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Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

RESEARCH ARTICLE BIOSCIENCE RESEARCH, 2023 20(3): 929-939. **OPEN ACCESS**

Challenges in The Personalized Remedial Therapy for Cancer Cure

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Cancer therapy is a big challenge from past many years. Researchers continuously tried to progress in cancer cure and tried to approach the solution at molecular level as well. From hundreds of experiments and researches, one solution comes out with limitation because of multiple molecular and cellular pathway involves in cancer. After lots of struggles most of the researchers conclude that personalized cancer therapy has potential to cure multiple cancer type. Many drugs have been tested but they did not give desired results in clinical trials. As in this review number of therapies have been discussed for cancer cure such as, therapy at molecular level, biomarker screening, immunotoxins, CAR-T cell therapy, immune Blockade therapy, Rebooting PTEN, KRAS Inhibitor, Engineered Oncolytic Virus and 'Don't eat me' signal. Such therapeutic approaches work incomparable but due to their limitations a life cannot put at risk. In order to search most accurate treatment of cancer, it is necessary to look on the limitation of every treatment because by solving the problem in every therapeutic strategy it is possible to search the most relevant response of the problem prevail in the cancer cure. Imagining technologies can be a tremendous tool which can play a role in close screening of most critical cancer such as lung and colon cancer and provide a better solution. Furthermore, there is lots of technologies and other remedies are also available which have been either used or under observation. There is a need of keeping eye on every possible solution which could be a turning point in cancer cure.

Keywords: cancer, receptor, tumor, therapy, treatment, antigen

INTRODUCTION

Researchers use the term of "pillars" for different type of cancer treatments. From the ancient times the first pillar of cancer cure was surgical removal of tumor, while there was no treatment available for blood cancers at that time. In 1986, the second pillar incorporated in the foundation of cancer treatment was radiotherapy. While in early 1940s, after discovery of derivative of nitrogen mustard (Goodman et al., 1946) as a treatment of lymphoma, cytotoxic chemotherapy was the beginning to treat cancers by using chemotherapeutic drugs (Sudhakar, 2009). Together these three pillars radiation, surgery and chemotherapeutic drugs- still use as a standard care to treat several patients. In late 1990s the forth pillar, "molecular targeted therapy" was a ground-breaking discovery in cancer treatment world (Rini & Campbell, 2007), in same era the fifth pillar "immunotherapy" was also added to fulfill the gap of cancer care by using human's immune system itself as a defense to cure cancer (Arruebo et al., 2011). The number of therapeutic drugs related to fourth and fifth pillars of cancer care are now dramatically increasing every year(McGuire, 2016).

Treatment also depends on the type of cancer because of diverse biological subsets which are differ in clinical behavior and ambiguous response to treatment (Ferté, André, & Soria, 2010). Instead of these circumstances, improvement in the cancer therapies have been experienced from past three decades(O'Leary, Krailo, Anderson, & Reaman, 2008). From 1950's to onward around 96% improvement was observed in testicular and breast cancer (National Cancer Institute). But unfortunately, several cancers like colon and lung cancer found to be difficult to cure due to which, it is utterly needed to improve the therapeutic strategies(Abramovitz

& Leyland-Jones, 2007; Collins & Workman, 2006).

Cancer progression or tumor development promote due to numerous cellular and molecular mechanisms. In order to identify the cancer type and its specific target, there is need to understand the mechanism of tumor development, cellular and non-cellular components, metastasis and growth of cell(William, Heymach, Kim, & Lippman, 2009). As a nature of cancerous cell, new strategies have been developed. It is also well-known fact that human tumors are mostly heterogenous due to which the concept of personalize cancer therapy have been spot(Altelaar, Munoz, & Heck, 2013; Pomper & Gelovani, 2008).

Challenges at molecular level

Latest technologies help in the development and utilization of tool and technique which have their own merits and demerit. Due to their limitations, it is very difficult to practices them continuously for all types of cancer such as, personalized cancer therapy in which epidermal growth factor receptor mutation showed sensitivity to EGFR tyrosine kinase inhibitor(Lynch et al., 2004). with the help of high throughput techniques which can examine the whole genome, metabolome, proteome, transcriptome and proteome large amounts of molecular data from tumor specimens can also be produce(Eriksen, 2019; Harris & McCormick, 2010). For more accuracy it is necessary to evaluate responsive treatment which include multiple executive process(Guo, Zou, & Wang, 2013). Through such process, better results could be developed. In order to compete the hitches of cancer, it is essential to face the challenges through innovative solutions. There are some techniques related to above five pillars, which are currently under usage to treat cancer mostly in developing countries(Wistuba, Gelovani, Jacoby, Davis, & Herbst, 2011; Yokoyama et al., 2013)

Biomarker Screening

Driver mutation, epigenetic modification and translocation usually helps in the treatment of cancer under the roof of term called biomarker(Alymani, Smith, Williams, & Petty, 2010). But due to the cellular changes at molecular level responsible for the alteration of signaling pathway which trigger the activation or inactivation of the tumor growth, progression and survival, these biomarkers not proved as a final option for personalized therapy(Levit & Patlak, 2010). Furthermore, different therapies proved to initiate those compensatory mechanisms which allows the or promote the cancer cells. Such complications urge to bring advanced technologies like gene array which enable to search the target of biomarkers in human body fluids more accurately(Altekruse, Kosary, & Krapcho, 2011) Through gene array the complication of understanding tumor becomes easy. successful examples of array assays translated into clinical applications include the oncotype DxR (Genomic Health, redwood City, Ca, USA) and mammaPrintR (Agendia, Amsterdam, the Netherlands) such assays have better tried to guide in the breast cancer treatment(Paik et al., 2004; Van't Veer et al., 2002). Driver mustion seems best option for personalized treatment but due to(Kübler & Albrecht, 2018) complexity of size of human genome it is critical to determine the driver as a therapeutic target.

Immunotoxins

There are some bacterial species which produce an extracellular protein called exotoxins. These exotoxins have capability to enter into a host cell and generate a cytotoxic response by targeting a specific cellular pathway, e.g. diphtheria toxin, pseudomonas exotoxin A, pertussis toxin, Shiga toxin and cholera toxin(Greaney, Leppla, & Moayeri, 2015). These exotoxins have two domains in their structure receptor binding domain (help in binding with host cell receptor) and toxin domain (generate a cytotoxic response)(Antignani & FitzGerald, 2013; Aruna, 2006; X. Wang & Quinn, 2010). Cancer cells overexpress different surface receptors like CD13, CD24, GPR161, HER2, EGFR, VEGF and several others (Kübler & Albrecht, 2018). These hormones are responsible for prognosis of cancer by promoting angiogenesis(Riemann, Kehlen, & Langner, 1999), facilitates invasion by degrading the extracellular matrix (Lu, Takai, Weaver, & Werb, 2011), inhibits cell-cell contact (Zeng & Hong, 2008), protect themselves from apoptosis (Fiandalo & Kyprianou, 2012), senescence (Y. Wang, Blandino, Oren, & Givol, 1998) and DNA damage repair (Gros, Gros, Jansen, & Vidal, 1985; Masuda et al., 1988). Researchers used a protein engineering technique to replace a receptor binding domain of immunotoxin with specific antibody which can bind with overexpressed receptor as a result toxin domain of protein enter into a cancer cell and cause cell death(Vitetta, Krolick, Miyama-Inaba, Cushley, & Uhr, 2019) (Lambert, Goldmacher, Collinson, Nadler, & Blättler, 1991). Single chain fragment variable 13 Exotoxin A (scFv13-ETA'), bispecific single chain fragment variable (bsscFv[13xds16]) and human myeloma 1.24 Exotoxin A (HM1.24-ETA') has been studied on different cancers (Chang et al., 2005; Grieger et al., 2017; Staudinger et al., 2014). Most of the time researchers target a receptors which only express on cancer cell not on normal cell but that is not the case always(Henke et al., 2006; Li, Huang, & Peng, 2005).

Figure 1 Shows the detailed mechanism of immunotoxins. Sometime, targeted The problem with the immunotoxin is, since the antibodies are highly specific to its antigen some time targeted receptor also present on normal cell, the presence of same receptor on normal cell also induce cell death in healthy tissues(Shan, Liu, & Wang, 2013) (Hertler & Frankel, 1989; Pastan, Hassan, FitzGerald, & Kreitman, 2007; Vallera, Panoskaltsis-Mortari, & Blazar, 1997; Wenning & Murphy, 1999).

Figure 1

CAR T Cell Therapy

Chimeric Antigen Receptor (CAR) T cell therapy is a type of immunotherapy in which T cell of patient is isolated from blood then genetically engineered CAR gene is inserted into T cell genome(Bonifant, Jackson, Brentjens, & Curran, 2016; Levine, Miskin, Wonnacott, & Keir, 2017; Newick, O'Brien, Moon, & Albelda, 2017). At molecular flow millions of CAR^+ T cell grow in laboratory then infuse back into patient's body, as a result, CAR^+ T cell express CAR proteins over its surface as a receptor which helps in binding of T cell specifically with cancer cell and induce a necrosis (Almåsbak, Aarvak, & Vemuri, 2016; Fraietta et al., 2018; Holzinger, Barden, & Abken, 2016).

Mostly, trials related to CAR T cell therapy based on CD19-targeted CAR T cells. ZUMA-1 phase 1 study KTE-C19, an autologous CD3ζ/CD28-based chimeric antigen receptor (CAR) T cell therapy is under consideration(Hombach & Abken, 2011; Locke, Neelapu, Bartlett, Lekakis, et al., 2017; Locke, Neelapu, Bartlett, Siddiqi, et al., 2017; Neelapu et al., 2016; Zhong, Matsushita, Plotkin, Riviere, & Sadelain, 2010). Some patients with Acute Lymphoid Leukemia (ALL) don't respond to CD19-targeted therapy(Gardner et al., 2016).

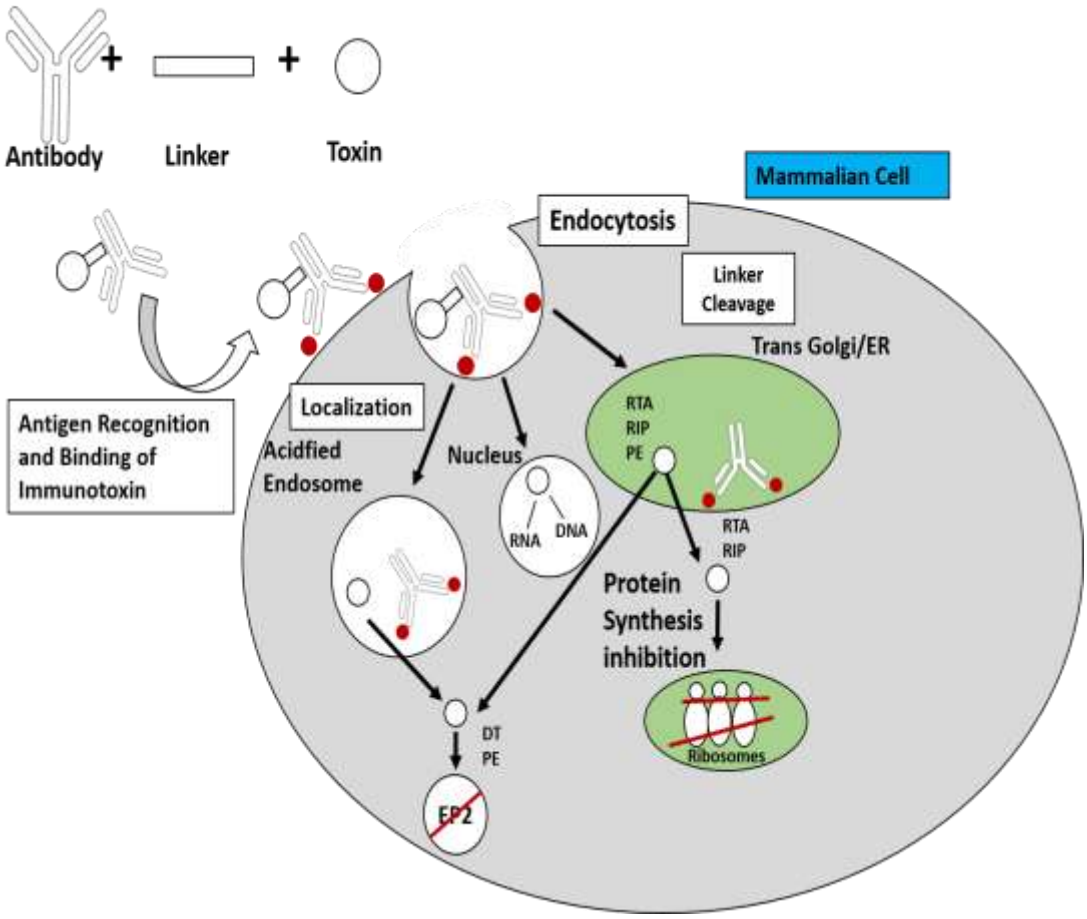

Figure 1: Molecular changes, link of antibody, binding of immunotoxin through antigen recognition, endocytosis, linker cleavage shows process of protein synthesis inhibition in mammalian cell.

In some patients who respond to the treatment their disease returns within one year. A phenomenon known as "antigen loss" found to be limitation of this technique (Bonifant et al., 2016). Figure 2 shows the flow of CAR T-cell therapy. **Figure 2.**

Immune Blockade Therapy

Immune checkpoints are regulators of immune system. Immune checkpoints are transmembrane proteins (ligands) present on immune cells like T cells and natural killer cells these proteins binds with antigens present on normal cell and detect them as self-molecules(Pardoll, 2012). Cancer cell have ability to overexpress these antigens like programmed death receptor 1 (PD-1) and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) which recognize by immune checkpoints as a self-antigen and do not kill them(Postow, Callahan, & Wolchok, 2015). Antibodies that inhibit the binding between immune checkpoints and cancer antigens were synthesized in laboratory then injected into

the patient's body. Result immune cell not recognized cancer antigen as a self-molecule and induce an Antibody Dependent Cell-Mediated Cytotoxicity (ADCC) in cancer cell(McGranahan et al., 2016). In some patients' immune checkpoint antibodies was recognize as nonself antigen by immune system and eliminate from the body before it reached at targeted tissues(Michot et al., 2016). Figure 3 describe the immune checkpoint blockade phenomenon. **Figure 3.**

Rebooting PTEN

Phosphatase and tensin homolog (PTEN) is a cancer silencer protein which is a focal negative controller of the PI3K/AKT flagging course that impacts various cell capacities including cell development, endurance, expansion and movement in a setting subordinate way. Initiated PI3Ks catalyze the development of PIP3 from PIP2, and the lipid phosphatase PTEN (phosphatase and tensin homolog erased on chromosome 10) straightforwardly goes against the movement of PI3Ks by dephosphorylating PIP3 into PIP2, hence going about as the focal negative controller of PI3K (Chow & Baker, 2006; Milella et al., 2015). PTEN, TSC1, TSC2, and LKB1 are all growth silencer qualities that contrarily manage mTORC1 action, and their acquired transformation brings about unmistakable familial conditions for certain common clinical elements

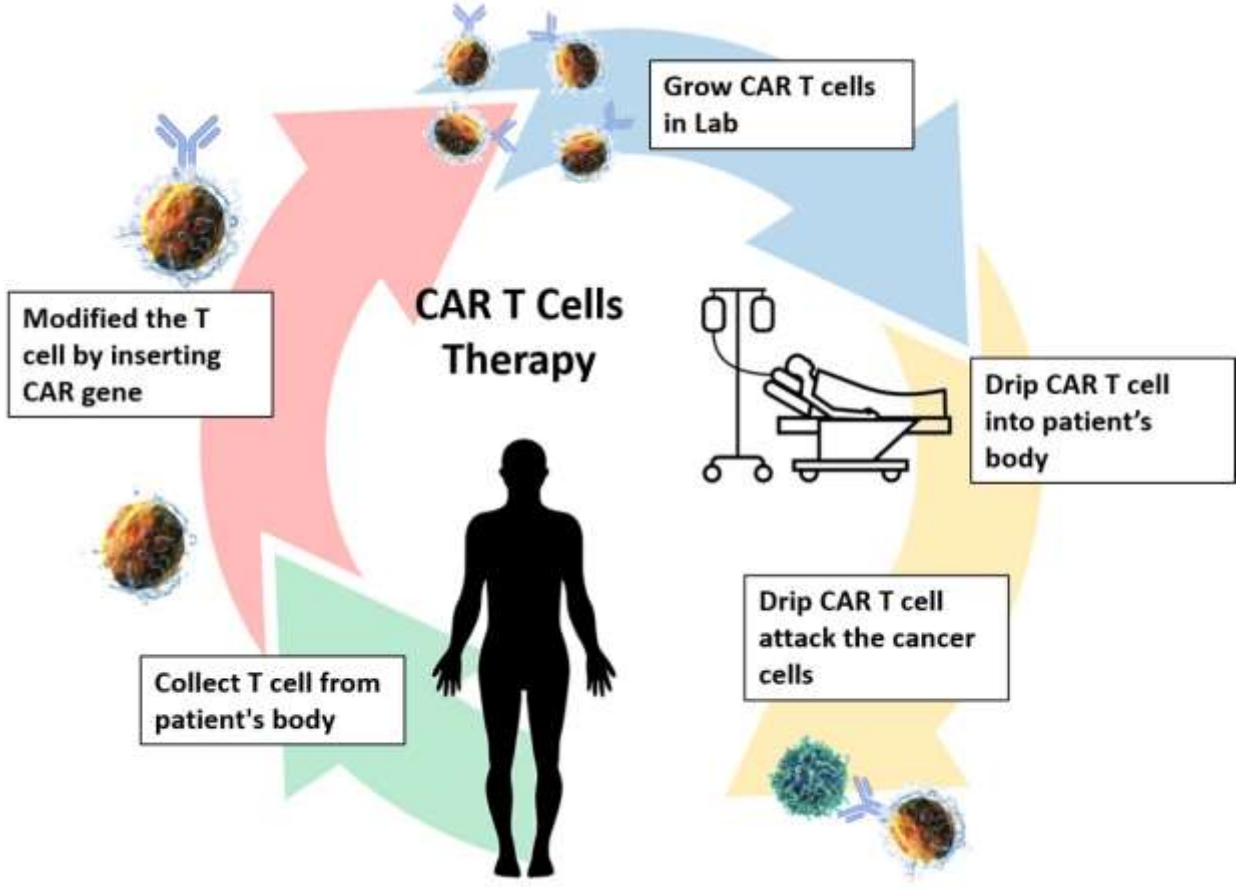

Figure 2: Systemic flow diagram of CAR T-cell therapy describe preparation and infusion of CAR T-cell in patient body.

including malignancy inclination and different hamartomas. Figure 4 shows the typical component of PTEN. As PTEN is growth silencer protein in the greater part of the disease cell, PTEN is observed to be dormant structure or failed (Ortega-Molina & Serrano, 2013; Parsons & Simpson, 2003). Researcher have figured out how to betray PTEN in malignancy cells so it smothers the development of disease cell without adjusting the development of typical cell (Luongo et al., 2019). **Figure 4.**

KRAS Inhibitor

KRAS is one the most studied proto-oncogene, its mutation is found to be present in approx. 30% of all human cancers(Liu, Wang, & Li, 2019). KRAS protein activate the Ras/MAPK pathway and P13K pathway. This activation starts by EGFR surface receptor which detect the signal from DNA by a protein TGF-alpha, EGFR activation transport the signal inside the cell through SOS protein which activate the Ras molecule. Ras protein initiate the series of reaction in cellular metabolic

reactions which leads the cell towards cell survival, proliferation and production of different cytokines as result, cell do not enter into a process of apoptosis or senescence(Martini, De Santis, Braccini, Gulluni, & Hirsch, 2014). Molecules which inhibit the KRAS function are found to be promising to inhibit the uncontrolled cell growth. In 2019 FDA has approved AMG 510 for phase II treatment of patients with KRAS G12C mutation for non-small cell lung cancer (NSCLC) who have already received prior treatment in Phase I(Canon et al., 2019). Figure 5 demonstrates KRAS protein activate the Ras/MAPK pathway and P13K pathway. **Figure 5**

Engineered Oncolytic Virus

Some viruses have potential to infect healthy cells and integrate into their genetic material into genome, replicates themselves and making a more copy of themselves (Kelly & Russell, 2007). The viruses having this property have potential to cause cancer like hepatitis B virus (HBV) is associated with liver cancer and the human papilloma virus (HPV) in cervical cancer and head and neck cancer(Chiocca, 2002). Another form of immunotherapy, in which genetically engineered oncolytic viruses has been prepared which have no disease causing genes but have immune stimulating genes(Melcher, 2019). These viruses have specificity to target cancer cell or affect the healthy immune system cells to trigger immune response against cancer(Russell, Peng, & Bell, 2012).

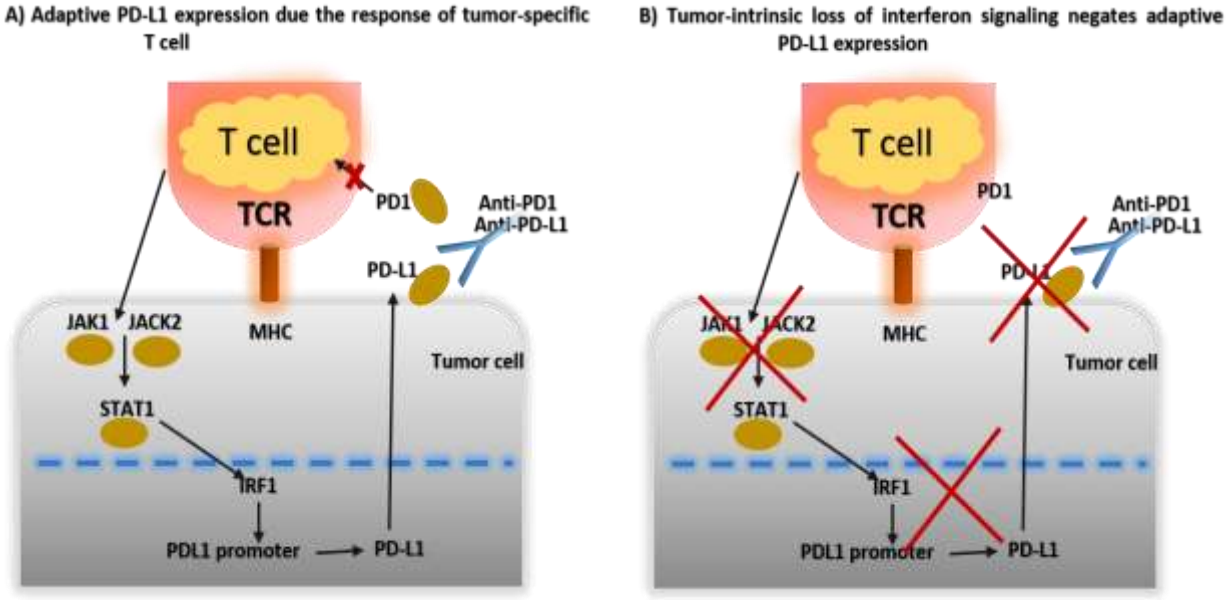

Figure 3: Molecular Mechanism of Immune Checkpoint Blockade. A) shows effective PD1-PD-L1 immune checkpoint blockade. B) Ineffective PD1-PD-L1 immune checkpoint blockade.

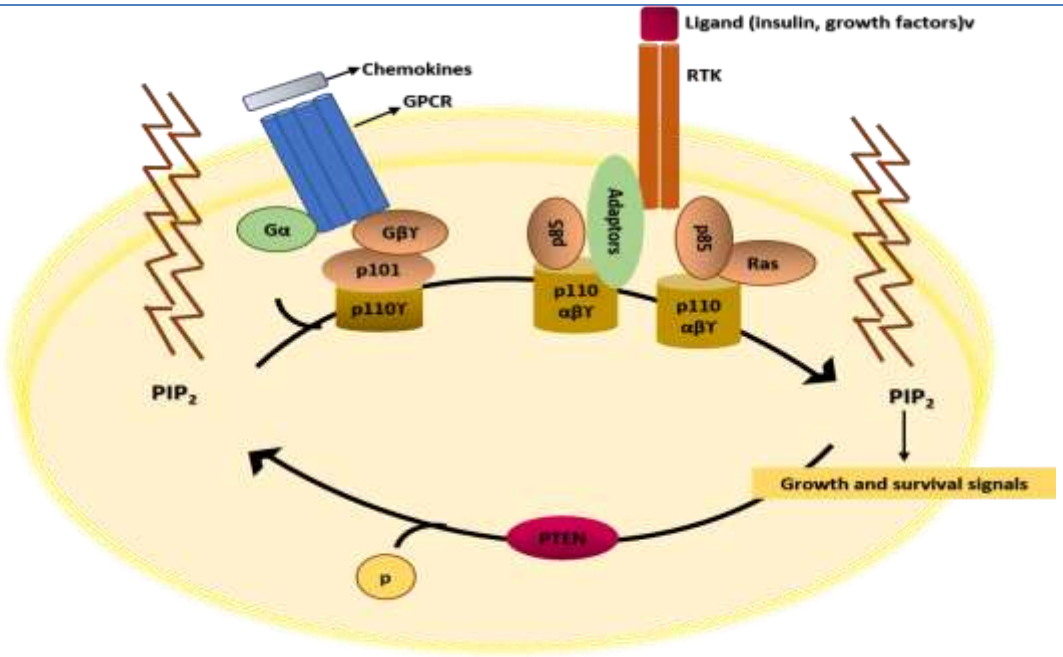

Figure 4: Normal function of tumor suppressor protein phosphate and tensin homolog

The just accessible oncolytic infection treatment endorsed by the FDA for the therapy of malignant growth is, T-VEC (Imlygic®): an adjusted herpes simplex infection (HSV) that taints cancer cells and advances their annihilation; supported for subsets of patients with melanoma (Coffin, 2016). Since infections can influence solid cells to actuate insusceptibility some time safe frameworks start to assault sound cells, so the utilization of oncolytic infection treatment is consistently conveying a risk (Marshall & Cairns, 2019).

'Don't eat me' signal.

Cancer cells have ability to overexpress different antiphagocytic isurfaceiproteinsicalledi 'don't eatime' signal. These proteins included CD47, CD24,

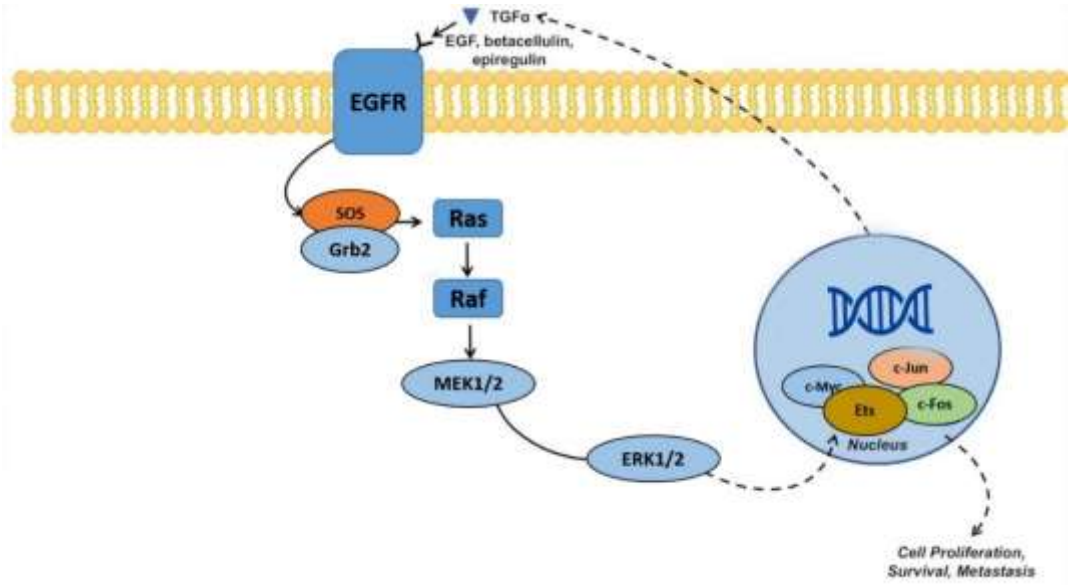

Figure 5: Activation of Ras/MAPK pathway and P13K pathway through controlling a cell proliferation

programmedicellideathiligand-1 (PD-L1) and beta-2 microglobulinisubunit of the major histocompatibilityiclass I complex (B2M)(M. Liu et al., 2019; Stano et al., 2009; Takimoto et al., 2019). When these surface proteins overexpress on cancer cell the binding between cancer cell an phagocytic cell do not initiate an immune response because antiphagocytic receptors as same as normal cell surface receptor (Aderem & Underhill, 1999). Phagocytic cell bind with cancer cell then release it without making any harm to it due to presence of antiphagocytic receptors. Monoclonal antibodies have been synthesized in laboratory which inhibit the binding between antiphagocytic surface proteins and macrophages as a result macrophage kills cancer cell by natural process called phagocytosis(Anderson et al., 2019).

CONCLUSIONS

Several therapies have been addressed in this review, but every therapeutic strategy has some drawback due to which none of these therapies got success completely. It is suggested from number of literatures that, those hurdles which create hitches in cancer therapy could be remove in more effective way if tumor tissue would take out at the time of tumor development and progression or metastases sampling which could be possible through imagining. Better process or medication could also be possible if early diagnosis would be done. Personalize medicine face hurdles because there is a need to overcome increasingly restrictive regulatory hitches. A number of procedures have been tested to evaluate the biomarkers around the globe. For finest results it is necessary to check or test the new therapeutic agent at best level. It is concluded that for accuracy in the experiment there is not only a need latest technology but there should be skilled person who can limit the harm and gives best possible answer of relative problem. Moreover, innovative ideas are also needed very badly which can save the time and energy and same time provide a solution of critical pathways which involves in activation and inactivation. Designated choice of specific infection causes identifying quality polymorphism which are answerable for the quantity of issues and assessing its relationship with parent illness the qualities encoding proteins which are associated with the development and advancement guideline of growth, like chemicals, are viewed as the most viewpoint and appealing competitors to address the basic cases. So particularly far as the physiological impact of any chemical is known to be straightforwardly identified with its receptor, proteomic approaches are proceeding to make types of progress in malignant growth research by assisting with clarifying complex flagging organizations that underlie tumorigenesis and infection movement. The utilization of proteomics as a frameworks science apparatus in malignancy research keeps on growing in extension and profundity, as it develops quickly into an all-around material technique for the examination of essentially any organic cycle.

Author contributions

Conceptualization; Tayyaba A. Faiza A.; writing rough draft; Faiza U., Sheikh U. A.; editing; Aliza F., Umer A.; Figures and final editing; Faiza A.
authors have read and agreed to the published version of the manuscript.

Funding statement

This study was not supported by any funding agency

Institutional Review Board Statement

There is no data related to bioethical concerns included in this study so there is no need for approved by the Bioethical Committee.

Informed Consent Statement

Not applicable.

Data Availability Statement

There are no supplementary files available.
There are no sources in the current document.

Acknowledgments

This work was supported by the Microbiology Department, Jinnah University for Women. We thank the Microbiology Department of Jinnah University for technical support.

Conflict of interest

The authors declared that present study was performed in absence of any conflict of interest.

Peer Review: ISISnet follows double blind peer review policy and thanks the anonymous reviewer(s) for their contribution to the peer review of this article.

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