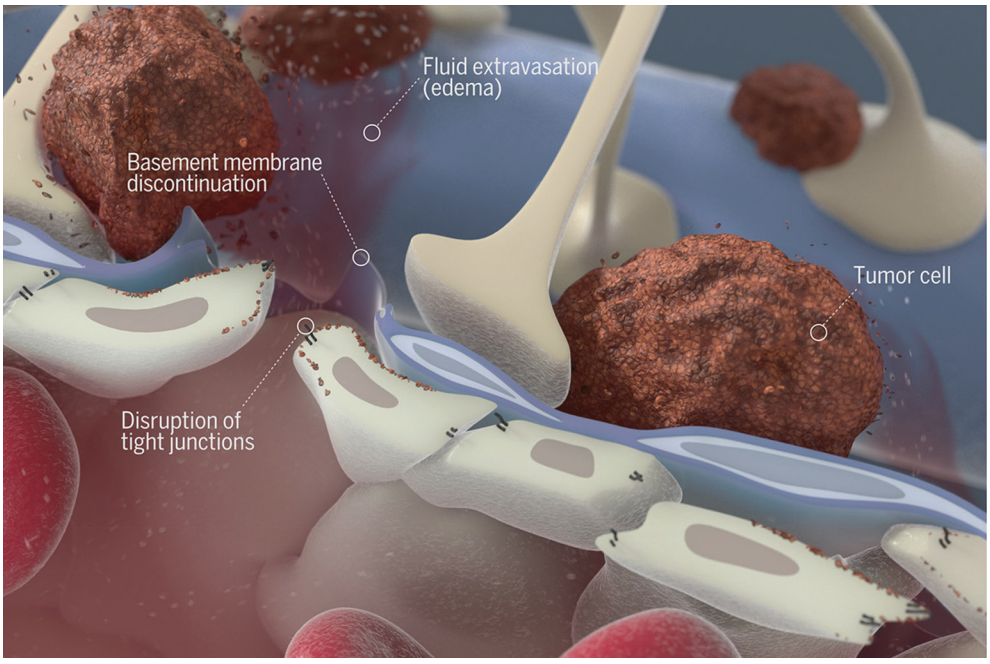

Figure 3 Blood–brain barrier disruption.

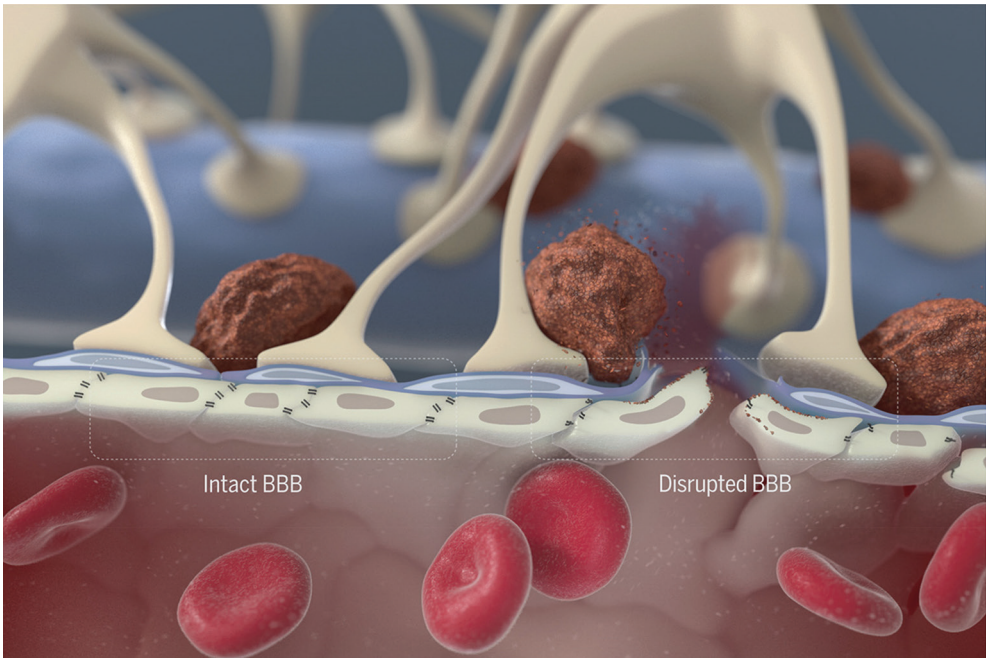

Figure 4 Regional heterogeneity of blood–brain barrier integrity.

brain tumours. Therefore, we provide here a concise and illustrated educational description of the anatomy and physiology of the BBB and current concepts on its role for targeted cancer therapies and immuno-oncology.

The blood–brain barrier (BBB) protects the central nervous system (CNS), which has limited self-renewal capacities, from potentially harmful substances and molecules by limiting their influx from the blood stream into the brain parenchyma. This mechanism is important to protect the function of the CNS, but may hamper effective systemic treatment of CNS malignancies. The BBB is composed of vascular and perivascular structures. Non-fenestrated endothelial cells connected by tight junctions limit the diffusion of large and hydrophilic molecules across the intact BBB. Further components of the BBB are a basement membrane, pericytes and the astrocyte foot processes, which link the BBB to the glial cell compartment (figure 1).[1 2] Efflux

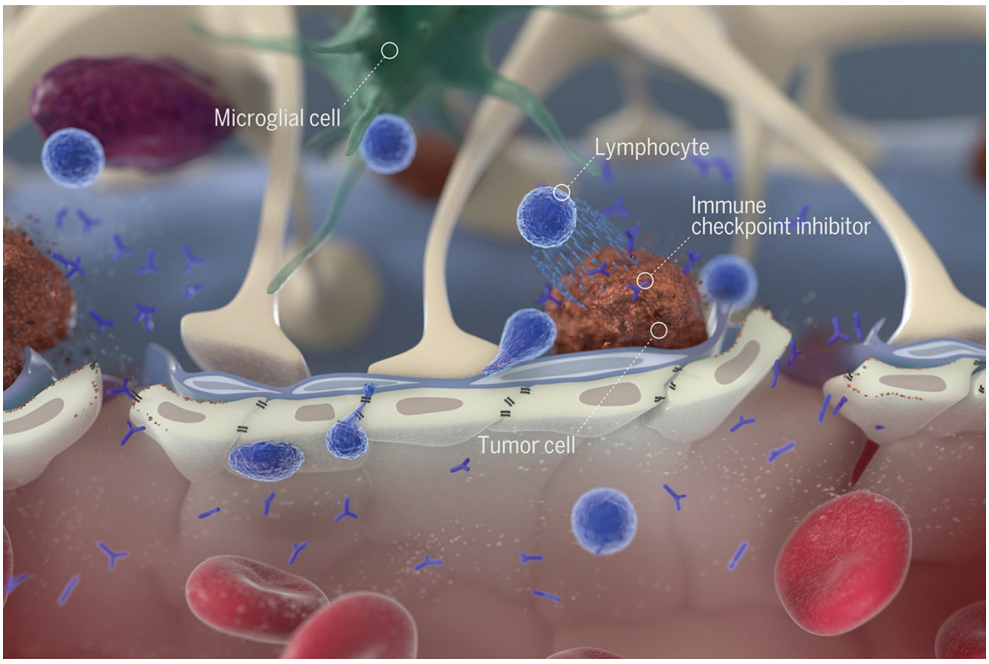

Figure 5 Immunotherapy and blood–brain barrier.

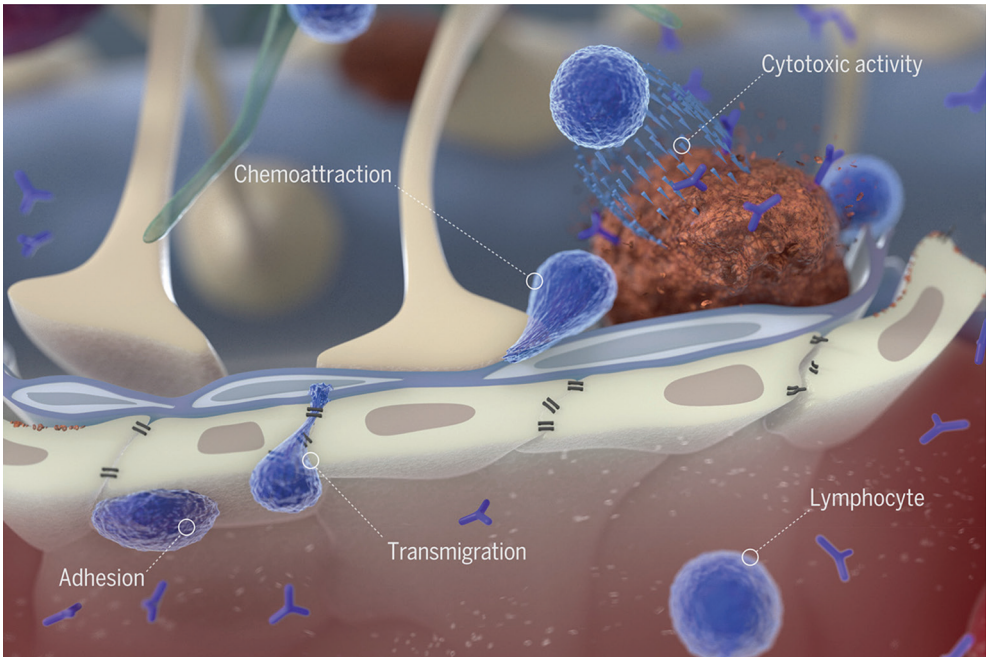

Figure 6 Lymphocyte extravasation.

pumps located on endothelial cells such as P-glycoprotein (Pgp), multidrug resistance proteins (MRP) and breast cancer resistance protein (BRCP) actively eject neurotoxic substrates in order to minimise their brain penetration (figure 2). Specific molecules needed for nutrition and function of the CNS can cross the BBB using transcellular or paracellular diffusion and specific influx mechanisms such as carrier-mediated, receptor-mediated or absorptive transcytosis (figure 2). In many brain tumours such as high-grade gliomas and brain metastases, there is at least partial BBB disruption, which is characterised by disintegration of tight junctions, basement membrane discontinuation and fluid extravasation into the CNS parenchyma (figure 3). Of note, even in malignant brain tumours (high-grade gliomas, brain metastases) the integrity of the BBB may not be impaired in all tumour parts and some tumour cells may be located in areas with an intact BBB that may limit drug penetration (figure 4). These areas of preserved BBB function are especially found at the invasion margin of the tumour but can heterogeneously be present within

the tumour tissue. Anti-cancer therapies including larger biologicals such as monoclonal antibodies are believed to reach tumour cells mainly in areas with BBB disruption (figure 5). Some smaller targeted agents, for example, some tyrosine kinase inhibitors, may cross the intact BBB and show robust intracranial activity possibly also in tumour areas with preserved BBB function.[3 4] Of note, activated cells of the immune system readily cross the intact BBB by transmigration after adhesion to endothelial cells. Furthermore, part of the activity of immunotherapies such as immune checkpoint modulators may depend on influences outside of the tumour tissue itself in peripheral immune sites, for example, regional lymph nodes. In line, immune-stimulating checkpoint inhibitors have shown efficacy against brain tumours (figure 6).[5–8] However, more research is needed to better understand brain penetration and intracerebral antitumour activity of modern drugs.

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Competing interests None declared.

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