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The mechanistic modes of Targeting immunometabolism in cancer: An innovative strategy: A narrative review

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Abstract

Previously we had detailed different gynaecological cancers, inclusive of high grade serous ovarian cancers(HGSOC),breast cancer(BC), Hepatocellular carcinoma(HCC), non small lung cancer (NSCLC),bile acids in cancer,colorectal cancer with etiopathogenesis, treatment yet 5 year survival is substantially poor. Additionally, considering a considerable association of obesity with escalating incidence of cancers recently the concept of immunometabolism for targeting cancers has emerged. Furthermore,we had detailed alterations in metabolism in depth including macrophage polarization, SIRT signaling pathway,in T2DM, targeting PI3K/ PTEN/ AKT signaling pathwaysin germ cell tumors and oocyte generation, MAPK/ERK andHippo/MST signaling for cancers, PD1/ PDL1 (programmed death1)/ (programmed death ligand1 pathways in ovarian cancers /&tecemotide therapy for NSCLC, PI3K/ AKT/mTOR signaling in T2DM treatment and autophagy role . With advancements of immunometabolic scientific research advantages of using innovative strategies is got for immune controlling . Propagative metabolic adaptation of tumor cells aids in generation of a fluorishing tumor microenvironment(TME),where immune cells get their capability of earlier killing totally eliminated all the time persists an unresolved conundrum despite the generation of immune checkpoints treatments. In current decade numerous studies on tumor immunometabolism have been displayed. Generating immunometabolism might promote formation of antitumor immunotherapies from the continuos crosstalk amongst metabolism and immunity. Here our concentration is over the crucial targets of every key signaling pathways,ii) the molecule existent in upstream as well as downstream signaling along with cell demise modulated by them and immunometabolic checkpoints that have been displayed to possess significant controlling part are further described.Thus the idea of this is provision of necessary knowledge regarding molecular signaling in immunometabolism context and targeting approaches in oncology research and emphasizes the manner this area guides advancements in treatment of tumors.

Keywords; Immunometabolism; PI3K/ AKT/mTOR; LKB-AMPK pathway; Immune checkpoints; Tumor microenvironment(TME)

1. Introduction

Cancer portrays a robust health challenge. Despite canonical treatments possess the capacity of prolongation of the life span,the existence of considerable inimical sequelae have stimulated scientific workers in generating therapeutic approaches which possess the capacity of in particular resulting in damaging tumor without influencing the normal cells[1]. Attaining insight regarding the plethora of effector molecules in reference to immunometabolism would impart greater clinical significance regarding researchers interest in tumor treatments[2]. Alternate metabolic pathways get controlled by the tumor cells for their adaptation as per nutrients. Cancer cells persistently illustrated metabolic reprogramming at the time of proliferation that modulates immune escape in addition to generation of resistance to

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chemotherapeutic agents[3]. Despite that compared to tumor cells, immune cells might not be possessing robust metabolic flexibility akin to tumor cells that in toto might be leading to a full bias immunorepressive state in reference to tumor microenvironment(TME) therefore facilitating malignant events [4].

Tumors apart from being accreted malignant cells they further portray a complicated ecosystem which is well distributed[5]. Cancer cells interact directly/indirectly with the encompassing cellular microenvironment as well as generate mechanistic modes for facilitating their survival[6].The conundrum of tumor cells flourish whereas cytotoxic immune cells get hampered in the TME has been a big hurdle regarding immunotherapy[7]. Nevertheless, a recent invention pointed that the cytotoxic immune cells possess the capacity of reprogramming the dominant metabolism of tumor cells ,thus reverting the variable variability in the TME is of advantage for the immune cells. Poznanski et al.[8], demonstrated that natural killer (NK) cells having Warburg metabolism in addition to flexibility of substrates apart from leading to sustenance of adaptability of metabolic effect, further significantly escalated the tumor demise causing capability during adverse TME situations [8].

Subsequent to substantial work in reference to cancer metabolism at the time of the past 20yrs,the recent propagation further displayed attractivesigns regarding metabolic targets having the capacity of manipulating anticancer immunity. The part of the immune signaling networks in case of immunometabolism apparently is an attractive field for researchers influencing the cancer treatment considerably [2]. Previously we had detailed different gynaecological cancers, inclusive of high grade serous ovarian cancers(HGSOC), breast cancer(BC), Hepatocellular carcinoma(HCC), with etiopathogenesis, treatment yet 5 year survival is substantially poor. Additionally, taking into account how there is a considerable, association of obesity with escalating incidence of cancers in obesity, recently the concept of immunometabolism for targeting cancers has been emerging. Furthermore,we had detailed alterations in metabolism in remarkable depth inclusive of macrophage polarization, SIRT signaling pathway,in type2 Diabetes mellitus((T2DM), targeting PI3K/ PTEN/ AKT signaling pathwaysin treatment of germ cell tumors besides in generation of oocyte, MAPK/ERK Along with Hippo/MST signaling for cancers, PD1/ PDL1 (programmed death1)/ (programmed death ligand1 pathways in ovarian cancers and tecemotide therapy for non small lung cancer (NSCLC),by targeting mucin, PI3K/ AKT/mTOR signaling in T2DM treatment by SGLT2 inhibitors and autophagy role in Diabetic cardiomyopathy in details[9-23] . Here our concentration is over the crucial targets of every key signaling pathways,ii) the molecule existent in upstream as well as downstream signaling along with cell demise modulated by them and immunometabolic checkpoints that have been displayed to possess significant controlling part are further described.Thus the idea of this is provision of necessary knowledge regarding molecular signaling in reference to immunometabolism along with targeting approaches in Oncology research in addition to emphasizes the manner this area guides advancements in treatment of tumors.

2. Methods

Here we conducted a narrative review utilizing search engine pubmed,google scholar ;web of science ;embase; Cochrane review library utilizing the MeSH terms like immunometabolism; phosphatidyl inositol 3 - kinase(PI3K) ; protein kinase B (AKT); mammalian target of programmed death1 (PD1)/ programmed death ligand1(PDL1) ;tumor microenvironment(TME) ; ATP citrate lyase(ACLY); LKB1-AMPK signaling pathway; Various immunometablic checkpoint; Indoleamine 2,3-dioxygenase 1(IDO); interleukin-4 i1(IL-4I1); MTHFD2 (methylene tetrahydrofolatedehydrogenase); Acyl CoenzymeA: cholesterol-acetyltransferase(ACAT); SIRT 2(Sirtuins) from 1956 till date in 2024 june

3. Results

We found a total of 600 articles out of which we selected 148 articles for this review.No meta-analysis was done.

3.1. Metabolic Reprogramming amongst the Tumor Cells

Studies have illustrated that metabolic reprogramming of tumor cells yields the probability for the cancer cells to undergo growth as well as proliferation in TME which has deficiency of nutrients[24].A design akin to that got invented in 1956 by the German biochemist Warburg O[25], pointed that the maximum tumor cells did not form energy canonically by the efficacious tricarboxylic acid cycle(TCA alias Kreb's cycle), however, rather ensure their nutrient supply on their own effort using glycolysis that is germanely not efficacious regarding energy generation[25,26]. Malignant cells having rapid growth generally possess200 times greater rate of glycolysis contrasted to normal tissue, in tissues that have good oxygenated milieu as well [27]. This kind of reprogrammed cellular metabolism is an emblem of cancer [28].

Heterogeneity of tumors in addition to greater requirement of nutrients imparts a complicated metabolic design. Apart from depending substantially over the glycolysis rate, neoplastic cells facilitate their own proliferation utilizing glutamine, serine, arginine, lipid , fatty acids for the sustenance of tough anabolic requirement as well as energy generation means[29].

3.2. Metabolic Programs amongst the Immune Cells

Once adaptation takes place to various tissue milieu, immune cells present in TME generate particular molecular properties[30]. Variable kind of immune cells possess particular nutritional needs utilizing T cell subsets as those whose properties have been well acknowledged regarding metabolic adaptation in TME[31]. Helper T cells as well as effector T cells consented to the Warburg effect by picking up considerable quantities of glucose in addition to amplification of glycolysis, further escalating Oxidative phosphorylation(OXPHOS) along with ingesting greater quantities of glutamine[32]. Compared to, such 2 kind of cells, regulatory T(Treg)cells as well as memory T cells persistently obtain maximum of their energy from the OXPHOS events despite subsequent to their activation when their predilection is for fatty acid instead of glucose along with amino acids[33].

Metabolic impairment of T cells might lead to some elimination of immune working [34]. For example hampering of pyruvate dehydrogenase kinase,a positive controller of aerobic glycolysis interferes with the balance amongst Teff along with Treg CD4+ T cell subsets, declining the capability of inflammatory Th17cells along with facilitating Treg generation [35].It has been pointed that controlling or reprogramming of metabolic changes in tumor infiltrating lymphocytes (TIL) might portray a plausible approach for revitalizing the impaired T cells regarding cancer treatment[36].Summarizing, the incorporation of metabolic actions of T cells with their working needs of every T cell lineage represents an imperative part for sustenance of immune homeostasis in addition to working.

4. Interactions amongst immune along with Metabolic signaling in TME

The continuous interaction amongst immune along with metabolic signals in TME aids immune as well as tumor cells possessing variable metabolic designs.Such metabolism of tumor cells result in considerable insufficiency of nutrient substrates inclusive of glucose along with glutamine in TME that leads to aberrant working of immune cell population encompassing T cells[7,37]. Based over the persistent interactions amongst immune along with Metabolic signals in TME in addition to actions of metabolic pathways in immune cells, incorporating immunometabolic signaling pathways with phosphatidyl inositol 3 - kinase(PI3K) / protein kinase B (AKT)/ mammalian target of rapamycin inhibitors (mTOR) as well as liver kinaseB 1- 5’ adenosine monophosphate(AMP) activated protein kinase(LKB1-AMPK) in the form of a central association amongst immune signaling along with metabolic pathways substantially impacts tumor propagation.

PI3K /Akt/ mTOR signaling portrays one of a maximum key significant intracellular signaling pathway, regulating necessary cellular working, however critical constituents of the pathway are usually decontrolled in different kinds of cancer[38]. For instance generally there is overactivation of the PI3K signaling, in case of breast cancer(BC), hampering of the PI3K diminishes the incidence of triple negative breast cancer(TNBC) in addition to estrogen receptor positive BC along with advancement and metastatic BC,mutations of PI3KCA might result in resistance to chemotherapy in addition to bad prognosis[39]. AMPK in the form of a central metabolism regulator of glucose as well as lipid metabolism comprises maximum significant signaling pathway with LKB1 pathway in reaction to nutrients as well as energy intracellular alterations.As implicated by a study in reference to AMPK- LKB1 hampering decided esophageal squamous cell carcinoma cell fate from cellular senescence to glutamine -addicted survival[40]. With the acquisition of greater immunometabolic studies,it has been illustrated that PI3K /Akt/ mTOR as well as LKB1-AMPK signaling pathways represent the critical signaling pathways that possess the capacity of considerably impacting tumor propagation in the persistent interaction amongst immune along with metabolic signals[41].

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4.1. PI3K / AKT signaling pathway

PI3K / AKT / mTOR has a tendency of being overactivated by cancer, that is believed to be an attractive therapeutic target[42]. Pacey activation of the PI3K takes place on receipt of an upstream signal stimulus influencing a cascade of downstream targets inclusive of AKT , mTOR, glycogen synthase kinase 3 β (GSK3 β), ATP citrate lyase(ACLY)etc, conducting parts by escalating anabolism as well as diminishing catabolism(see Figure1)[rev in 43].

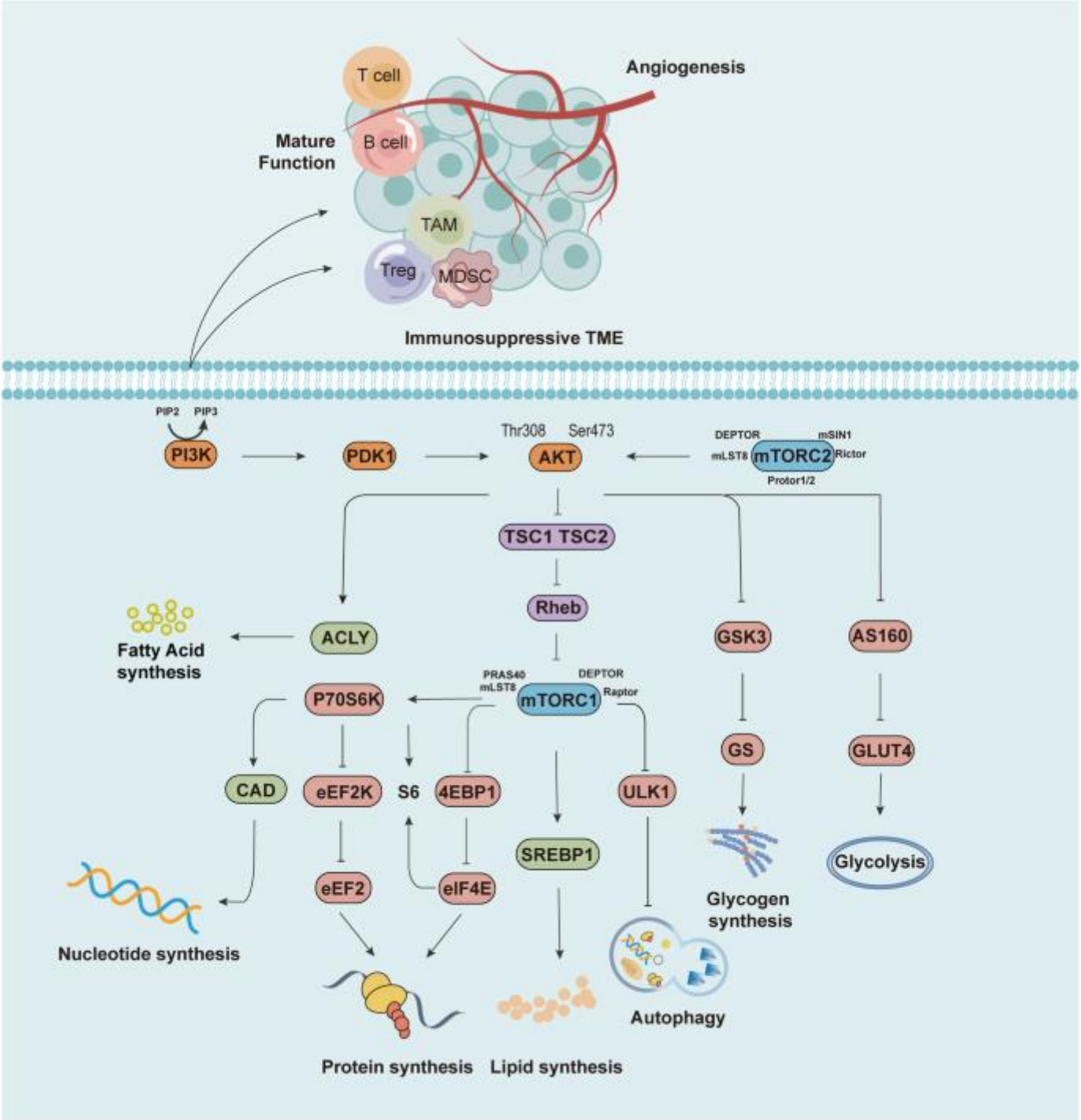

Figure 1 Courtesy ref no-43-Upon receipt of upstream signals, the PI3K/AKT/mTOR pathway is activated by phosphorylation, acting on a series of downstream signaling molecules to promote the anabolism of fatty acids, nucleotides, proteins, lipids, glycogen, and effector functions of immune cells.

In view of the PI3K signaling possesses the maximum significant part in cellular metabolism, acquisition of insight regarding PI3K controlled metabolic reprogramming yield provision of understanding regarding cancer therapeutic probability of pathway hampering agents[44].

4.1.1. PI3K

PI3K portrays an intracellular phosphatidyl inositol kinase possessing a dimeric structure with active serine /threonine(Ser/Thr) kinase[41]. Categorization of PI3K is made based on structure in addition to substrate specificity into Classes I,II, along with III[42]. The TypeIA PI3K catalytic subunit is inclusive of 3 proteins,p110α, p110β along with p110δ in addition to TypeIB PI3K catalytic subunit, p110γ[47]. The signaling pathway comprisingof PI3K as well as its downstream signaling molecules are imperative regarding cell viability, cycling along with other physiological working in mammals[48]. This further aids in signaling pathways modulated by PI3K germane to a plethora of disease fields for instance tumor treatments, cellular metabolism, generation of inflammation as well as immunity[49]. Activation of the PI3K takes place by signals from tyrosine kinases or G- protein coupled receptors(GPCRs) [50]. On getting an upstream signal, PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate(PIP2), generating remarkable quantities of phosphatidylinositol 3,4,5-trisphosphate(PIP3), thus enrolling phosphoinositide- dependent protein kinase 1(PDK1)-that phosphorylates the 308 region which activates PI3K[51]. Additionally, PDK1 possesses the capacity of activating mTOR complex2(mTORC2), which activates AKT signaling downstream of tryptophan 473 regions[rev in detail by us in ref no18].

Since PI3K is broadly correlated with a myriad of intraorganic events,they impact intricately cellular metabolic events in addition to immune system with the activation of PI3K might be implicated in numerous biological events of immune cell generation, activation or migration[52]. PI3K actions on one side influence the working of B as well as T cells[53].Okkenhaug's group etal.[54], observed elimination of PI3Kδworking in B as well as T cells in a mouse model of p110δ mutations aided in the generation of combined immunodeficiency syndrome[54]. PI3K actions further influence neutrophils, macrophages, NK Cells, dendritic cells(DC) [55].i) formation of reactive oxygen species (ROS) by neutrophils for leading to death of microorganisms is based on p110γ along with p110β PI3K[56].2) NK cells maturation as well as working are crucially correlated with p110δ inclusive of cytokines liberation as well as cytotoxicity.3) PI3K formsTMEthat is attractive for tumor growth, basically by facilitating tumor associated macrophages(TAM), Treg as well as myeloid derived suppressor cells (MDSC),where PI3Kδdominates the immunorepressive working of Treg as well as MDSC[57]. Additionally, PI3K signaling is particularly critical in case of tumor angiogenesis. Acknowledged the plethora of actions of PI3K over TME, PI3K hampering agents, facilitate proliferation of anti -tumor cells along with infiltration of immune cells to some degree, promoting a positive immunomodulatory effectiveness.

PI3K in general is broadly overactivated by cancer, as well as immune decontrolling, presenting in the form of a significant association amongst escalated tumor microvessel density in addition to escalated invasive capacity of tumor cells .This has resulted in scientific workers to attempt generation of therapeutic PI3K hampering agents along with although drug resistance in addition to botherations of tolerability it has been recommended for marketing. Concentration of earlier studies was all the time over generating Pan hampering agents . Nevertheless, with the propagation of the research work escalated toxicities which proved to be the restricting factors in generating hampering agents, Bayers developed Copansilib which targets p110α along with p110δ arriving last, however has been recommended for recurrent follicular lymphoma in 2017[58]. Furthermore,Duvelisib portrays a p110δ along with p110γ hampering agent which was introduced in 2018[59]. PI3K hampering agents that are subtype particular are highlighted in this research conundrum, basically alpelisib,a PI3K hampering agent got introduced in 2019[60].Idelalisib, portrays a p110δ hampering agent meant for chronic lymphatic leukaemia introduced in 2014[61] in addition to myriad of agents in clinical studies.In particular PI3K hampering agents impact efficacy i) in view of absence of PI3K δ along with PI3Kγ is correlated with dysfunctional immune reactions as well as Bcell generation; hampering of signaling from Bcell receptors might be utilized in Bcell lymphoma[62].2) Certain studies have utilized PI3K hampering agents IPI-549, as well as Silyminin for targeting tumor associated fibroblasts for influencing anticancer actions, the manner corroborated by significant declined Treg as well as MDSC, in addition to repression of angiogenesis as well as generation of collagen in tumor tissues [63].3) Acknowledged that p110δ is dominant in the immunorepressive working of Treg as well as MDSC the manner detailed earlier, the p110δ hampering agents might aid in generating positive immune milieu along with facilitate cytotoxic T cell reactions[57,64]. In toto the dependence of regulatory immune cells over the PI3K pathway might be getting treatment utilizing PI3K hampering agents for the liberation of immunorepression in addition to restoration of CD8+T cell actions.

4.1.2. Protein kinase B (PKB/AKT)

AKT alias PKB portrays a Ser/Thr kinase comprising of 3 allomorphic kinds[65]. Once the Thr308 as well as Ser473 regions of AKT get completely activated by the phosphorylationof PIP3 as well as mTORC2, therefore influence a cascade

of downstream substrates leading to escalated anabolism in addition to diminished catabolism[66]. Particularly AKT initially hampers the negative controlling actions of AKT substrate of 16kDa(AS160) on glucose transporter 4 (GLUT4) ,aiding cells to translocate GLUT4 possessing vesicles along with allowing the entry of glucose into the cell for the glycolysis[67].2) AKT hampers glycogen synthase kinase 3 (GSK3), therefore eliminates the hampering of glycogen synthase in addition to facilitate glycogen generation aiding in glucose uptake by cells with ease.3) AKT causes phosphorylation as well as activation of ACLY for facilitating generation of fatty acids(FA)4) AKT hampers tuberous sclerosis complex(TSC1/2)via phosphorylation as well as results in unbinding of Ras homologue enriched in the brain(RHeb),permitting RHeb to cause activation of mTORC1[68].

AKT influences the immune system in 2 main manners i) theAkt pathway controls the activation phenotype of macrophages in addition to modulate macrophage reactions by inflammatory along with metabolic signaling[69]. Categorization of macrophages is done into M1 as well as M2 kinds[70,rev by us23]. M1kind macrophages are implicated in positive immune reactions in addition to carry out immune surveillance working. Compared to,weak antigen presenting capability along with liberated cell factors factorof M2 kind macrophages modulate immune repression, where AKT might work. AKT works in conferring protection in controlling the evolution of the memory CD8+T cells reactions. The manner observed by Rogel A etal.[71], AKT possesses a key part in the immune surveillance of memory CD8+T cells, the manner illustrated that the AKT deficiency influences the survival of effector cells once transformation takes place to the memory CD8+T cells, resulting in diminished quantities of memory CD8+T cells as well as enfeebled secondary immunity. Furthermore, frail/debilitated AKT results in deficient some tumor fighting effector cell kinds of memory CD8+T cells, which results in diminished capacity in addition to reduced efficacy against tumors[71] .

AKT directly impacts a plethora of tumor generating events. Acknowledged, the considerable significant part of AKT,it is a pointer to an attractive therapeutic target as well as variable AKT hampering agents are undergoing clinical work[72].At present allosteric AKT hampering agents in clinical trials for instance MK-2206,BAY1125976 along with miransertib in addition to ATP competitively hampering agents for instance capivasertib along with ipatasertib[73]. ATP competitively hampering agents directly target the kinase structural domain for hampering its action. Activating mutations along with aberrant expression of the AKT pathway are correlated with generation of numerous cancers for instance breast cancer along with lung cancer[74].A natural product obtained from the Brassica vegetables,3 chloroacetylindoles illustrated a corroborated non competitive AKT1 in addition to AKT2 hampering agent, validated for the repression of colorectal cancer cell growth stimulating apoptosis *in vivo,* as well as *in vitro*[75].

4.1.3. Mammalian target of rapamycin(mTOR)

Presence of mTOR takes place in the form of 2 complexes; mTOR complex1(mTORC1) as well as mTOR complex2(mTORC2) are the main controllers of the cellular metabolism. A plethora of studies have illustrated that the activation of mTORC1is correlated with metabolic reprogramming[76].i) mTORC1 phosphorylation results in activation of p70 ribosomal protein S6 kinase (P70S6K), the maximum significant signaling core downstream of its signaling pathway for facilitating the intracellular pyrimidines development, peptides translation generation, peptide chain elongation in addition to other pathways leading to protein generation ii) mTORC1 might further synergistically escalate protein generation by hampering 4E binding protein 1(4EBP1) via phosphorylation followed by eukaryotic translation initiation factor(eIF4E) might activate S6 ribosomal unit in addition to activate ribosomes[77,rev by us in ref15]iii) Lastly mTORC1 hampers cellular autophagy by hampering uncoordinated 51-like kinase1 (ULK1), a significant starter of generation of double membrane autophagosome as well as its maturation via phosphorylation[rev by us in ref17] .

mTOR possesses a plethora of immunological functions, basically modulating the differentiation along with working of the immune cells in addition to possessing key part in the memory cells generation.While mTOR is controller of differentiation, survival as well as metabolic reprogramming of T cell subsets[78]. Conversely mTOR decides the proliferation cells in addition to maturation of Treg,Th17 cells, along with NK cells production as well as impacts effector working along with cytotoxicity[79]. Furthermore, mTOR plays a key part in controlling cell demise, basically in autophagy, ferroptosis,sweltering cell demise .Acknowledged the dual part of autophagy in repressing cancer at the time of early stage whereas sustenance of tumor metabolism, growth as well as survival facilitating tumor generation at the time of later stage. Thereby hampering autophagy with the utilization of mTOR hampering agents at particular times might escalate the metabolic stress over the cancer cells for promoting cell demise.The Oncogenic activation of PI3K - AKT - mTOR might be hampered by ferroptosis in cancer cells via downstream sterol regulatory element binding protein 1c(SREBP1c)/scd modulated adipogenesis, thereby combination of mTOR hampering agents in addition to other ferroptosis inducing agents with the idea of cancer therapy might prove to be a substantially good therapeutic target[80]. Wang et al.[81], illustrated an innovative mechanistic modes by which mTORC2 signaling facilitated the

sustenance of longevity of memory CD4+ T cells by hampering the initiation of ferroptosis[81]. Furthermore, this study illustrated the main kind of memory CD4+ T cells ferroptosis once their was existence of mTORC2 deficiency via knockdown along with overexpression experiments of GPX4, a critical enzyme in the ferroptosis pathway.Evavold etal.[82] , conducted a new study, where they observed mTORC1 facilitated gasdermin D modulated inflammatory cell demise by regulating ROS generation by mitochondria[82].

4.1.4. Glycogen synthase kinase 3 (GSK3)

Glycogen synthase kinase 3 (GSK3) further portrays a downstream target of AKT[83]. AKT results in phosphorylation along with hampers GSK3 followed by proteasomal breakdown for facilitating glycogen generation[84]. Studies have illustrated that GSK3 is unnaturally substantially regulated in different cancers in addition to posseses oncogenic actions. Thereby GSK3 is considered to be a player that might plausibly work in the form of a candidate which might prove to be offering cure for cancer[85]. Despite GSK3 hampering agent have illustrated poor effectiveness in studies, further corroboration is existent that they possess the capacity of hampering the growth of some cancers[86].For instance,CichockiF etal.[87], displayed that in the presence of GSK3 hampering agent CHIR99021, the generation of tumor necrosis factor alpha(TNF-α) as well as interferon-γ (IFN-γ) by NK cells was significantly escalated, which increased NK cytotoxicity, adding fuel for immunotherapy of cancer[87]. Additionally, scientific workers have further illustrated that downregulation of GSK-3 expression utilizing siRNA hampering or hampering of GSK-3 expression with small molecule hampering agents both downregulate PD-1 quantities to accelerate the capability of $CD8^+$ T cells in bringing about demise of cancer cells[88].

4.1.5. ATP citrate lyase(ACLY)

ATP citrate lyase(ACLY) portrays a critical enzymes which catalyze the generation of fatty acid in addition to basically represents a main enzyme implicated in the generation of acetylCoA at the level of cell membrane in myriad of tissues[89]. The manner acknowledged previously, malignantly accruing tumor cell display extensive requirement of ACLY with the significant upregulation of fatty acids(FAs) biogenesis in different tumor cells[90]. Present work points that ACLY expression occurs substantially in a broader variety of cancers inclusive of breast, lung, brain, gastric, colorectal, prostate,kidney cancers which ensures that ACLY is probably an efficacious therapeutic target for cancer by impacting lipid metabolism[90,91]. Hatzivassilou G et al.[92], displayed that the knocking down of ACLY in the form of critical enzyme incorporating glucose along with lipid metabolism. Acknowledged the critical working in lipid metabolism ,ACLY hampering agents were generated earlier for the metabolic diseases, restricted growth as well as survival of aerobic glycolytic tumor cells *in vitro* in addition to reduced tumor generation *in vivo*[93].Nevertheless, recently the ACLY hampering agents have garnered considerable interest in the form of a favourable anticancer agent with the accumulating corroboration pointing that cancer apart from being a genetic disease is further a metabolic disease[94]. For ACLY hampering agent - Bempedoic acid [(ETC-1002),8 hydroxy-2,2,14,14-tetramethylpentadecanedonic acid] generated by Esperion therapeutics as a liver- particular hampering agent[rev by us] ,received recommendations by USFood and Drug Administration(FDA) in 2020 in the form of a non statin low density lipoprotein- cholesterol (LDL-C)for atherosclerotic cardiovascular disease (CVD) as well as utilization for cancer treatment therapeutics[94,rev by us in ref20].

5. LKB1-AMPK signaling pathway

One more crucial signaling pathway which correlated cellular metabolism with carcinogenesis is LKB1-AMPK. LKB1 represents a tumor repressor Ser/Thr kinase which is widely correlated with the cellular metabolism along with proliferation in addition to different cellular pathophysiological events[95]. AMPK comprises of a catalytic subunit as well as β in addition to γ controlling subunit, that portrays a significant central controller regarding sensing in addition to controlling the homeostasis of cellular energy metabolism[96].On the binding of AMPK to γ subunit, modifications of the activation complex might occur escalating the proneness of substrates phosphorylation at the threonine 172 region[97]. Additionally, the escalating intracellular quantities of Ca^{2+} by calcium calmodulin dependent protein kinase kinase(CAMKK2) possess the capacity of direct phosphorylating at the threonine 172 region[98]. Once cells undergo physiological stressful situations leading to inadequate energy metabolism resulting in a reduction in ATP quantities ultimately AMPK will further get activated[99]. LKB1-AMPK signaling influences core working in the modulation of cellular metabolism, survival as well as proliferation in the existence of energy stress.This basically presents by modulating protein, glucose along with lipid metabolism in mammals in addition to autophagy as well as mitochondrial homeostasis, which incorporates practically maximum of the physiological as well as metabolic actions of the living organism. In the form of a crucial energy sensor, AMPK possesses a cascade of downstream targets for influencing a broad variety of controlling actions[100]. These are inclusive of facilitating catabolism by declining utilization of ATP in addition to diminishing anabolism for escalating ATP generation, thus sustenance of intracellular energy homeostasis[101]. Thereby concluding crosstalking of AMPK with mTOR for generating a complicated master metabolic

networks regulates catabolism along with anabolism in addition to impact the necessary working of the organism(see Figure2).

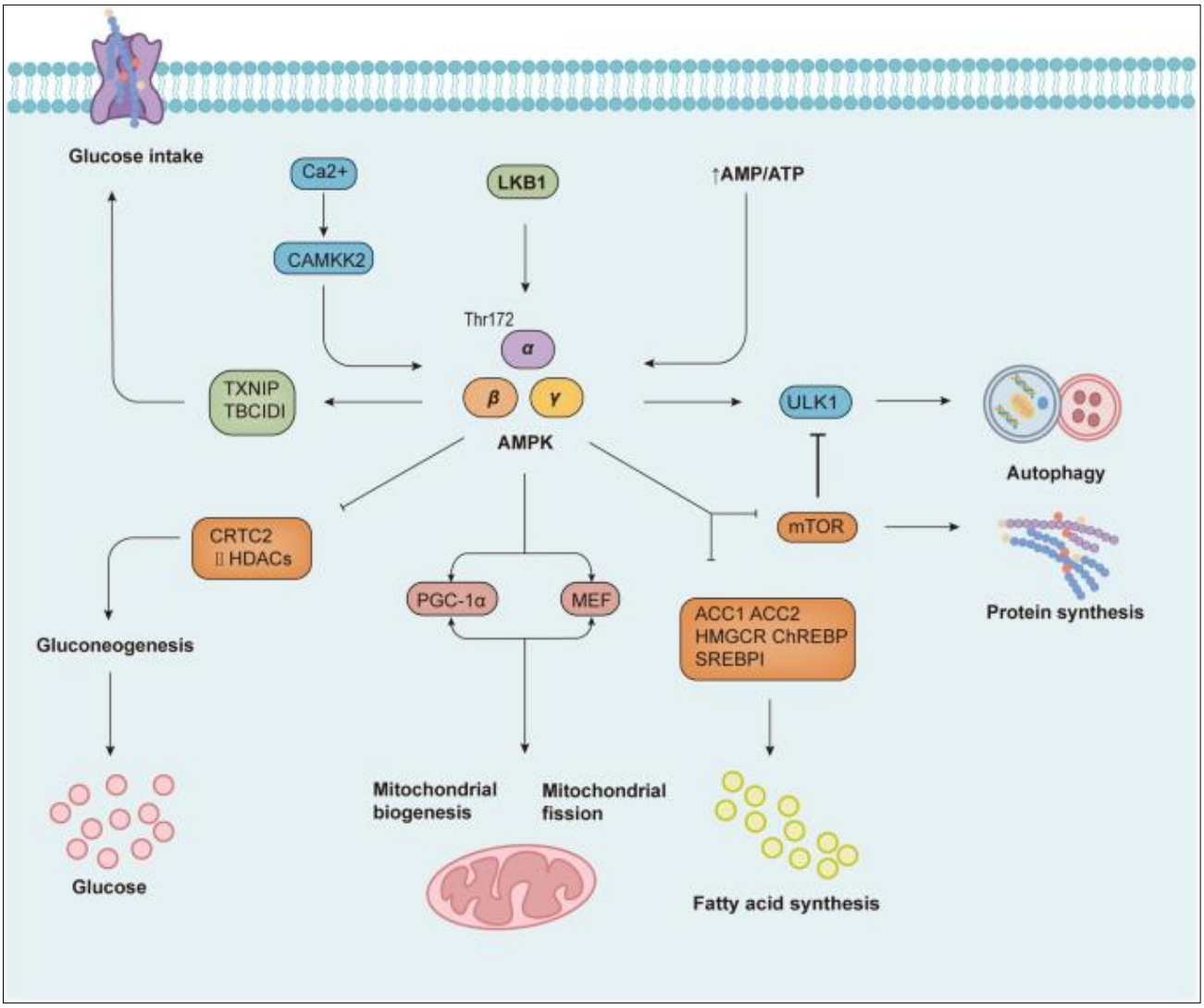

Figure 2 Courtesy ref no-43-AMPK can be activated directly by LKB1 or in response to increased intracellular Ca^{2+} and lower ATP levels, acting on a range of downstream signaling molecules to inhibit fatty acid synthesis, protein synthesis, gluconeogenesis, promote glucose uptake, promote autophagy, and maintain mitochondrial function.

The manner described earlier AMPK activation causes downregulation of mTORC1, which on the other hand activates the expression of autophagy associated proteins[102]. Activation of AMPK further phosphorylates ULK1 in addition facilitates its working; thereby activating autophagy events[103].Apart from associating immune signaling as well as cellular metabolism LKB1 might further control mitochondria associated working[104]. It has further been displayed that AMPK negatively controls ferroptosis by repressing fatty acid(FA) biogeneration[105], the manner revealed by the study performed by Lietal. [105], from the group of Gao who demonstrated that avoidance of ferroptosis by LKB1-AMPK occurred by hampering of acetylCoA carboxylase1(ACC1) the rate restricting enzyme for FA biogeneration[105].A cooperative study performed by Lee etal. [106], from the group of GanB further illustrated that AMPK possessed the capacity of hampering ACC1, therefore diminished generation of polyunsaturated chain fatty acids (PUFA's), as well as finally repressing ferroptosis[106]. Clarity is there that AMPK might be generated in the form of therapeutic target for diseases correlated with metabolic conditions . Conversely Bi etal. [107], showed that repressing LKB1-AMPK signaling pathway escalated glycolysis in Hepatocellular carcinoma(HCC) cells, which on the other hand escalated the stemness of the tumor cells, thereby aiding their growth in unregulated trajectory[107].

LKB1 possess unique working in the differentiation in addition to working of T cells,acting in the form of key checkpoint, which cooperates with AMPK in central controlling of lymphocyte metabolism as well as working [108].

LKB1works in the form of a key cytokine for T cell generation, thereby aiding in growth in addition to survival of thymocytes. Scientific work conducted by MaclverNJ etal. [109], corroborated that LKB1 is implicated in the controlling of glucose along with lipid metabolism in T cell lymphocytes, whereas Tcells possessing absence of LKB1 displayed bad metabolic adaptation[109]. Thereby concluding interference with LKB1-AMPK axis injures T cell metabolism in addition to overactivates mTORC1 signaling in reference to modulating the expansion of proinflammatory Tcells . LKB1 further aids in metabolic relaxing as well as antitumor immunity of DCs. Yang etal. [110], reported that LKB1 axis was responsible for generating metabolic rest in DCs for restricting over expansion of Treg in addition to Th 17 cell compartmentalization leading to sustenance of immune balance or facilitate antitumor immune reactions [110]. Apart from that LKB1 is implicated in the sustenance of viability as well as working of Treg by modulating Treg metabolism[111].

In view of the well acknowledged phenotypic actions of AMPK activation on metabolism, AMPK has already been earmarked in the form of an attractive target for therapy of metabolic syndrome(MetS) as well as cancer[112]. As per the region of effects, AMPK activators get categorized into direct activators along with indirect activators. Usually crosstalking of direct activators occur directly with particular AMPK subunits to lead to activation of AMPK by altering its form for instance aminoimidazole-4 carboxamide-riboside(AICAR) in addition to thienopyridone(A-769662). Indirect activators portray variable modulators that possess the capacity of indirectly activating AMPK by disrupting ATP generation or calcium accrual, basically originating from plants for instance resveratrol,curcumin as well as metformin. Acknowledged the complicated association amongst AMPK in addition to cancer AMPK activators presently are concentrating on preclinical as well as clinical studies on the treatment of obesity, T2DM as well as Non alcoholic fatty liver disease(NAFLD) in addition to CVD.

6. Various Immunometablic Checkpoints

Observations from the immune checkpoints have yielded newer targets regarding cancer treatment which further have been illustrated in melanoma as well as non small cell lung cancer(NSCLC)[113]. Nevertheless, just a practically negligible proportion of the patients have illustrated significant effectiveness.With acquisition of greater insight in reference to mechanistic modes of tumor metabolism resistance to immune checkpoint treatment might arise from tumor cell stimulated decontrolling of immune cell metabolism that results in immunorepression [114]. Therefore it might be of benefit to utilize metabolic pathways for obtaining tumor cell demise or reverting the metabolic susceptibility of tumor cells for targeting cancer. The recently displayed immunometablic checkpoints having significant probability might yield innovative understanding regarding antitumor treatments.

6.1. Indoleamine 2,3-dioxygenase 1(IDO)

Earlier we had reviewed the role of Indoleamine 2,3-dioxygenase 1(IDO) in DM regarding mitochondrial melatonergicpathway with crosstalk of gut microbiome, pancreatic cells and activation of bystander memory $CD8^{+}$T cells [rev by us in 115]. IDO is implicated in the breakdown of tryptophan that gets metabolised to N formyl kynurenine[116]. Greater IDO expression has a positive correlation with bad prognosis in different kind of tumors[117]. IDO facilitates ‘‘metabolic immune controlling’’ via catalytic oxidative catabolism of the essential amino acid tryptophan in addition to kynurenine(Kyn) pathway [118]. Metabolites of Kyn pathway possess the capacity of influencing immunorepressive actions by working in the form of natural immunoreactive ligand for the aryl hydrocarbon receptor(AhR), which activates Treg as well as MDSC in addition to hampering immune cells working for instance effector T cells[119]. Immune cells possess considerable dependence on tryptophan, with deletion of tryptophan resulting due to overexpression of IDO causing insufficient immune reaction[120]. Additionally, in a study conducted by ZhangX etal. [121], in a colitis associated colon cancer illustrated that Treg stimulated immune tolerance might get repressed by hampering IDO expression in addition to activation in the tumor cells[121]. Whereas concentration of maximum work for a remarkable time period had been on deletion of tryptophan for immunorepressive actions ,an innovative work by Flore A etal. [122], from the group of MurrayPJ illustrated that IDO facilitated tumor generation by transportation of the IDO metabolite Kyn into cells through SLC7A 11 as well as hampering ferroptosis in the tumor .Till present time IDO hampering agents for instance navaximod, epacadostat, linrodostat, indoximod are getting utilized as immunomodulator effects solely or in combination with other antitumor treatments[123]. Thereby drawing conclusions that indepth work over the present small molecule hampering agents, inventing IDO hampering agents having greater effectiveness in addition to improvement of the effectiveness of the combination treatments is the main motto of further work on IDO hampering agents.

6.2. Interleukin-4 i1(IL-4I1)

AhR portrays a ligand activated transcription factor which gives provision of flexibility to cells regarding sensing alterations in situations for instance environment, diet, metabolites in addition to microbial constitution[124]. AhR was

originally believed to be a modulator of digoxin impacting toxicity in addition to with propagation of work by scientific researchers,it was corroborated to be impacting main working in cancer along with immunity[125].The manner described previously IDO works in activation of AhR by eliminating tryptophan in addition to accreting Kyn via Kyn pathway. Nevertheless, the bothersome propagation achieved with the IDO hampering agents in combination with immune checkpoints blockade treatment indicate that there might be other pathways of AhR activation which resulted in the mechanistic modes involved in generation of tolerance to IDO hampering agents in tumor cells. Wang etal. [126], from the grp of OpitzCA isolated by screening as well as evaluating a wide variety of tumor patients, with the maximum association observed amongst IL-4I1 in addition to AhR actions. These outcomes pointed that IL-4I1 is a tumor generated metabolic enzyme which basically is responsible for catabolism of tryptophan for activation of AhR, escalating combativeness as well as hampering antitumor immunity[126].The observed outcomes point that IL-4I1 alters the antitumor CD8+T cells reactions ,facilitates cancer growth, influences survival of patients as well as might hamper immune checkpoint hampering agents therapeutic effectiveness. Thereby IL-4I1 might be a well illustrated immunometabolic checkpoint[127].

6.3. Acyl CoenzymeA: cholesterol-acetyltransferase(ACAT)

Acyl CoenzymeA: cholesterol-acetyltransferase(ACAT) portray an enzyme which is implicated in the transformation of cholesterol to cholesteryl esters via the acetylation of cholesterol[128]. Two of the genes encoding ACAT have been isolated alias ACAT1 as well as ACAT2, with ACATs working as necessary actors regarding cellular cholesterol homeostasis[129]. ACAT2 induction got illustrated in certain HCCs tissues for generating metabolic pathways for tumor cells that in turn hampers antitumor immunity [130]. Schmidt etal. [131], from the group of Malini MK further observed that controlling cholesterol metabolism might possess distinct working directly targeting viruses in addition to tumors, whereas further escalating clearance of viruses by T cells[131]. Additionally, Yang etal. [132], displayed that hampering of ACAT1escalated the quantities of cholesterol in CD8+T cell membrane , escalated the signaling of these cells that kill, generating greater efficacious synapses as well as cause greater sensitivity to antigens, that in turn results in improvement of immune effectiveness[161] ACAT hampering agents portray cholesterol modulating agents for instance Avasimibe which possess great tolerability in clinical trials in the form of cholesterol declining agents in addition to accessible studies pointed that use of Avasimibe combination with programmed death 1(PD1) antibodies might result in further improvement of the effectiveness of tumor immunotherapy. ACAT apparently is a promising metabolic controlling target, along with blockade of the cholesterol metabolic pathways modulated by ACAT might plausibly work in the form of therapeutic target in cancer patients.

6.4. SIRT 2(Sirtuins)

Sirtuins portray a silent information regulator 2 family of proteins- SIRT family)-reviewed by us[rev in ref no22]. SIRT 2 reflects a family of NAD^+/ nicotinamide adenine dinucleotide(NAD^+)-based protein deacetylases along with ADP ribosyl transferases having corroborated key working in neurodegenerative diseases. Despite that certain studies regarding SIRT2 possessing double paradoxical parts in facilitating in addition to hampering have raised hurdles in deeper studies[133]. SIRT 2 is implicated in the regulation of the cell metabolism, cell cycle as well as TME[134]. Currently SIRT 2 has been observed to be a crucial immunometabolic checkpoint regarding reprogramming of T cell metabolism. Hamaidi etal.[135], observed that enhanced expression of Oxidative phosphorylation(OXPHOS) along with glycolysis of the T cells in SIRT 2 deficienct mice led to enhanced T cell proliferation in addition to their capability of resulting in cell demise,following which it demonstrated greater anti tumor actions . These outcomes revealed that repression of SIRT 2 facilitated metabolic reprogramming of T cells,ideally implicated in aerobic glycolysis as well as mitochondrial respiration, sustenance of T cells effector working in metabolically stressed TME[135]. Despite, the debate regarding SIRT 2 is cancer facilitating or cancer repressing is existent till date,as per certain studies SIRT 2 hampering agents have illustrated as being lucrative in cancer therapy [136].

6.5. MTHFD2 (methylene tetrahydrofolatedehydrogenase)

Methylene tetrahydrofolate dehydrogenase(MTHFD2) represents an imperative enzyme in cellular one carbon unit metabolism which catalyzes the formation of methylene tetrahydrofolate from the formyl tetrahydrofolate by nicotinamide adenine dinucleotide($NADP^+$) in the form of hydrogen acceptor as well as forming nicotinamide adenine nucleotide phosphate(NADPH) [137]. Folate metabolism is a crucial metabolic event in organisms with provision of folate intermediates for facilitating single carbon metabolism, where changes in folate metabolism or upregulation of the expression of single carbon metabolizing enzymes are believed tobe implicated in the greater risk of cancer[138]. Overexpression of MTHFD2 in different kinds of cancer cells escalating PD-L1 expression in addition to immune escape of tumor cells was evaluated[139]. Additionally, MTHFD2 expression is intricately correlated with mTORC1 signaling, that regulates proteins, lipid as well as nucleotide formation in normal in addition to cancer cells[140]. Recently MTHFD2 was displayed to be a metabolic checkpoint of cells as well as hampers anti inflammatory Treg cells along with

is a plausible therapeutic target amongst 1C metabolism. The mechanistic modes are hampering of MTHFD2 results in exhaustion of purine pool, accreting purine biogenerating intermediates as well as diminishing of mTORC1 signaling[141].Thereby conclusions drawn being MTHFD2 is to certain degree oncogenic, that might be believed tobe therapeutic target in addition to pointer in the form of a biomarker for cancer as well as further research trajectory should substantially aim to unravel the mechanistic modes by which it facilitates the propagation as well as augments the propagation of functional hampering agents[142].

7.Recent Advancements

Tumour-reactive plasma cells (TRPCs) have been displayed to be positively correlated with long-term survival of patients with different cancers. Nevertheless, apart from tumour-specific antigen (TSA)-induced T cells which have precise actions against tumours, plasma cells need TSA to derive particular reactions. Thereby , the look out for a TSA appropriate for B-cell recognition is mandatory. Recently Chenetal.[147], described, the working of tumour-reactive plasma cells. Additionally, they evaluated the idea of screening for neoantigen-reactive plasma cells,getting stimulation from T-cell screening strategies. Whereas,hurdles are present for instance epitope anticipation in addition to efficient screening, the generation of innovative strategies might result in the inventing of considerably particular plasma cells for adoptive cell therapy. In conclusion, tumour-reactive plasma cells are emerging as powerful players in cancer immunotherapy. Their capability to produce antibodies against a variety of antigens, particularly neoantigens, opens new vistas for individualized treatments. Overcoming problems in epitope anticipation as well as screening would be key in garnering the complete capability of these plasma cells for the advantage of cancer patients(see Figure3,4).

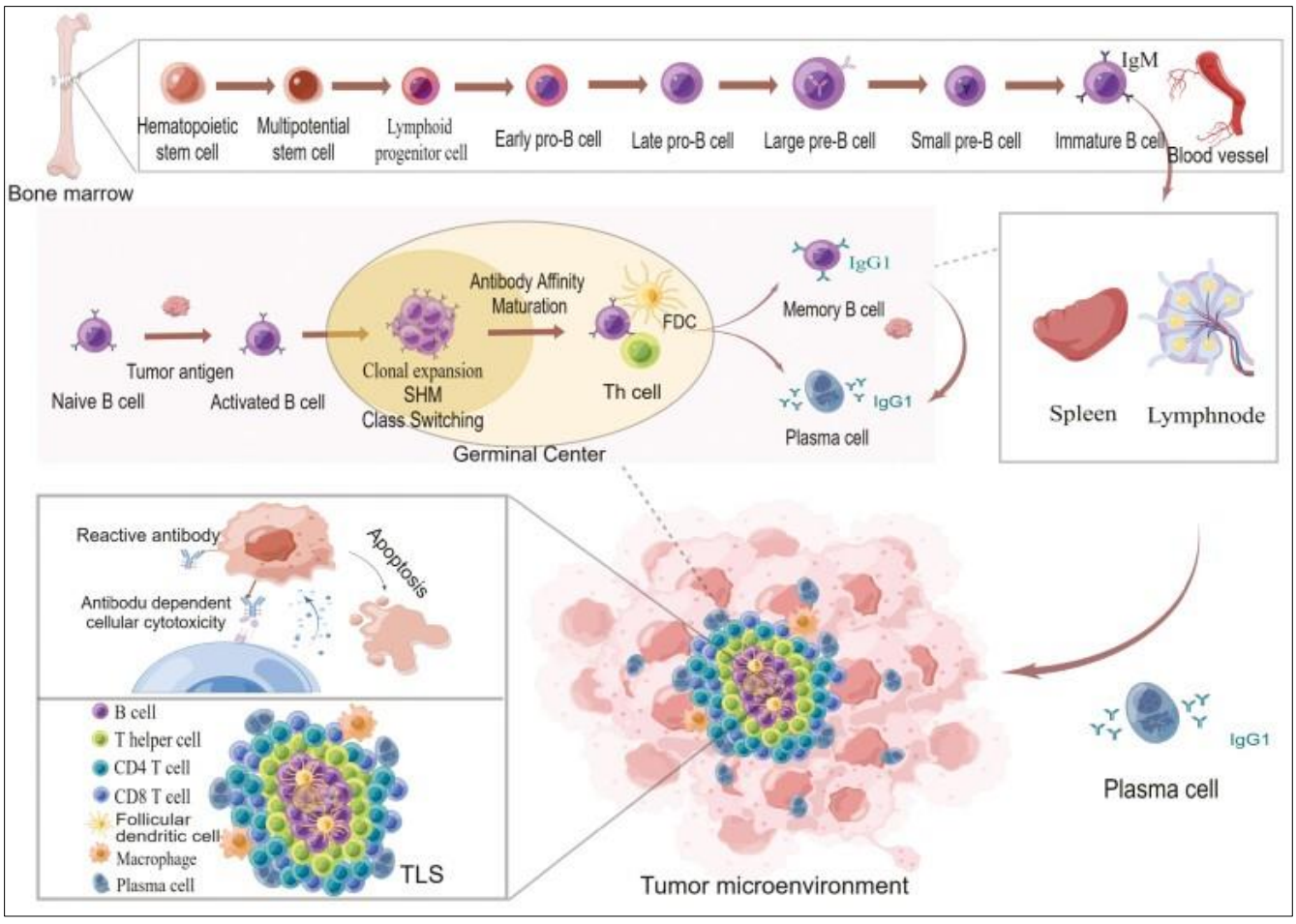

Figure 3 Courtesy ref no-147-Development and differentiation of tumour-reactive plasma cell. Haematopoietic stem cells arise from bone marrow and undergo continuous differentiation to pro-B cells and eventually to pre-B cells, which then produce IgM and express it on their cell surface, becoming immature B cells. These B cells later migrate via blood vessels to secondary lymphoid organs. Naive B cells within the spleen and lymph nodes are activated following stimulation by free tumour antigens and proceed to clone and expand in the germinal centre, undergoing somatic hypermutation (SHM) and class switching. Only B cells with high antigen affinity are able to interact with more antigens on the surface of follicular dendritic cells, take up the antigen, and present it through MHC-II pathway. Then helper T

cells recognise them and activate B cells. This process is repeated for about 2–3 weeks until B cells producing high-affinity antibodies are generated. At this point, differentiated B cells leave the germinal center, becoming memory B cells and plasma cells. Plasma cells then leave the secondary lymphoid organ and migrate to the site of the tumour, surrounding it in the periphery of tertiary lymphoid structures, and meanwhile producing a large number of specific antibodies, exerting neutralization and ADCC effects.

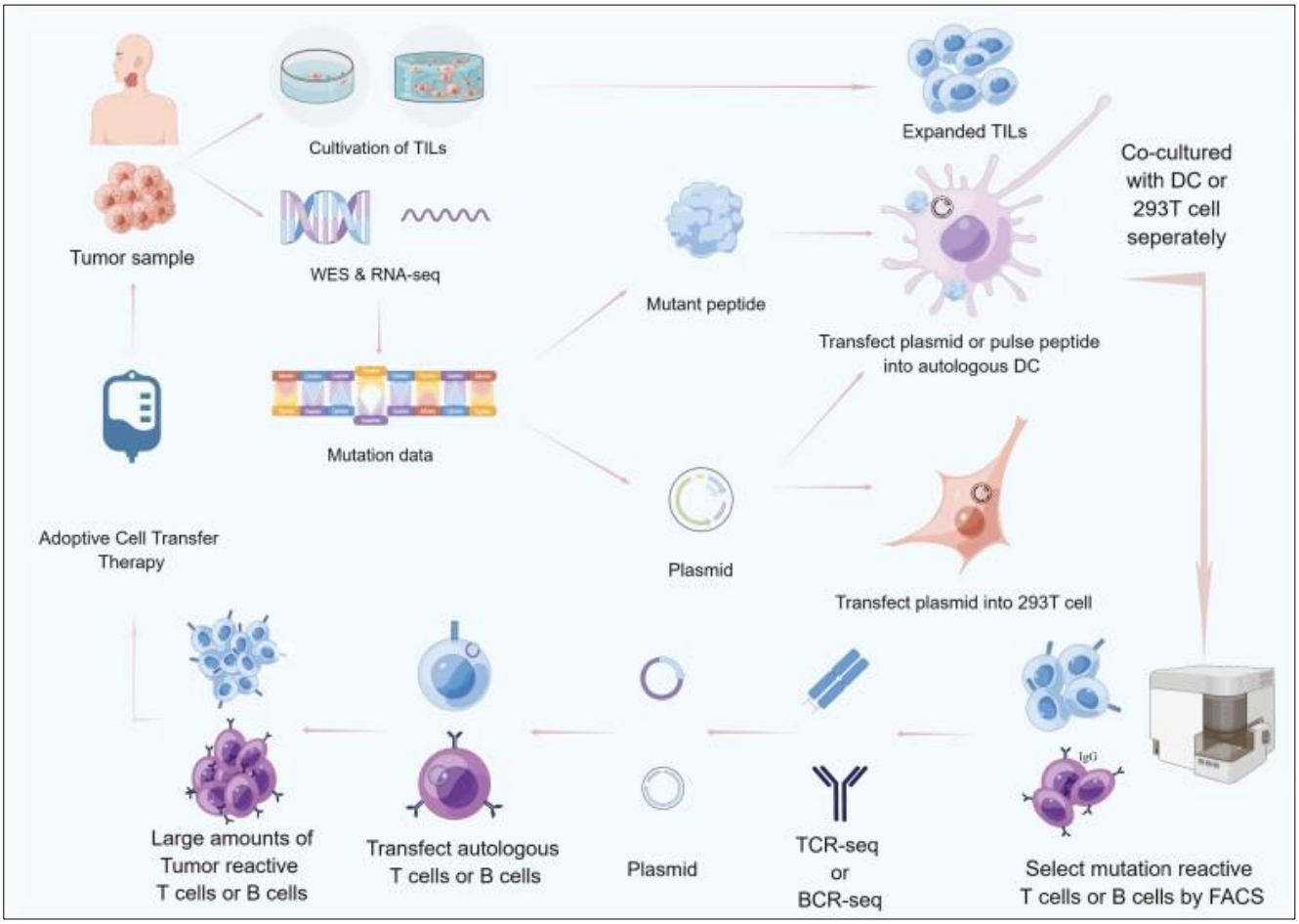

Figure 4 Courtesy ref no-147-Screening of neoantigen-reactive TILs. Tumour samples are obtained from the patient, with a portion of the samples being separated and cultured to obtain amplified TILs. Another portion is used for WES and RNA-seq to acquire mutation information for synthesising mutated peptides and plasmids. The plasmids are transfected into dendritic cells, and the mutated peptides are pulsed onto dendritic cell surfaces, which are cocultured with TILs to simulate the MHCI and MHCII pathways of T-cell immune responses. Through transfecting plasmids into 293T cells, recombinant protein is expressed and cocultured with TILs to simulate B-cell immune responses. Activated T cells and B cells are sorted by flow cytometry for TCR-seq and BCR-seq to obtain sequence information and construct plasmids. The plasmids are transfected into autologous T cells or B cells, respectively to obtain tumour-reactive T cells or B cells containing specific TCR or BCR. These cells are expanded *in vitro* and adoptive transferred into patient for personalised treatment.

Recently Kumari etal.[148],displayed how neoantigen identification and dendritic cell(DC) based vaccines for lung cancer immunotherapy might be developed. Immunotherapies possesses the capacity of treating numerous cancers, including tough -to-treat cases for instance lung cancer. In view of its tolerability, long persistence of therapeutic reaction, along with effectiveness in a spectrum of patients, immunotherapy might further aid in the treatment of lung cancer, which has restricted treatment choices.Tumor-specific antigens (TSAs) for cancer vaccinations in addition to T-cell therapies are tough to invent.Neoantigens (NeoAgs) from genetic mutations, irregular RNA splicing, protein alterations, or viral genetic sequences in tumor cells yield a solution. NeoAgs, unlike TSAs, are non-self as well as possess the capacity of resulting in an immunological reaction. Next-generation sequencing (NGS) in addition to bioinformatics possess the capacity of rapidly estimate as well as anticipate tumor-specific NeoAgs. Substantially immunogenic NeoAgs yield individualized or generalized cancer immunotherapies. Dendritic cells (DCs), which take origin as well as control T-cell reactions, are broadly studied potential immunotherapeutic therapies for lung cancer in addition to other cancers.

DC vaccines are stable, dependable , along with safe in clinical trials. The goal of this article was to evaluate the current status, restrictions, reactions in addition to prospective clinical utilizationof DC vaccines, in addition to the isolation as well as selecting major histocompatibility complex (MHC) class I along with II genes forNeoAgs. The aim of Kumari etal.[148],was to reason out DC biology along with activate DC manipulation to aid researchers for developmentof substantially robust cancer vaccines for patients(see Figure5for basics of neoantigen).

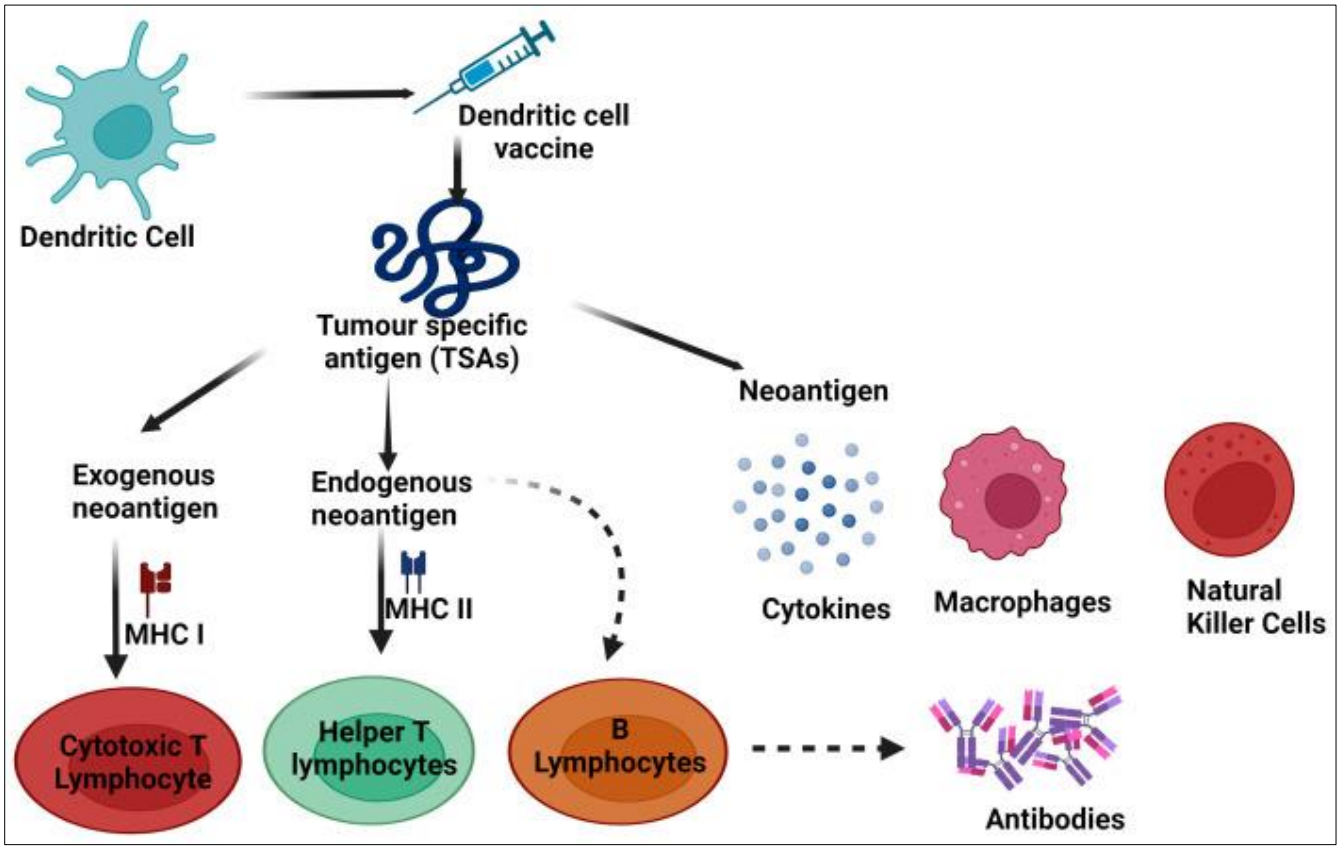

Figure 5 Schematic view of how tumor-specific antigens (neoantigens) initiate both innate and adaptive immune responses. Macrophages and natural killer (NK) cells participate in the innate response, directly targeting tumor cells. DCs present neoantigens via MHC class I molecules to activate cytotoxic T lymphocytes (CTLs), inducing tumor cell destruction. Simultaneously, DCs present antigens via MHC class II to T helper lymphocytes, prompting a cytokine release that amplifies CTL and B-cell activity. This intricate interplay unleashes a robust adaptive immune response, bolstered by various effectors like cytokines, macrophages, and NK cells. DC vaccines directly deliver neoantigen to DCs, facilitating antigen presentation to T cells and fostering a vigorous immune reaction against tumors. This orchestrated immune response, mediated by CTLs, T helper cells, B cells, and other effectors, underpins effective anti-tumor immunity, crucial for combating cancer progression(created with BioRender.com).

7. Conclusions

With the different immune checkpoint(IC) hampering agents as well as chimeric antigen receptor T cell treatments with lead being taken by programmed death/ programmed death-ligand 1(PD-1/PD-L1) pathways with immunotherapies getting generated might be believed to have converted the therapy of a plethora of cancers to certain degree[143]. Even currently the reaction rates of patients differ broadly to the accessible immune therapies inclusive of common generation of resistance to immune checkpoint treatments [144]. An escalated quantities of immunometabolic studies have displayed an attractive tendency to escalate anticancer actions via metabolic targets in addition to immunometabolism which offers a wide chance of enhancement of cancer treatment by manipulating TME regarding isolation of innovative anticancer targets [145]. In view of Warburg action reprogramming of cancer cells guides the metabolic decontrolling resulting in partial cause of immunotherapies failing that are T cell dependent. Escalating corroboration pointed that the metabolic adaptations of T cells estimate their working the manner described earlier,by reprogramming of T cell metabolism via immune checkpoints for instance IDO, IL-4I1, as well as SIRT 2 leading to improvement of anticancer immune effectiveness. Additionally, Guo etal.[146], observed that IL-10/Fc possess the capacity of development of efficacious metabolic reprogramming via upregulation of OXPHOS which might result in

restoration of T cell that have been depleted as well as accelerate the cancer immunotherapy reaction[146]. Thereby isolation of mechanistic modes of metabolic susceptibility of immune cells as well as adding exogenous metabolic flexibility for restoration of capacity of resulting in cell demise of tumor cells apparently is a greater plausible strategy.

Here we have described the critical signaling pathways implicated in immunometabolism as well as certain recently revealed immunometabolic checkpoints inclusive of the manner they influence working in addition to fate of immune cells via metabolic pathways in turn control the tumour immune events. Probably on one side the concentration of further immunometabolic work would be generation of considerable efficacious targeted agents which in combination are implicated in escalating specificity as well as safety for improvement of cancer immunotherapies combined with IC hampering agents, regarding overcoming drug resistance. Conversely, the present immunometabolic scientific work has absence of earnest findings in reference to molecular controlling of mechanistic modes of aberrant immune cell metabolism in TME that sees to it that clinical treatment of immunometabolism have absence of plausible innovative approaches as well as targets.

Till date there has been incorporation of metabolic as well as immune domains, however, there are absence of clinical trials performing asssessment of metabolic crosstalking amongst immune as well as cancer cells in human tumors. Tumour cell metabolism which have heterogeneity causes dysfunctional antitumor immunity to certain degree, thereby clinical studies need to confer metabolic benefits to immune cell populations via different pathways regarding improvement of cancer therapies in addition to patients prognosis. Therefore there is requirement of acquisition of insight regarding complicated working of immunometabolic signaling pathways in the TME for helping in getting advantageous cancer immunotherapies .

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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