Mmunotherapy-Based Rational Combinations for RCC

Subjects: Oncology

Contributor: Hye Won Lee

Advanced imaging techniques for diagnosis have increased awareness on the benefits of brain screening, facilitated effective control of extracranial disease, and prolonged life expectancy of metastatic renal cell carcinoma (mRCC) patients. Brain metastasis (BM) in patients with mRCC (RCC-BM) is associated with grave prognoses, a high degree of morbidity, dedicated assessment, and unresponsiveness to conventional systemic therapeutics. The therapeutic landscape of RCC-BM is rapidly changing; however, survival outcomes remain poor despite standard surgery and radiation, highlighting the unmet medical needs and the requisite for advancement in systemic therapies. Immune checkpoint inhibitors (ICIs) are one of the most promising strategies to treat RCC-BM.

Keywords: brain metastases ; renal cell carcinoma ; immune checkpoint inhibitors ; treatment resistance ; tumor immune microenvironment ; combination ; tyrosine kinase inhibitor ; radiotherapy

1. Introduction

Renal cell carcinomas (RCC) comprise a heterogeneous histologic subtype of malignant neoplasms arising from the nephron, and widely vary with respect to the underlying pathogenesis, genomic/molecular characteristics, and clinical treatment, including the susceptibility to conventional therapeutics [1][2][3][4][5][6][7][8]. Sequential events in the molecular etiopathogenesis of Von Hippel–Lindau (VHL)-inactivated metastatic RCC (mRCC) can be summarized as constitutive activation of the hypoxia-inducible factor (HIF) pathway due to loss of VHL activity, fostering global changes in the metabolome, genome, and epigenome in apoptotic, cell cycle regulatory, and mismatch repair pathways, angiogenesis, metabolic adaptations, and immune evasion [1][2][3][4][5][9][10].

Systemic therapy against mRCC has evolved significantly over the past two decades [11][12][13][14]. Vascular endothelial growth factor (VEGF)-tyrosine kinase inhibitors (TKIs) (e.g., sunitinib, pazopanib, axitinib, tivozanib, lenvatinib, and cabozantinib) or mammalian target of rapamycin (mTOR) pathway inhibitors (e.g., everolimus and temsirolimus) were used in the 2000s for mRCC, either combined or as a monotherapy [11][12][13][14]. A validation study of the International Metastatic RCC Database Consortium (IMDC) system revealed that the median overall survival (OS) significantly improved in the 2000s as compared to that observed in the cytokine era (favorable risk: 43.2 months, intermediate risk: 22.5 months, and poor risk: 7.8 months) [15]. Unfortunately, the 5-year OS rate for mRCC remains under 30% despite the TKI-based approach [11][12][13][14].

2. Clinical Implications and Unmet Needs of Brain Metastases from RCC

Brain metastases (BM) is generally associated with a very poor prognosis and high degree of morbidity, requiring urgent multidisciplinary care, and is relatively unresponsive to conventional systemic therapy [11][16][17][18][19][20][21][22][23][24][25]. BM is also a serious condition that causes headaches, focal neurological deficits, altered mental status or gradual cognitive impairment, epileptic seizures driven by increased intracranial pressure by vasogenic edema, or alterations in cerebrospinal fluid (CSF) flow, thereby impairing the quality of life (QOL) [11][17][18][19][25][26][27]. Unfortunately, BM is not a rare finding in mRCC (8%–15%), and its prevalence has increased in the past two decades [16][17][18][19][20][21][22]. The median OS of RCC patients with BM (RCC-BM) is only 5–8 months [16][17][18][19][20][21][22]. Therefore, early detection and effective treatment of BM is an unmet medical need for mRCC [11][17][19][25]. Improved clinical outcomes of extracranial metastases by the introduction of TKIs and immune checkpoint inhibitors (ICIs) has led to the adoption of improved imaging techniques for BM, thereby increasing awareness of the benefit of brain screening [11][17][18][19][20][27].

As advances in both local and systemic therapies provide better survival outcomes, mRCC patients with solitary BM and good performance status (PS) can benefit from early detection of asymptomatic BM [11][19][25][28]. Nevertheless, current surveillance guidelines for patients with RCC do not recommend brain imaging, unless BM is clinically suspected [11][29][30]. A large mRCC cohort study to investigate the rate of incidental BM highlighted that a relevant proportion of patients with mRCC (4.3%) may harbor occult BM through brain imaging as a part of eligibility assessments for clinical trial [16].

These data suggested that the risk of asymptomatic brain involvement extends to those with favorable risk features per IMDC risk assessment [16][19]. Sarcomatoid dedifferentiation, T2-4 disease, tumor size >10 cm, regional node involvement, and thoracic and osseous sites of extracranial disease, initial presence with metastatic disease at diagnosis and disease progression during first-line therapies were independent BM-associated risk factors for mRCC [16][19][20][25][31][32]. Consistent evaluation of risk and identification of highly sensitive and accurate algorithmic screening approaches are required to characterize mRCC patients with a considerably high propensity for BM, given that early detection may improve clinical outcomes and decrease the potential risks of aggressive multimodality treatment in patients with mRCC [11][16][19][25][28][31].

Unfortunately, brain lesions may be detected only after establishment of a microenvironment supportive of tumor growth and visible proliferation using magnetic resonance imaging (MRI) or computed tomography scans; however, these technologies are not sensitive enough to detect very early metastases [11][19][25][28]. Alternative approaches that can enable early diagnoses of BM are thus being explored based on liquid biopsy of circulating tumor DNA obtained from the CSF [33]. The implications of liquid biopsies for BM are notable, as they facilitate early detection and molecular profiling of a brain lesion to initiate the most appropriate treatment. Finally, prognostic factors are important for determining the optimal treatment modality for RCC-BM [11].

3. Immunosuppressive Pro-Metastatic Brain-Specific Tumor Microenvironment (TME)

The immune landscape of RCC-BM is less characterized than those of primary brain cancers [34][35]. The central nervous system (CNS) is protected by several functional barriers, including the blood–brain barrier (BBB) and blood–CSF barrier [34][35][36][37]. The BBB consists of endothelial cells with low transcytosis rates and high expression of efflux pumps that are connected by continuous tight junctions [34][35][36][37]. In addition, two basement membranes, embedded pericytes, and astrocytic terminal processes contribute to the BBB functions [34][35][36][37]. By comparison, the blood–CSF barrier is formed by choroid plexus epithelial cells that are connected via tight junctions, with choroid plexus capillaries having fenestrations and intercellular gaps that enable the free movement of molecules between these compartments [34][35][36][37]. Diffusion restriction of systemic agents into the CNS is considered a potential obstacle for intracranial efficacy of multiple TKIs and ICIs [16]. However, in patients with BM, the BBB is leaky and is substituted by a blood–tumor barrier (BTB) with a wider fenestration, leading to a higher efflux of fluid [17][34][37][38][39].

The development of BM disrupts the BBB damaged by a prominent neuroinflammatory response and anti-tumor treatment, such as surgery and/or radiotherapy, and is often characterized by abnormal vascular sprouting, allowing an influx of circulating myeloid and lymphoid cells, which are generally absent in the brain parenchyma, into the CNS [17][27][35][37][38]. The composition of the brain-specific immunosuppressive TME revealed cancer-specific enrichment of immune cells with pronounced differences in proportional abundance of microglia, infiltrating monocyte-derived macrophages, neutrophils, and T cells, playing a major role in BM progression, and creating a multitude of potential targets [38].

CNS myeloids, microglia and border-associated myeloid cells (BAMs), vitally contribute to brain homeostasis and diseases [38][40][41]. At homeostasis, microglia are the brain's equivalent of tissue-resident macrophages, representing 5%–15% of adult brain cells [37][40][41]. BAMs reside specifically in the meninges, choroid plexus, or perivascular macrophages associated with blood vessels [34][37][38][42]. Microglia and BAMs have different gene expression signatures, with BAMs being characterized by high CD38 and major histocompatibility complex (MHC) class Ⅱ, thus supporting their role as antigen presenting cells [34][38][42]. In addition, peripheral bone marrow-derived myeloid cells (BMDMs) may infiltrate the brain parenchyma and contribute to neuroinflammation [38][42]. CNS myeloids promote BM via chemokine (C-X-C motif) ligand 10 (Cxcl10) signaling and negative immune checkpoints that foster an immune suppressive niche, indicating blocking V-type immunoglobulin domain-containing suppressor of T cell activation (VISTA) and programmed cell death ligand 1 (PD-L1) signaling as an effective immune strategy [34][35][37][38][42].

Another predominant (up to 30% of the tumor mass) immune subset of BM TME are tumor-associated macrophage (TAM)-peripheral bone marrow-derived myeloid cells (BMDMs) [34][35][37][38][42]. They can be localized in the advancing tip of the tumor, blood vessels, or perinectrotic areas, where they play a role in tumor cell motility, establishment of metastatic niche, or angiogenesis, respectively [34][35][37][38][42]. Tissue-invading TAM-BMDMs with complex multifaceted phenotypes show a distinctive signature trajectory, revealing tumor-driven instructions along with contrasting tumor-infiltrating lymphocyte (TIL) activation and exhaustion [34][38][42]. When stimulated and reprogrammed by cancer cells, TAM-BMDMs can secrete immunosuppressive biomolecules, including transforming growth factor-β (TGF-β), interleukin (IL)-10, and arginase [37][43]. As TAM-BMDMs are implicated in BM promotion and exhibit gene signatures that are associated with

wound healing, antigen presentation, and immune suppression [34][35][38][42], selective depletion or blockade of TAM-BMDM recruitment could lead to effective T cell activation and execution of anti-tumor effector functions [27][34][38][42].

A range of lymphoid cells, including B and T cells, as well as innate lymphoid, natural killer (NK), and NK T cells, may be found within the CSF of the meninges, choroid plexus, and ventricles, although they are absent from the brain parenchyma [27][37][40]. RCC-BM leads to a moderate T cell influx, and T cells are predominantly localized within the stromal compartments of the tumor [35]. Tumor cells may also produce indolamine 2,3-dioxygenase (IDO), which stimulates the accumulation of regulatory T cells (Treg) and suppresses T cell activity by depleting tryptophan from the TME [37][38][42][44]. Importantly, the presence of PD-L1$^+$ TAMs has been correlated with Treg frequencies in several solid tissue tumors [38][42][45]. Tregs secrete IL-10, IL-4, and IL-13, which may trigger the development of TAMs with immunosuppressive properties and suppression of cytotoxic CD8$^+$ T cell responses [38][42][46]. The major changes in T cell activation in BM are the activation and exhaustion of CD8 tissue resident memory and effector memory subsets, displaying high amounts of both co-stimulatory and co-inhibitory molecules, as well as proliferation markers [35][38][42].

4. Multimodal ICI-Based Therapeutic Strategies for RCC-BM

RCC-BM poses unique clinical challenges because treatment of BM is complex, and a variety of factors, including anticipated patient survival, competing risks, and long-term toxicities should be considered while selecting the appropriate treatment strategy [11][17][47]. The brain, being a vital organ, is unable to regenerate upon damage, thus accounting for major limitations for therapy [11][17][47][48]. For instance, neurosurgery cannot always be performed, and radiotherapy has the risk of irreversibly limiting brain plasticity, which could evolve into a potentially lethal radionecrosis [48]. Three key indicators favor a good prognosis and thus more aggressive treatment: a KPS score > 70, age < 65 years, and controlled extracranial metastases [47][49].

The current approach for RCC-BM typically includes surgery (pathologic diagnosis and cerebral decompression) versus standalone radiotherapy and/or systemic therapies, with the overall goal of selecting the optimal treatment for an individual patient to maximize QOL and survival outcomes [17][47][48][49][50]. Surgery and radiation are the mainstays of therapy and have proven neurological and palliative benefits [17][47][49][50][51]. Medical therapies for RCC-BM can be divided into two broad categories: symptomatic management and tumor-targeting therapies. Corticosteroids, such as dexamethasone, represent the main symptomatic treatment in addition to pain medications because of their minimal mineralocorticoid effect and control intracerebral edema in BM [17]; however, the beneficial effects of steroids are not permanent, and a rapid taper is typically recommended to minimize drug-related adverse effects [17]. In addition, increased understanding of the role of immunosuppression in the pathophysiology of metastatic diseases reveals the potential harm of steroid-associated immunosuppression, thereby encouraging minimal steroid exposure and alternatives to steroid therapy [17].

4.1. ICIs Based on T Cell Exhaustion in RCC-BM

Although most patients with RCC-BM are excluded from important clinical trials because of poor prognosis and few validated treatment guidelines [11][48], this trend is diminishing given the increasing importance of clinical significance and a better knowledge of the underlying pathogenesis. The remaining majority of systemic therapies for RCC-BM dramatically changed with the introduction of ICIs and TKIs based on complex microenvironmental niche–tumor interactions, neuroinflammatory cascades, and neovascularization involved in establishing a new BM [11][17][47][48]. The richness and activation of BM TMEs regarding cellular subtypes, frequencies, and functional states parallels their favorable clinical response to ICIs [42]. Checkpoint interactions, such as PD-1:PD-L1, CTLA4:B7-1/2, T-cell immunoglobulin and mucin domain-3 (TIM-3):Galectin-9, and lymphocyte activation gene-3 (LAG-3):MHC class Ⅱ, play an important role in immune evasion of cancers [1]. Drug Administration (FDA) for mRCC include those that block co-inhibitory molecules, such as cytotoxic T-lymphocyte activating protein-4 (CTLA-4), PD-1, and PD-L1, thus facilitating T cell effector function and anti-tumor response [52][53].

Costimulation with CD28 or 4-1BB can increase anti-tumor activity [54][55]. CD28 costimulation can increase T cell anabolic metabolism, while the CD28 family members PD-1 and CTLA4 suppress T cell metabolic reprogramming [54]. CTLA4 inhibits CD28 signaling and PI3K/Akt/mTORC1 signaling, resulting in decreased glycolysis and mitochondrial oxidative capacity [56]. Blocking the negative regulators of PD-1 and CTLA4 that impair CD28 signaling to inhibit T cell release facilitates anti-tumor activity [54]. CD8$^+$ T cells continuously formulate their exhaustion states on account of exposure to suppressive gradients in the TME [57]. T cell exhaustion is the conversion of the state of CD8$^+$ T cells from antineoplastic to immune-functionally impaired due to long-term persistence of tumor antigens and/or the suppressive TME [58][59]. The exhausted CD8$^+$ T-cell phenotype has been associated with an increased risk of tumor progression [60][61], increased

dysfunctional dendritic cells (DCs) [62], and elevated numbers of immune cells, namely M2-polarized macrophages, resting mast cells, resting memory $CD4^+$ T cells, and $CD4^+$ $Foxp3^+$ Tregs [60][63][64][65]. Coinhibitory receptors, such as PD-1 and CTLA-4, are traditionally envisioned as exhaustion markers of T cells [59][66], which is the theoretical ICB.

Additionally, the prognostic impact of exhausted $CD8^+$ T cell infiltration in mRCC is only through stratification into specific subgroups [60][62][64][67][68][69][70]. For example, $CXCL13^+$ $CD8^+$ T cells exhibit elevated levels of markers, such as PD-1, Tim-3, T cell immunoreceptor with Ig and ITIM domains (TIGIT) and CTLA-4, higher Ki-67 expression, and lower levels of activated markers, such as tumor necrosis factor α (TNF-α) and interferon γ (IFN-γ) [67][71]. Furthermore, the abundance of intratumoral $CXCL13^+$ $CD8^+$ T cells was positively correlated with immunoevasive TME accompanied by increased T helper 2 cells, TAMs, $CD4^+$ $Foxp3^+$ Tregs, and decreased NK cells [67]. The HIF-1-TGF-β pathway might serve as a crucial molecule in connecting $CXCL13^+$ $CD8^+$ T cells and TME, [67][72][73][74]. Neoantigen reactivity is coupled to a CXCL13-secreting ‘‘exhausted’’ phenotype, possibly induced by chronic TCR signaling [75]. The selective expression of CCR5 and CXCL13 in neoantigen-specific T cells further suggests that a key feature of ICI-responsiveness is the ability to sustain ongoing priming and recruitment of tumor reactive T cells supported by $CXCR5^+$ lymphocytes [76][77]. Interestingly, patients with higher numbers of $CD39^+$ $CD8^+$ T cells showed improved responses to sunitinib, a multi-TKI, suggesting that evaluation of the exhausted phenotype for $CD8^+$ T cells may help in clinical decision making or therapy selection [61].

Many receptors in the immunoglobulin superfamily (such as CD28, and inducible T cell co-stimulator) and TNF receptor superfamily (TNFSF) exert costimulatory actions [78]. TNFSRF9 is thought to be an antigen stimulation-inducible co-stimulatory receptor, which is transiently expressed on activated $CD8^+$ T, activated $CD4^+$ T, and NK cells [64][79][80]. Co-stimulatory signaling mediated by TNFRSF9 promotes T cell proliferation, secretion of cytokines, resistance to activation-induced cell death, and development of memory T cells [80]. $TNFRSF9^+$ $CD8^+$ T cells possess both exhaustion (PD-1, TIM-3, CTLA-4, and TIGIT) and effector phenotype (IFN-γ, granzyme B, and Ki-67) [79]. This dual phenotype of $TNFRSF9^+$ $CD8^+$ T cells indicates that these cells may not be terminally exhausted; however, they could respond to ICB [79]. The functional status of $TNFRSF9^+$ $CD8^+$ T cells might partly result from the complicated interactions among immune cells (helper T cells, $CD8^+$ T cells, and myeloid cells) within the tumor, and high enrichment of $TNFRSF9^+$ $CD8^+$ T cells could be a predictor of immunotherapy and a novel therapeutic target in mRCC [79].

4.2. ICIs Based on Targeting Immunometabolomics in RCC-BM

RCC is essentially a metabolic disease characterized by a reprogramming of energetic metabolism, and many genes that are mutated in RCC encode proteins that have roles in cellular processes regulating oxygen and glucose consumption [54]. In particular the metabolic flux through glycolysis is partitioned [81][82][83][84], and mitochondrial bioenergetics and oxidative phosphorylation are impaired, as well as lipid metabolism [82][85][86]. In addition, RCC is one of the most immune-infiltrated tumors [87][88]. Emerging evidence suggests that the activation of specific metabolic pathway have a role in regulating angiogenesis and inflammatory signatures [89][90]. Features of the TME heavily affect disease biology and may affect responses to systemic therapy [91]. VHL mutations that occur in mRCC increased transcriptional activity of its target genes, such as *VEGF*, glucose transporter 1, and erythropoietin, independent of oxygen levels, promoting angiogenesis, and immunosuppression [54]. The complexity of cellular interactions and depletion of available nutrients may create an environment of nutrient competition for T cells, and buildup of waste products that may impair T cells [92]. RCC-BM demonstrated metabolic changes leading to alterations in pathways associated with energy metabolism and oxidative stress, as well as the accumulation of immunosuppressive metabolites, such as tryptophan (TRP) [54][92]. Enhanced activity across an array of interconnected oncogenic signaling networks centered on the PI3K-AKT pathway represents a generalizable feature across different BM histologies [92].

The analysis of metabolic pathways intrinsic to immune cell types, also known as immunometabolism, could identify markers of immune function based on the distinct metabolic requirements of these cells at each stage of differentiation [93]. At the single-cell level, costimulation shifted the percentage of cells from a baseline resting state into two primary branches: one that was enriched in IL-2 signaling and glycolysis and another that exhibited pathways of glycolysis, oxidative phosphorylation, and Myc signaling [54]. This bioenergetic switch is consistent with the known Myc regulation of metabolic reprogramming during T cell activation [54]. Activation, together with signaling through the costimulatory molecule CD28, augments signaling through the PI3K/Akt/mTORC1 pathway to increase glucose and mitochondrial metabolism, and enable robust proliferation and effector function [94][95].

Metabolic reprogramming dictates the fate and function of stimulated T cells and microenvironment of tumors coupled with chronic exposure to neoantigens can impair the metabolism of TILs [54][96][97]. Stimulated T cells are highly dependent on metabolic reprogramming from catabolic oxidative metabolism to anabolic metabolism with elevated glucose consumption and aerobic glycolysis to develop effector functions [98][99][100]. T cell activation leads to increased Myc and PI3K/Akt/mTORC1 signaling activity to promote glucose uptake and mitochondrial metabolism for growth and energetics,

and to regulate signaling and gene expression pathways [95][101][102]. $CD8^+$ T cells in RCC can be subject to metabolic barriers that lead to adaptations, such as reduced ability to absorb glucose for downstream glycolysis, fragmented and functionally altered mitochondria with low respiratory capacity, and elevated production of reactive oxygen species (ROS) [97][103]. These changes are critical for effector T cell function, as $CD8^+$ $PD\text{-}1^+$ cells subject to inhibition of glucose metabolism fail to develop into effector subsets and have a reduced capacity to favor suppressive Treg fates [54][103]. RCC $CD8^+$ TILs have altered metabolic and functional parameters, suggesting reduced metabolism and failure of antigen receptor stimulation to activate a predominant effector memory phenotype [54].

In addition, PD-1 signaling suppresses T cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation (FAO) [54][56]. While $CD8^+$ RCC TIL gene expression exhibits classical markers of chronic stimulation and enrichment of metabolic pathways, including FAO, glycolysis, and cholesterol homeostasis, a large portion of cells could be stimulated to reprogram metabolism and induce effector functions [54]. The link between very long chain fatty acid-containing lipids and response to ICI in RCC can be explained by enhanced peroxisome signaling in activated T cells, which leads to a metabolic switch to fatty acid catabolism [104]. Lastly, increased conversion of TRP to kynurenine by IDO leads to inhibition of T cell function and is involved in the regulation of the immunosuppressive TME of mRCC [54][105].

References

1. Wang, X.; Lopez, R.; Luchtel, R.A.; Hafizi, S.; Gartrell, B.; Shenoy, N. Immune evasion in renal cell carcinoma: Biology, clinical translation, future directions. Kidney Int. 2021, 99, 75–85.
2. Ricketts, C.J.; De Cubas, A.A.; Fan, H.; Smith, C.C.; Lang, M.; Reznik, E.; Bowlby, R.; Gibb, E.A.; Akbani, R.; Beroukhim, R.; et al. The Cancer Genome Atlas Comprehensive Molecular Characterization of Renal Cell Carcinoma. Cell Rep. 2018, 23, 313–326.e5.
3. Shenoy, N.; Pagliaro, L. Sequential pathogenesis of metastatic VHL mutant clear cell renal cell carcinoma: Putting it together with a translational perspective. Ann. Oncol. 2016, 27, 1685–1695.
4. Perazella, M.A.; Dreicer, R.; Rosner, M.H. Renal cell carcinoma for the nephrologist. Kidney Int. 2018, 94, 471–483.
5. Hsieh, J.J.; Purdue, M.P.; Signoretti, S.; Swanton, C.; Albiges, L.; Schmidinger, M.; Heng, D.Y.; Larkin, J.; Ficarra, V. Renal cell carcinoma. Nat. Rev. Dis. Primers 2017, 3, 17009.
6. Srigley, J.R.; Delahunt, B.; Eble, J.N.; Egevad, L.; Epstein, J.I.; Grignon, D.; Hes, O.; Moch, H.; Montironi, R.; Tickoo, S.K.; et al. The International Society of Urological Pathology (ISUP) Vancouver Classification of Renal Neoplasia. Am. J. Surg. Pathol. 2013, 37, 1469–1489.
7. Geissler, K.; Fornara, P.; Lautenschlager, C.; Holzhausen, H.J.; Seliger, B.; Riemann, D. Immune signature of tumor infiltrating immune cells in renal cancer. Oncoimmunology 2015, 4, e985082.
8. Cancer Genome Atlas Research Network. Comprehensive molecular characterization of clear cell renal cell carcinoma. Nature 2013, 499, 43–49.
9. Sato, Y.; Yoshizato, T.; Shiraishi, Y.; Maekawa, S.; Okuno, Y.; Kamura, T.; Shimamura, T.; Sato-Otsubo, A.; Nagae, G.; Suzuki, H.; et al. Integrated molecular analysis of clear-cell renal cell carcinoma. Nat. Genet. 2013, 45, 860–867.
10. Hamilton, E.; Infante, J.R. Targeting CDK4/6 in patients with cancer. Cancer Treat. Rev. 2016, 45, 129–138.
11. Matsui, Y. Current Multimodality Treatments against Brain Metastases from Renal Cell Carcinoma. Cancers 2020, 12, 2875.
12. Atkins, M.B.; Tannir, N.M. Current and emerging therapies for first-line treatment of metastatic clear cell renal cell carcinoma. Cancer Treat. Rev. 2018, 70, 127–137.
13. Chakiryan, N.H.; Jiang, D.D.; Gillis, K.A.; Green, E.; Hajiran, A.; Hugar, L.; Zemp, L.; Zhang, J.; Jain, R.K.; Chahoud, J.; et al. Real-World Survival Outcomes Associated With First-Line Immunotherapy, Targeted Therapy, and Combination Therapy for Metastatic Clear Cell Renal Cell Carcinoma. JAMA Netw. Open 2021, 4, e2111329.
14. Khan, Y.; Slattery, T.D.; Pickering, L.M. Individualizing Systemic Therapies in First Line Treatment and beyond for Advanced Renal Cell Carcinoma. Cancers 2020, 12, 3750.
15. Bosse, D.; Lin, X.; Simantov, R.; Lalani, A.A.; Derweesh, I.; Chang, S.L.; Choueiri, T.K.; McKay, R.R. Response of Primary Renal Cell Carcinoma to Systemic Therapy. Eur. Urol. 2019, 76, 852–860.
16. Steindl, A.; Alpar, D.; Heller, G.; Mair, M.J.; Gatterbauer, B.; Dieckmann, K.; Widhalm, G.; Hainfellner, J.A.; Schmidinger, M.; Bock, C.; et al. Tumor mutational burden and immune infiltrates in renal cell carcinoma and matched brain metastases. ESMO Open 2021, 6, 100057.

17. Achrol, A.S.; Rennert, R.C.; Anders, C.; Soffietti, R.; Ahluwalia, M.S.; Nayak, L.; Peters, S.; Arvold, N.D.; Harsh, G.R.; Steeg, P.S.; et al. Brain metastases. Nat. Rev. Dis. Primers 2019, 5, 5.

18. Massard, C.; Zonierek, J.; Gross-Goupil, M.; Fizazi, K.; Szczylik, C.; Escudier, B. Incidence of brain metastases in renal cell carcinoma treated with sorafenib. Ann. Oncol. 2010, 21, 1027–1031.

19. Dudani, S.; de Velasco, G.; Wells, J.C.; Gan, C.L.; Donskov, F.; Porta, C.; Fraccon, A.; Pasini, F.; Lee, J.L.; Hansen, A.; et al. Evaluation of Clear Cell, Papillary, and Chromophobe Renal Cell Carcinoma Metastasis Sites and Association With Survival. JAMA Netw. Open 2021, 4, e2021869.

20. Sun, M.; De Velasco, G.; Brastianos, P.K.; Aizer, A.A.; Martin, A.; Moreira, R.; Nguyen, P.L.; Trinh, Q.D.; Choueiri, T.K. The Development of Brain Metastases in Patients with Renal Cell Carcinoma: Epidemiologic Trends, Survival, and Clinical Risk Factors Using a Population-based Cohort. Eur. Urol. Focus 2019, 5, 474–481.

21. Bowman, I.A.; Bent, A.; Le, T.; Christie, A.; Wardak, Z.; Arriaga, Y.; Courtney, K.; Hammers, H.; Barnett, S.; Mickey, B.; et al. Improved Survival Outcomes for Kidney Cancer Patients with Brain Metastases. Clin. Genitourin. Cancer 2019, 17, e263–e272.

22. Takeshita, N.; Otsuka, M.; Kamasako, T.; Somoto, T.; Uemura, T.; Shinozaki, T.; Kobayashi, M.; Kawana, H.; Itami, M.; Iuchi, T.; et al. Prognostic factors and survival in Japanese patients with brain metastasis from renal cell cancer. Int. J. Clin. Oncol. 2019, 24, 1231–1237.

23. Xue, J.; Chen, W.; Xu, W.; Xu, Z.; Li, X.; Qi, F.; Wang, Z. Patterns of distant metastases in patients with clear cell renal cell carcinoma--A population-based analysis. Cancer Med. 2021, 10, 173–187.

24. Chandrasekar, T.; Klaassen, Z.; Goldberg, H.; Kulkarni, G.S.; Hamilton, R.J.; Fleshner, N.E. Metastatic renal cell carcinoma: Patterns and predictors of metastases-A contemporary population-based series. Urol. Oncol. 2017, 35, 661.e7–661.e14.

25. Tong, Y.; Huang, Z.; Hu, C.; Chi, C.; Lv, M.; Song, Y. Construction and Validation of a Convenient Clinical Nomogram to Predict the Risk of Brain Metastasis in Renal Cell Carcinoma Patients. Biomed. Res. Int. 2020, 2020, 9501760.

26. Gerstenecker, A.; Nabors, L.B.; Meneses, K.; Fiveash, J.B.; Marson, D.C.; Cutter, G.; Martin, R.C.; Meyers, C.A.; Triebel, K.L. Cognition in patients with newly diagnosed brain metastasis: Profiles and implications. J. Neurooncol. 2014, 120, 179–185.

27. Sevenich, L. Turning “Cold” into “Hot” Tumors-Opportunities and Challenges for Radio-Immunotherapy Against Primary and Metastatic Brain Cancers. Front. Oncol. 2019, 9, 163.

28. Suarez-Sarmiento, A., Jr.; Nguyen, K.A.; Syed, J.S.; Nolte, A.; Ghabili, K.; Cheng, M.; Liu, S.; Chiang, V.; Kluger, H.; Hurwitz, M.; et al. Brain Metastasis From Renal-Cell Carcinoma: An Institutional Study. Clin. Genitourin. Cancer 2019, 17, e1163–e1170.

29. Ljungberg, B.; Albiges, L.; Abu-Ghanem, Y.; Bensalah, K.; Dabestani, S.; Fernandez-Pello, S.; Giles, R.H.; Hofmann, F.; Hora, M.; Kuczyk, M.A.; et al. European Association of Urology Guidelines on Renal Cell Carcinoma: The 2019 Update. Eur. Urol. 2019, 75, 799–810.

30. Ward, R.D.; Tanaka, H.; Campbell, S.C.; Remer, E.M. 2017 AUA Renal Mass and Localized Renal Cancer Guidelines: Imaging Implications. Radiographics 2018, 38, 2021–2033.

31. Kotecha, R.R.; Flippot, R.; Nortman, T.; Guida, A.; Patil, S.; Escudier, B.; Motzer, R.J.; Albiges, L.; Voss, M.H. Prognosis of Incidental Brain Metastases in Patients With Advanced Renal Cell Carcinoma. J. Natl. Compr. Cancer Netw. 2021, 19, 432–438.

32. Bianchi, M.; Sun, M.; Jeldres, C.; Shariat, S.F.; Trinh, Q.D.; Briganti, A.; Tian, Z.; Schmitges, J.; Graefen, M.; Perrotte, P.; et al. Distribution of metastatic sites in renal cell carcinoma: A population-based analysis. Ann. Oncol. 2012, 23, 973–980.

33. Escudero, L.; Martinez-Ricarte, F.; Seoane, J. ctDNA-Based Liquid Biopsy of Cerebrospinal Fluid in Brain Cancer. Cancers 2021, 13, 1989.

34. Guldner, I.H.; Wang, Q.; Yang, L.; Golomb, S.M.; Zhao, Z.; Lopez, J.A.; Brunory, A.; Howe, E.N.; Zhang, Y.; Palakurthi, B.; et al. CNS-Native Myeloid Cells Drive Immune Suppression in the Brain Metastatic Niche through Cxcl10. Cell 2020, 183, 1234–1248.e25.

35. Hu, Z.I.; McArthur, H.L.; Ho, A.Y. The Abscopal Effect of Radiation Therapy: What Is It and How Can We Use It in Breast Cancer? Curr. Breast Cancer Rep. 2017, 9, 45–51.

36. 2020 ASHG awards and addresses. Am. J. Hum. Genet. 2021, 108, 373–374.

37. Pasqualini, C.; Kozaki, T.; Bruschi, M.; Nguyen, T.H.H.; Minard-Colin, V.; Castel, D.; Grill, J.; Ginhoux, F. Modeling the Interaction between the Microenvironment and Tumor Cells in Brain Tumors. Neuron 2020, 108, 1025–1044.

38. Klemm, F.; Maas, R.R.; Bowman, R.L.; Kornete, M.; Soukup, K.; Nassiri, S.; Brouland, J.P.; Iacobuzio-Donahue, C.A.; Brennan, C.; Tabar, V.; et al. Interrogation of the Microenvironmental Landscape in Brain Tumors Reveals Disease-Specific Alterations of Immune Cells. Cell 2020, 181, 1643–1660.e17.

39. Percy, D.B.; Ribot, E.J.; Chen, Y.; McFadden, C.; Simedrea, C.; Steeg, P.S.; Chambers, A.F.; Foster, P.J. In vivo characterization of changing blood-tumor barrier permeability in a mouse model of breast cancer metastasis: A complementary magnetic resonance imaging approach. Investig. Radiol. 2011, 46, 718–725.

40. Louveau, A.; Harris, T.H.; Kipnis, J. Revisiting the Mechanisms of CNS Immune Privilege. Trends Immunol. 2015, 36, 569–577.

41. Silvin, A.; Ginhoux, F. Microglia heterogeneity along a spatio-temporal axis: More questions than answers. Glia 2018, 66, 2045–2057.

42. Friebel, E.; Kapolou, K.; Unger, S.; Nunez, N.G.; Utz, S.; Rushing, E.J.; Regli, L.; Weller, M.; Greter, M.; Tugues, S.; et al. Single-Cell Mapping of Human Brain Cancer Reveals Tumor-Specific Instruction of Tissue-Invading Leukocytes. Cell 2020, 181, 1626–1642.e20.

43. Zhang, I.; Alizadeh, D.; Liang, J.; Zhang, L.; Gao, H.; Song, Y.; Ren, H.; Ouyang, M.; Wu, X.; D'Apuzzo, M.; et al. Characterization of Arginase Expression in Glioma-Associated Microglia and Macrophages. PLoS ONE 2016, 11, e0165118.

44. Wainwright, D.A.; Balyasnikova, I.V.; Chang, A.L.; Ahmed, A.U.; Moon, K.S.; Auffinger, B.; Tobias, A.L.; Han, Y.; Lesniak, M.S. IDO expression in brain tumors increases the recruitment of regulatory T cells and negatively impacts survival. Clin. Cancer Res. 2012, 18, 6110–6121.

45. Harter, P.N.; Bernatz, S.; Scholz, A.; Zeiner, P.S.; Zinke, J.; Kiyose, M.; Blasel, S.; Beschorner, R.; Senft, C.; Bender, B.; et al. Distribution and prognostic relevance of tumor-infiltrating lymphocytes (TILs) and PD-1/PD-L1 immune checkpoints in human brain metastases. Oncotarget 2015, 6, 40836–40849.

46. Mantovani, A.; Marchesi, F.; Malesci, A.; Laghi, L.; Allavena, P. Tumour-associated macrophages as treatment targets in oncology. Nat. Rev. Clin. Oncol. 2017, 14, 399–416.

47. McMahon, J.T.; Faraj, R.R.; Adamson, D.C. Emerging and investigational targeted chemotherapy and immunotherapy agents for metastatic brain tumors. Expert Opin. Investig. Drugs 2020, 29, 1389–1406.

48. Masmudi-Martin, M.; Zhu, L.; Sanchez-Navarro, M.; Priego, N.; Casanova-Acebes, M.; Ruiz-Rodado, V.; Giralt, E.; Valiente, M. Brain metastasis models: What should we aim to achieve better treatments? Adv. Drug Deliv. Rev. 2021, 169, 79–99.

49. Soffietti, R.; Abacioglu, U.; Baumert, B.; Combs, S.E.; Kinhult, S.; Kros, J.M.; Marosi, C.; Metellus, P.; Radbruch, A.; Villa Freixa, S.S.; et al. Diagnosis and treatment of brain metastases from solid tumors: Guidelines from the European Association of Neuro-Oncology (EANO). Neuro Oncol. 2017, 19, 162–174.

50. Schmieder, K.; Keilholz, U.; Combs, S. The Interdisciplinary Management of Brain Metastases. Dtsch. Arztebl. Int. 2016, 113, 415–421.

51. Sittenfeld, S.M.C.; Suh, J.H.; Murphy, E.S.; Yu, J.S.; Chao, S.T. Contemporary Management of 1-4 Brain Metastases. Front. Oncol. 2018, 8, 385.

52. Xu, W.; Atkins, M.B.; McDermott, D.F. Checkpoint inhibitor immunotherapy in kidney cancer. Nat. Rev. Urol. 2020, 17, 137–150.

53. Rappold, P.M.; Silagy, A.W.; Kotecha, R.R.; Hakimi, A.A. Immune checkpoint blockade in renal cell carcinoma. J. Surg. Oncol. 2021, 123, 739–750.

54. Beckermann, K.E.; Hongo, R.; Ye, X.; Young, K.; Carbonell, K.; Healey, D.C.C.; Siska, P.J.; Barone, S.; Roe, C.E.; Smith, C.C.; et al. CD28 costimulation drives tumor-infiltrating T cell glycolysis to promote inflammation. JCI Insight 2020, 5, e138729.

55. Menk, A.V.; Scharping, N.E.; Rivadeneira, D.B.; Calderon, M.J.; Watson, M.J.; Dunstane, D.; Watkins, S.C.; Delgoffe, G.M. 4-1BB costimulation induces T cell mitochondrial function and biogenesis enabling cancer immunotherapeutic responses. J. Exp. Med. 2018, 215, 1091–1100.

56. Patsoukis, N.; Bardhan, K.; Chatterjee, P.; Sari, D.; Liu, B.; Bell, L.N.; Karoly, E.D.; Freeman, G.J.; Petkova, V.; Seth, P.; et al. PD-1 alters T-cell metabolic reprogramming by inhibiting glycolysis and promoting lipolysis and fatty acid oxidation. Nat. Commun. 2015, 6, 6692.

57. Blank, C.U.; Haining, W.N.; Held, W.; Hogan, P.G.; Kallies, A.; Lugli, E.; Lynn, R.C.; Philip, M.; Rao, A.; Restifo, N.P.; et al. Defining 'T cell exhaustion'. Nat. Rev. Immunol. 2019, 19, 665–674.

58. Wherry, E.J.; Kurachi, M. Molecular and cellular insights into T cell exhaustion. Nat. Rev. Immunol. 2015, 15, 486–499.

59. Thommen, D.S.; Schumacher, T.N. T Cell Dysfunction in Cancer. Cancer Cell 2018, 33, 547–562.

60. Giraldo, N.A.; Becht, E.; Vano, Y.; Petitprez, F.; Lacroix, L.; Validire, P.; Sanchez-Salas, R.; Ingels, A.; Oudard, S.; Moatti, A.; et al. Tumor-Infiltrating and Peripheral Blood T-cell Immunophenotypes Predict Early Relapse in Localized Clear Cell Renal Cell Carcinoma. Clin. Cancer Res. 2017, 23, 4416–4428.

61. Qi, Y.; Xia, Y.; Lin, Z.; Qu, Y.; Qi, Y.; Chen, Y.; Zhou, Q.; Zeng, H.; Wang, J.; Chang, Y.; et al. Tumor-infiltrating CD39(+)CD8(+) T cells determine poor prognosis and immune evasion in clear cell renal cell carcinoma patients. Cancer Immunol. Immunother. 2020, 69, 1565–1576.

62. Giraldo, N.A.; Becht, E.; Pages, F.; Skliris, G.; Verkarre, V.; Vano, Y.; Mejean, A.; Saint-Aubert, N.; Lacroix, L.; Natario, I.; et al. Orchestration and Prognostic Significance of Immune Checkpoints in the Microenvironment of Primary and Metastatic Renal Cell Cancer. Clin. Cancer Res. 2015, 21, 3031–3040.

63. Du, B.; Zhou, Y.; Yi, X.; Zhao, T.; Tang, C.; Shen, T.; Zhou, K.; Wei, H.; Xu, S.; Dong, J.; et al. Identification of Immune-Related Cells and Genes in Tumor Microenvironment of Clear Cell Renal Cell Carcinoma. Front. Oncol. 2020, 10, 1770.

64. Chevrier, S.; Levine, J.H.; Zanotelli, V.R.T.; Silina, K.; Schulz, D.; Bacac, M.; Ries, C.H.; Ailles, L.; Jewett, M.A.S.; Moch, H.; et al. An Immune Atlas of Clear Cell Renal Cell Carcinoma. Cell 2017, 169, 736–749.e18.

65. Zhang, S.; Zhang, E.; Long, J.; Hu, Z.; Peng, J.; Liu, L.; Tang, F.; Li, L.; Ouyang, Y.; Zeng, Z. Immune infiltration in renal cell carcinoma. Cancer Sci. 2019, 110, 1564–1572.

66. Clark, D.J.; Dhanasekaran, S.M.; Petralia, F.; Pan, J.; Song, X.; Hu, Y.; da Veiga Leprevost, F.; Reva, B.; Lih, T.M.; Chang, H.Y.; et al. Integrated Proteogenomic Characterization of Clear Cell Renal Cell Carcinoma. Cell 2019, 179, 964–983.e31.

67. Dai, S.; Zeng, H.; Liu, Z.; Jin, K.; Jiang, W.; Wang, Z.; Lin, Z.; Xiong, Y.; Wang, J.; Chang, Y.; et al. Intratumoral CXCL13(+)CD8(+)T cell infiltration determines poor clinical outcomes and immunoevasive contexture in patients with clear cell renal cell carcinoma. J. Immunother Cancer 2021, 9, e001823.

68. Granier, C.; Dariane, C.; Combe, P.; Verkarre, V.; Urien, S.; Badoual, C.; Roussel, H.; Mandavit, M.; Ravel, P.; Sibony, M.; et al. Tim-3 Expression on Tumor-Infiltrating PD-1(+)CD8(+) T Cells Correlates with Poor Clinical Outcome in Renal Cell Carcinoma. Cancer Res. 2017, 77, 1075–1082.

69. Braun, D.A.; Hou, Y.; Bakouny, Z.; Ficial, M.; Sant'Angelo, M.; Forman, J.; Ross-Macdonald, P.; Berger, A.C.; Jegede, O.A.; Elagina, L.; et al. Interplay of somatic alterations and immune infiltration modulates response to PD-1 blockade in advanced clear cell renal cell carcinoma. Nat. Med. 2020, 26, 909–918.

70. Kawashima, A.; Kanazawa, T.; Kidani, Y.; Yoshida, T.; Hirata, M.; Nishida, K.; Nojima, S.; Yamamoto, Y.; Kato, T.; Hatano, K.; et al. Tumour grade significantly correlates with total dysfunction of tumour tissue-infiltrating lymphocytes in renal cell carcinoma. Sci. Rep. 2020, 10, 6220.

71. Zheng, Z.; Cai, Y.; Chen, H.; Chen, Z.; Zhu, D.; Zhong, Q.; Xie, W. CXCL13/CXCR5 Axis Predicts Poor Prognosis and Promotes Progression Through PI3K/AKT/mTOR Pathway in Clear Cell Renal Cell Carcinoma. Front. Oncol. 2018, 8, 682.

72. Workel, H.H.; Lubbers, J.M.; Arnold, R.; Prins, T.M.; van der Vlies, P.; de Lange, K.; Bosse, T.; van Gool, I.C.; Eggink, F.A.; Wouters, M.C.A.; et al. A Transcriptionally Distinct CXCL13(+)CD103(+)CD8(+) T-cell Population Is Associated with B-cell Recruitment and Neoantigen Load in Human Cancer. Cancer Immunol. Res. 2019, 7, 784–796.

73. Kobayashi, S.; Watanabe, T.; Suzuki, R.; Furu, M.; Ito, H.; Ito, J.; Matsuda, S.; Yoshitomi, H. TGF-beta induces the differentiation of human CXCL13-producing CD4(+) T cells. Eur. J. Immunol. 2016, 46, 360–371.

74. Xu, T.; Ruan, H.; Song, Z.; Cao, Q.; Wang, K.; Bao, L.; Liu, D.; Tong, J.; Yang, H.; Chen, K.; et al. Identification of CXCL13 as a potential biomarker in clear cell renal cell carcinoma via comprehensive bioinformatics analysis. Biomed. Pharmacother. 2019, 118, 109264.

75. Ghorani, E.; Reading, J.L.; Henry, J.Y.; de Massy, M.R.; Rosenthal, R.; Turati, V.; Joshi, K.; Furness, A.J.S.; Aissa, A.B.; Saini, S.K.; et al. The T cell differentiation landscape is shaped by tumour mutations in lung cancer. Nat. Cancer 2020, 1, 546–561.

76. Luchtel, R.A.; Bhagat, T.; Pradhan, K.; Jacobs, W.R., Jr.; Levine, M.; Verma, A.; Shenoy, N. High-dose ascorbic acid synergizes with anti-PD1 in a lymphoma mouse model. Proc. Natl. Acad. Sci. USA 2020, 117, 1666–1677.

77. Helmink, B.A.; Reddy, S.M.; Gao, J.; Zhang, S.; Basar, R.; Thakur, R.; Yizhak, K.; Sade-Feldman, M.; Blando, J.; Han, G.; et al. B cells and tertiary lymphoid structures promote immunotherapy response. Nature 2020, 577, 549–555.

78. Mayes, P.A.; Hance, K.W.; Hoos, A. The promise and challenges of immune agonist antibody development in cancer. Nat. Rev. Drug Discov. 2018, 17, 509–527.

79. Li, Y.; Wang, Z.; Jiang, W.; Zeng, H.; Liu, Z.; Lin, Z.; Qu, Y.; Xiong, Y.; Wang, J.; Chang, Y.; et al. Tumor-infiltrating TNFRSF9(+) CD8(+) T cells define different subsets of clear cell renal cell carcinoma with prognosis and immunotherapeutic response. Oncoimmunology 2020, 9, 1838141.

80. Vinay, D.S.; Kwon, B.S. 4-1BB signaling beyond T cells. Cell Mol. Immunol. 2011, 8, 281–284.

81. Lucarelli, G.; Loizzo, D.; Franzin, R.; Battaglia, S.; Ferro, M.; Cantiello, F.; Castellano, G.; Bettocchi, C.; Ditonno, P.; Battaglia, M. Metabolomic insights into pathophysiological mechanisms and biomarker discovery in clear cell renal cell carcinoma. Expert Rev. Mol. Diagn. 2019, 19, 397–407.

82. Bianchi, C.; Meregalli, C.; Bombelli, S.; Di Stefano, V.; Salerno, F.; Torsello, B.; De Marco, S.; Bovo, G.; Cifola, I.; Mangano, E.; et al. The glucose and lipid metabolism reprogramming is grade-dependent in clear cell renal cell carcinoma primary cultures and is targetable to modulate cell viability and proliferation. Oncotarget 2017, 8, 113502–113515.

83. Ragone, R.; Sallustio, F.; Piccinonna, S.; Rutigliano, M.; Vanessa, G.; Palazzo, S.; Lucarelli, G.; Ditonno, P.; Battaglia, M.; Fanizzi, F.P.; et al. Renal Cell Carcinoma: A Study through NMR-Based Metabolomics Combined with Transcriptomics. Diseases 2016, 4, 7.

84. Lucarelli, G.; Galleggiante, V.; Rutigliano, M.; Sanguedolce, F.; Cagiano, S.; Bufo, P.; Lastilla, G.; Maiorano, E.; Ribatti, D.; Giglio, A.; et al. Metabolomic profile of glycolysis and the pentose phosphate pathway identifies the central role of glucose-6-phosphate dehydrogenase in clear cell-renal cell carcinoma. Oncotarget 2015, 6, 13371–13386.

85. Lucarelli, G.; Rutigliano, M.; Sallustio, F.; Ribatti, D.; Giglio, A.; Lepore Signorile, M.; Grossi, V.; Sanese, P.; Napoli, A.; Maiorano, E.; et al. Integrated multi-omics characterization reveals a distinctive metabolic signature and the role of NDUFA4L2 in promoting angiogenesis, chemoresistance, and mitochondrial dysfunction in clear cell renal cell carcinoma. Aging 2018, 10, 3957–3985.

86. Bombelli, S.; Torsello, B.; De Marco, S.; Lucarelli, G.; Cifola, I.; Grasselli, C.; Strada, G.; Bovo, G.; Perego, R.A.; Bianchi, C. 36-kDa Annexin A3 Isoform Negatively Modulates Lipid Storage in Clear Cell Renal Cell Carcinoma Cells. Am. J. Pathol. 2020, 190, 2317–2326.

87. Vuong, L.; Kotecha, R.R.; Voss, M.H.; Hakimi, A.A. Tumor Microenvironment Dynamics in Clear-Cell Renal Cell Carcinoma. Cancer Discov. 2019, 9, 1349–1357.

88. Tamma, R.; Rutigliano, M.; Lucarelli, G.; Annese, T.; Ruggieri, S.; Cascardi, E.; Napoli, A.; Battaglia, M.; Ribatti, D. Microvascular density, macrophages, and mast cells in human clear cell renal carcinoma with and without bevacizumab treatment. Urol. Oncol. 2019, 37, 355.e11–355.e19.

89. Netti, G.S.; Lucarelli, G.; Spadaccino, F.; Castellano, G.; Gigante, M.; Divella, C.; Rocchetti, M.T.; Rascio, F.; Mancini, V.; Stallone, G.; et al. PTX3 modulates the immunoflogosis in tumor microenvironment and is a prognostic factor for patients with clear cell renal cell carcinoma. Aging 2020, 12, 7585–7602.

90. Lucarelli, G.; Rutigliano, M.; Ferro, M.; Giglio, A.; Intini, A.; Triggiano, F.; Palazzo, S.; Gigante, M.; Castellano, G.; Ranieri, E.; et al. Activation of the kynurenine pathway predicts poor outcome in patients with clear cell renal cell carcinoma. Urol. Oncol. 2017, 35, 461.e15–461.e27.

91. Ghini, V.; Laera, L.; Fantechi, B.; Monte, F.D.; Benelli, M.; McCartney, A.; Leonardo, T.; Luchinat, C.; Pozzessere, D. Metabolomics to Assess Response to Immune Checkpoint Inhibitors in Patients with Non-Small-Cell Lung Cancer. Cancers 2020, 12, 3574.

92. Fukumura, K.; Malgulwar, P.B.; Fischer, G.M.; Hu, X.; Mao, X.; Song, X.; Hernandez, S.D.; Zhang, X.H.; Zhang, J.; Parra, E.R.; et al. Multi-omic molecular profiling reveals potentially targetable abnormalities shared across multiple histologies of brain metastasis. Acta Neuropathol. 2021, 141, 303–321.

93. Artyomov, M.N.; Van den Bossche, J. Immunometabolism in the Single-Cell Era. Cell Metab. 2020, 32, 710–725.

94. Zheng, Y.; Delgoffe, G.M.; Meyer, C.F.; Chan, W.; Powell, J.D. Anergic T cells are metabolically anergic. J. Immunol. 2009, 183, 6095–6101.

95. Klein Geltink, R.I.; O'Sullivan, D.; Corrado, M.; Bremser, A.; Buck, M.D.; Buescher, J.M.; Firat, E.; Zhu, X.; Niedermann, G.; Caputa, G.; et al. Mitochondrial Priming by CD28. Cell 2017, 171, 385–397.e11.

96. Thommen, D.S.; Koelzer, V.H.; Herzig, P.; Roller, A.; Trefny, M.; Dimeloe, S.; Kiialainen, A.; Hanhart, J.; Schill, C.; Hess, C.; et al. A transcriptionally and functionally distinct PD-1(+) CD8(+) T cell pool with predictive potential in non-small-cell lung cancer treated with PD-1 blockade. Nat. Med. 2018, 24, 994–1004.

97. Scharping, N.E.; Menk, A.V.; Moreci, R.S.; Whetstone, R.D.; Dadey, R.E.; Watkins, S.C.; Ferris, R.L.; Delgoffe, G.M. The Tumor Microenvironment Represses T Cell Mitochondrial Biogenesis to Drive Intratumoral T Cell Metabolic Insufficiency and Dysfunction. Immunity 2016, 45, 374–388.

98. Jacobs, S.R.; Herman, C.E.; Maciver, N.J.; Wofford, J.A.; Wieman, H.L.; Hammen, J.J.; Rathmell, J.C. Glucose uptake is limiting in T cell activation and requires CD28-mediated Akt-dependent and independent pathways. J. Immunol. 2008, 180, 4476–4486.
99. Siska, P.J.; Rathmell, J.C. T cell metabolic fitness in antitumor immunity. Trends Immunol. 2015, 36, 257–264.
100. Michalek, R.D.; Gerriets, V.A.; Jacobs, S.R.; Macintyre, A.N.; MacIver, N.J.; Mason, E.F.; Sullivan, S.A.; Nichols, A.G.; Rathmell, J.C. Cutting edge: Distinct glycolytic and lipid oxidative metabolic programs are essential for effector and regulatory CD4+ T cell subsets. J. Immunol. 2011, 186, 3299–3303.
101. Wang, R.; Dillon, C.P.; Shi, L.Z.; Milasta, S.; Carter, R.; Finkelstein, D.; McCormick, L.L.; Fitzgerald, P.; Chi, H.; Munger, J.; et al. The transcription factor Myc controls metabolic reprogramming upon T lymphocyte activation. Immunity 2011, 35, 871–882.
102. Geltink, R.I.K.; Kyle, R.L.; Pearce, E.L. Unraveling the Complex Interplay Between T Cell Metabolism and Function. Annu. Rev. Immunol. 2018, 36, 461–488.
103. Qiu, J.; Villa, M.; Sanin, D.E.; Buck, M.D.; O'Sullivan, D.; Ching, R.; Matsushita, M.; Grzes, K.M.; Winkler, F.; Chang, C.H.; et al. Acetate Promotes T Cell Effector Function during Glucose Restriction. Cell Rep. 2019, 27, 2063–2074.e5.
104. Mock, A.; Zschabitz, S.; Kirsten, R.; Scheffler, M.; Wolf, B.; Herold-Mende, C.; Kramer, R.; Busch, E.; Jenzer, M.; Jager, D.; et al. Serum very long-chain fatty acid-containing lipids predict response to immune checkpoint inhibitors in urological cancers. Cancer Immunol. Immunother. 2019, 68, 2005–2014.
105. Sumitomo, M.; Takahara, K.; Zennami, K.; Nagakawa, T.; Maeda, Y.; Shiogama, K.; Yamamoto, Y.; Muto, Y.; Nukaya, T.; Takenaka, M.; et al. Tryptophan 2,3-dioxygenase in tumor cells is associated with resistance to immunotherapy in renal cell carcinoma. Cancer Sci. 2021, 112, 1038–1047.
