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Review article

Understanding the biology and advent of physics of cancer with perspicacity in current treatment therapy

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ABSTRACT

Cancer has become a key healthcare problem worldwide. The background of cancer research has brought the advent of cross-disciplinary collaborations that has enabled us to get an idea of the disease mechanisms at spatial and temporal scales. Understanding the combination of biology and physics of cancer presents a promising field of research with apprehensions in better clarity over both cellular and molecular mechanisms impacting cancer therapy. Investigation of cancer biology has provided a wealth of knowledge on cancer initiation and propagation and has provided newer treatment strategies in the fight against cancer. Understanding the physics of cancer provides wonderful set of equations that take advantage of mechanisms of force production, propagation by the cancer cells and mechanical properties of the tumor tissue. The spatial tissue arrangement in which the tumor growth occurs can be better understood with biophysics. Thus, the combination of biology and physics of cancer contributes crucially in impacting the correct treatment of cancer. The present review is aimed at providing an overview of regulatory networks, regulation of cell division and differentiation, the signal transduction pathways and integration of all sciences including physics, biology, and medicine which is very well needed to tackle the war against cancer and thus influence cancer therapy. These circuits will help us understand whether the therapy will work wonders or cause failure. As cancer is much more than a genetic disease, more insights into the malignancy with physical approaches are designed to use cancer therapy effectively.

1. Introduction

Cancer is one of the most complex diseases affecting the health of a large population globally. It is the leading cause of mortality worldwide with 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 as estimated by GLOBOCON, a project under the International Agency for Research on Cancer (IARC), which provides global statistics of cancer incidence and mortality [1]. The highest percentage of cancer prevalence in both sexes is observed in lung followed by breast, prostate and colorectal cancer for incidence and colorectal, stomach and liver cancer for deaths. In a survey done by the World Health Organization (WHO) in 2015, cancer is approximately accountable for the major global deaths before 70 years of age in 91 of 172 countries [2].

Cancer incidence and mortality are ever-increasing globally [3]. The reasons for rising in cancer morbidity and mortality are due to the major factors like aging [4], rising population, unhealthy diet and westernization of lifestyle and mainly due to the environmental factors and the presence of cancer-causing agents in food, water, air and the exposure to sunlight and chemicals [5]. Cancer incidence is also associated with many risk factors, like tobacco and alcohol use, radiation, air pollution [6], obesity, and infectious agents. Cigarette smoking is the chief cause of oncogenesis [7]. It comprises of more than 73 carcinogens like 4-(*N*-methyl-N-nitrosamino)-1–(3-pyridyl)-1-butanone and its derivatives [8].

Diet and lifestyle changes are the other key factors that increase the risk of cancer. A healthy balanced diet along with a reduction in additional body fatness decreases the possibility of most cancers [9]. Many researchers put forward that a high intake of meat is linked with increased risk of certain cancers [10]. Some of the dietary carcinogens include mycotoxins, dioxins, N-nitroso compounds, and oxidative agents are major sources of carcinogenesis in humans. Invasive cancer risk is also interlinked to ultraviolet light exposure. Rising solar radiation increases the occurrence of cancer [11].Viruses and bacteria are the other oncogenic factors, contributing to about 7% of all cancers.

Cancer is originated from the Latin term “cancrum” that means crab. These resemble the crab limbs which signify to hold on and never let go, referring to the swollen veins around the tumor. Cancer is a group of different types of cancer diseases characterized by abnormal growth of cells in the body leading to the development of masses called tumors. The two main categories of tumors are benign and malignant

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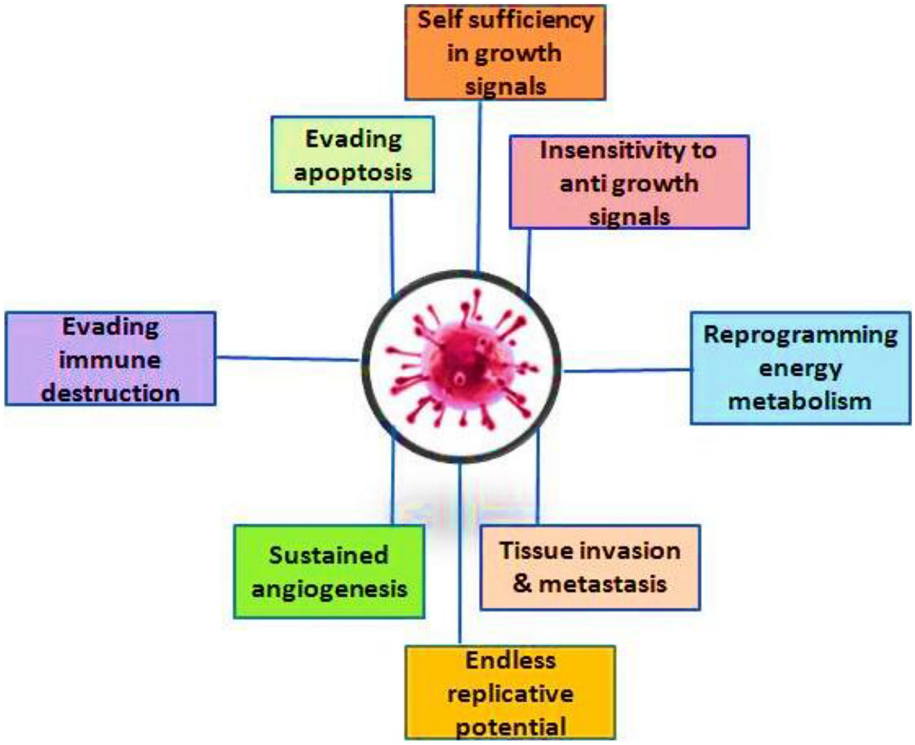

Fig. 1. Major hallmarks of cancer.
The characteristics the cancer cells achieve over a period of time during the transformation of normal cells to the malignant tumor cells.

[12]. Benign tumors are slow-growing masses that do not invade the surrounding tissue. They are less harmful as they remain localized can be easily removed by surgery. On the other hand, malignant tumors are invasive, that have the potential to destroy the adjacent tissues.

From years ago, biologists have provided amazing details concerning the cell division, growth, and differentiation to perform their vital functions. In this review, we will get an overview of the cancer biology and mechanisms that trigger cancer and understand how these biological processes are influenced by the concepts of physics. From dealing with the basics of cancer biology, our approach on cancer in terms of physics is rapidly gaining interest [13]. While the spotlight on cancer research was to reveal the genetic basis of tumors, physical relations in tumor progression are now been focused. Therefore, an insight into cancer physics will help us lay down the foundation of the physical interactions in cells and tumor growth.

Biophysicists, mathematicians, engineers, and biologists have been linking physical theories to understand about cancerous growth and their underlying principles to enhance cancer detection and management. These can be seen from the exponential growth at the interface of physical sciences and oncology which have been viewed through quick progress in science, imaging, and nanotechnology. The delivery of anticancer drugs to their appropriate targets with the help of cancer biology will bring rapid advances in the diagnosis and treatment of cancer with the application of concepts from physics [14]. This article provides insights into the aspects of molecular biology and provides a tool for analysis at a cellular level and detects changes in tumor cells linked to malignancy. Here we discuss the application of principles of physics to oncology to get an understanding of all aspects of cancer biology from the tumor growth to the progression, detection, and treatment of cancer.

2. Cancer biology

Cancer occurs by a progression of successive mutations in genes that alter the cellular processes like cell proliferation, differentiation, transcription and gene expressions. Cancer cells gain a degree of self-sufficiency and result in uncontrolled growth and division. Cancer is regarded as “disease of mutations” in the cell genome that destroys the equilibrium between cell division and quiescence. Alterations in the DNA progression lead to mutations through rapid proliferation followed by a second mutation leading to succeeding mutations and expansion of these cells to tumourous growth and therefore these mutations result in malignant tumors which rupture the membranes causing metastasis [15].The phenomenon of normal cell translation receptive to homeostatic response into cells able to grow self-sufficiently is known as carcinogenesis. These processes can occur at different levels like genetic, epigenetic or cellular levels. Looking at the mutations arising in oncogenesis, these are the alterations of the genome of a specific cell. This comprises of numerous mutations like point mutation, frame-shift mutations, chromosomal abnormalities, loss or gain of gene functions, epigenetic changes to DNA like the methylation of cytosine in CpG sites resulting in down-regulation of a gene [16].

In one frame cancer can be termed as a genetic disease. The cancer cells undergo mutations, consisting primarily of different classes of genes that provide a pathway for molecular involvement. The cancerous cells have developed a unique mechanism by which they can activate or inactivate the proliferative signaling cascades [17].The failure of the cell regulatory circuit affects normal cell proliferation. It is a complex disease that depends on the signals from the neighboring cells in the tissue and the surrounding environment. Hence this was summarized in a model, indicating the variations in cancer cell physiology. The six hallmarks of cancer provide an organizing principle for understanding the complexities of this deadly disease and give an idea about tumor growth and metastatic dissemination [18]. These are the multiple abilities attained by cancer cells during the progression of the disease which provides background about cancer biology. These include a rise in self-sufficient growth signals, lack of sensitivity to growth-inhibitory signals, escaping from apoptosis and immune destruction, metastasis, and expansion of angiogenesis [19]. Apart from the fundamental hallmarks, reprogramming of energy metabolism and

avoiding immune destruction are the two other budding hallmarks. The tumor microenvironment also provides extensive applicability of these concepts that will gradually develop new means of treating cancer [20]. The traits leading to the development of cancer known as the hallmarks of cancer are shown in Fig. 1.

Mostly cancer drug development is a biology driven process; therefore, the insight into cancer biology is of utmost importance to understand the various aspects of cancer like the oncogene activation, inactivation of tumor suppressor genes, mutagenesis due to external factors and epigenetic alterations. Cancer disturbs the normal functioning of vital genes that affect the cell cycle and leads to a mutation in genes. Generally, gene mutations are classified into two types, dominant and recessive mutations. In dominant mutation, an abnormal gene is present in a pair of genes like the oncogenes [21]. The tumor suppressor gene involves the recessive mutations which affect the pair of a gene. Consequently, these mutations convert the normal cells into a cancerous cell resulting in activation or inactivation of genes [22].

Cancer cells remain in the active state of division without having control over the homeostatic mechanism of the cells they generate oncogenic proteins that duplicate the normal growth signals. Oncogenic transformation makes the cancerous cells gain autonomy from growth signals leading to unregulated growth [23]. As a result, they produce their own signals and convey them among signaling proteins by a phenomenon called as signal transduction pathway. The main cellular mechanism used by cancer cells to promote self-sufficiency of growth factor is depended on the signaling cascade of the growth factor. The major changes are seen in the extracellular growth signal, in the receptors and intracellular signaling messengers [24].

The genes contributing to malignancy are the new targets and the molecular pathways incorporated on which these genes act are recognized as promising targets for the treatment. Proto-oncogenes stimulate cell division by coding for those proteins. Oncogenes are changed versions of the proto-oncogenes that code for these signaling molecules that stimulate proliferation and trigger mutation. Oncogenes are malignant genes that have a vital role in cancer development. RAS is an oncogene that functions as an on-off switch in the signaling pathway. Any mutation in RAS leads to rapid cell growth by letting the signaling cascade to remain “on” as illustrated in Fig. 2. Many types of tumors are associated with mutation in RAS or MYC which are examples of proto-oncogenes [25]. RAS is mutated in the majority of cancer and this is the earliest mutated prototypic oncogenes showing how cancer is initiated through these mutations. RAS behaves as a molecule playing a significant role in signal transduction. The binding of GTP leads to RAS in an activated state. Prototypic RAS hydrolyzes GTP to GDP taking RAS into an inactive state. Mutations in this reduce the capacity of the molecule to function as a GTPase. Since there is no release of GTP by the mutated RAS it behaves as an activated signal transduction molecule. The RAS mutations are seen on codons 12, 13 and 16.

We know that Oncogenes mainly associated with the cancer progression encode proteins have activities that are easily reconciled with the malignant phenotype of cancer cells. These alterations in gene regulation are closely linked to the inappropriate cellular proliferation that leads to malignancy which is a prime feature of the cancerous cells. Similarly, other genes involved in cancer development give an idea that an understanding of cancer at the molecular level would provide new opportunities in the therapeutic field of cancer treatment. Tumor suppressor genes are another set of driver genes that act by inhibiting cellular propagation and tumor progression. Tumor suppressor gene inactivation causes abnormal cell proliferation developing into cancer. They involve proteins that act as checkpoints for cell propagation or cell ceasing. A tumor suppressor protein is p53, a transcription factor and a vital protein in the cell cycle regulation that binds to DNA and activates the transcription protein called p21.p21 blocks the activity of a cyclin-dependent kinase required for progression through G1 allowing the cell to repair the DNA before it is replicated. Cyclin-dependent kinases are the chief control switches of the cell cycle. If the DNA damage is so prevalent where it is impossible to restore, p53 elicits cell death [26]. Fig. 3 illustrates the normal function of the p53 gene which helps to regulate the cell cycle controls.

Mutations in the tumor suppressor gene produce abnormal inhibition of cell growth and division. Cancer of the retina known as the

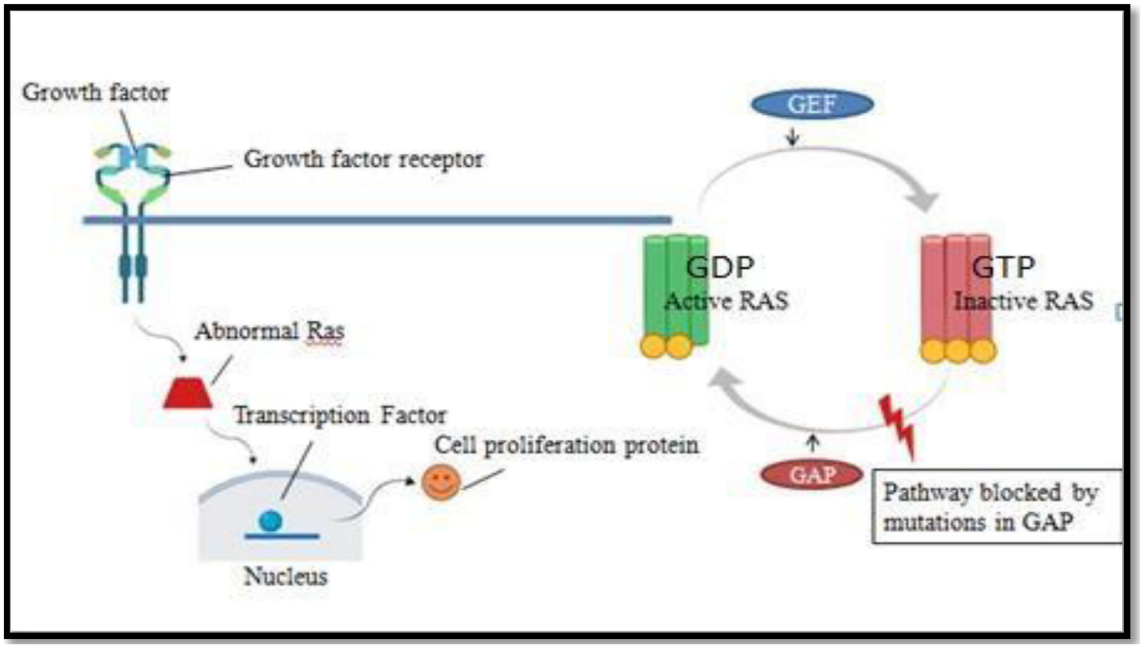

Fig. 2. Illustration of alterations in the RAS signaling pathway.
Growth factors are vital for the regulation of cellular processes and receptors are membrane-bound proteins that accept signals and transcription factors are specific DNA binding proteins. RAS is an important oncoprotein that binds to GDP (Guanine nucleotide diphosphate) in an inactive state and in its active state to GTP (Guanine nucleotide triphosphate). GEF (Guanine nucleotide exchange factor) stimulation acts by activating the inactive RAS by interchanging its GDP for GTP. Further RAS hydrolyzes GTP to GDP returning to its inactive state and this is triggered by GAP (GTPase-activating protein).

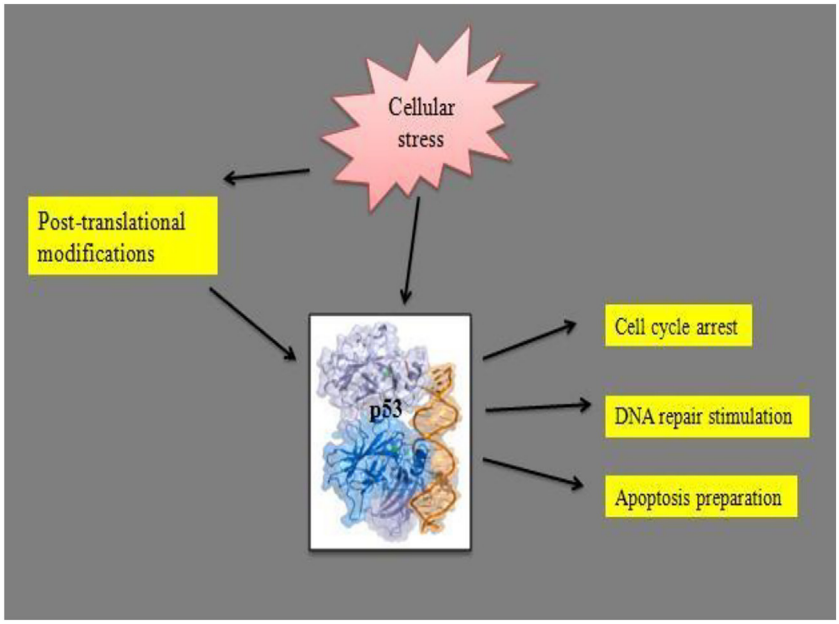

Fig. 3. The normal function of p53 protein.

hereditary retinoblastoma, that occurs in early childhood is an example of the same [27]. These genes are studied at different levels for finding the heterozygosity that helps in the detection of many malignant conditions like retinoblastoma in patients. A rise in the frequency of p53 mutations helps in the diagnosis of cancer. More frequency of p53 mutations provides diagnostic tools [28].

Another pair of driver genes is the DNA repair gene that is associated with this heterogeneous disease. A mutation in the DNA repair gene prevents DNA from being repaired and allows additional mutations to build up in the cell. *XP* (Xeroderma pigmentosum) is the damage to the DNA repair gene in individuals exposed to UV radiation and has an increase in the occurrence of different skin cancers. Another example is the Bloom syndrome, an inherited disorder in which the mutated gene, *BLM*, essential for sustaining the steady structure of chromosomes and people with this syndrome show the higher occurrence of chromosome breaks, that causes oncogene activation [29]. Understanding the molecular aspects related to genes gives us the basis to use DNA repair inhibitors for therapeutic use in the treatment of cancer [30]. Additionally the likelihood to target particular changes in the DNA repair of the normal and the cancer cells has provided an exciting therapeutic target [31].

Many of the chemotherapeutic treatments are aimed at targeting the cell division process as illustrated in Fig. 4. To understand the mechanism of action of chemotherapy and the drug development at particular cell stages it is important to be familiar with tumor biology and cell kinetics. In the cell cycle at the G0 phase, no cell division takes place. G1 phase cells are located for synthesizing new proteins in the cell cycle. S phase is the synthesis phase where DNA synthesis and chromosome duplication occurs. G2 phase is the preparatory phase of mitosis and the M phase is the mitotic phase where chromosomes separate and division of cytoplasm occurs. Gaining knowledge about cancer biology has allowed developing drugs that can target certain phases of the cell cycle [32].

Intracellular signaling also includes signals that suppress cell division that is associated with the progression of cancer. Genes controlling cell division processes are referred to as tumor suppressor genes. Any mutations in inactivation of these genes result in loss-of-function mutations since no proliferative capacity is remaining. Anti-growth signals forcefully activate dividing cells into the G0 phase of the cycle or a post-mitotic phase [33]. Cancer cells bypass these anti-growth signals to undergo autonomous growth and multiplication. Several damaged genes in cancer cells are linked with the cell cycle checkpoint. Any disturbance in the cell cycle progression through S-phase often results in cell death and chromosomal mutations. Normal cells grow and divide in an organized pattern, which leads to the proper functioning of the cell division cycle. Mutations in genes lead to uncontrolled growth and division of the cancerous cells. The stages occurring in the cell cycle are timely controlled to ensure cell division only if necessary and the loss of regulation is the main hallmark of cancer [34].

Cell cycle checkpoints scrutinize the progression of the cell cycle in a particular position to repair any DNA damage caused. Loss of appropriate cell cycle checkpoints is related to the development of human cancer. If the damage to DNA is not taken into account it leads to a mutagenic episode during DNA replication that results in an interruption in progression through S-phase would result in chromosomal abnormalities or cell senescence [35]. All these episodes are related to carcinogenesis, therefore the genes damaged in cancer cells play a role in cell cycle checkpoint management [36].

Knowing about the cell cycle episodes is essential to develop better treatment opportunities in cancer. Chief merit of studying the biological concepts has helped researchers to understand the targets for drug discovery and therapeutic involvement [37]. This approach has helped at different levels like in target identification by understanding the network of regulatory pathways and using those novel points as drug targets. By developing such therapies researchers can utilize the knowledge of cellular dynamics based on finding particular targets as per the individual cancer patients. As shown in a model called as the cell cycle module that shows the inputs using thresholds that govern G1/S transitions, the regulatory links and signaling cascades are mentioned that affect tumorigenesis [38]. The model makes use of two growth sensitive thresholds that regulate entry into the S-phase that are altered in cancerous cells. Such a model can be utilized in both investigational studies as well as data analysis by checking the responses of cancer cells to intra and extracellular factors. The expansion of such approaches to tumors holds potential in developing better treatment opportunities.

Cancer interferes with the functioning of important genes due to loss of homeostatic control [39]. This leads to abnormal cell proliferation. Tumors possessing driver mutation result in genetic changes that lead to inherited disorders and oncogenic development [40]. These

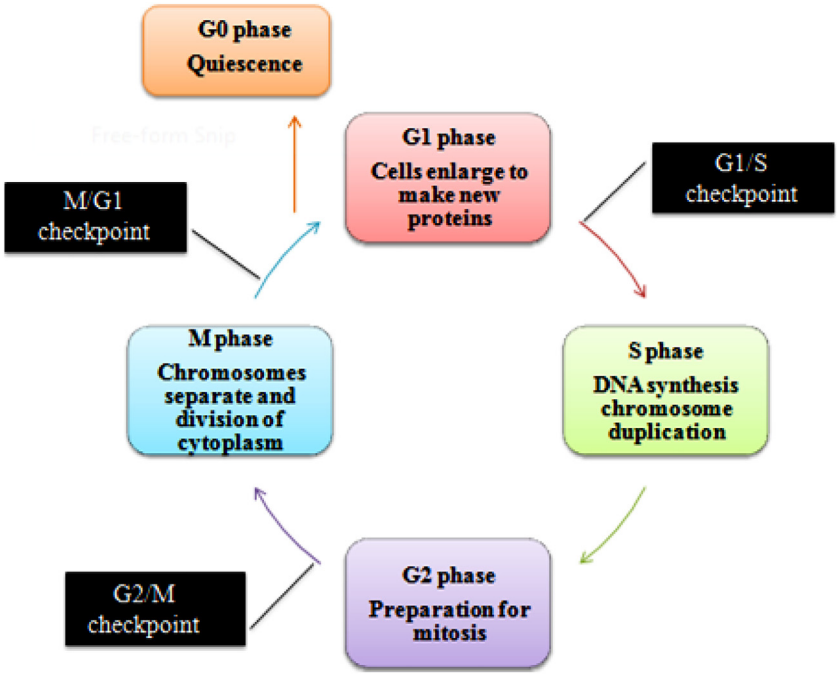

Fig. 4. Different stages of the normal cell cycle i.e. G1 phase, S phase, G2 phase and, M phase and there are cell cycle checkpoints at the G1 and G2 which stop the cell from moving into S or M and the non-dividing stage is the G0.

include point mutations as seen in the Ras gene, deletions associated with the Erb-B gene and PTEN gene, chromosomal rearrangements with gene BCR-ABL generating an oncogenic type of tyrosine kinase ABL, inversions or amplification associated with Myc gene. Alterations in the methylation phase of promoter genes also affect the oncogenesis process [41,42]. Cancer being viewed traditionally from a genetic perspective was the major reason for neoplasia but this prototype has also been understood from disruption of epigenetic regulatory mechanisms. Both of which finally involve abnormal gene expression take benefit from each other through oncogenesis [43]. Variations in the epigenetic system can direct genetic mutations, and genetic mutations in epigenetic regulators can result in a varied epigenome [44]. For instance, in acute myeloid leukemia, the mutations of DNMT3A occur. This occurs due to alteration of C to T at a CpG site, since the exon methylation occurs by an enzyme this process can be considered as an epigenetic alteration. The successive5mC deamination leads to genetic mutation [45]. This represents the vital need for maintenance of the equilibrium between the epigenetic and the genetic interactions and any alterations in this balance leads to a disease condition [46].

Tumor growth is not only about rapid cell proliferation but also can be viewed from a different perspective of reduction in programmed cell death called apoptosis [47]. The resistance to apoptosis is a hallmark of different cancers. Tissue homeostasis is an equilibrium involving cell division and cell death and any deregulation in this balance has been linked to many forms of cancer. Cancer cells can resist the apoptotic pathways in many ways and the commonest among all is a mutation of the p53 tumor suppressor genes resulting in loss of proapoptotic regulators. p53 also referred to as the guardian of the cell plays a vital part in cell response to stress and any loss of function in p53 leads to impaired apoptosis [48]. Proliferative disorders like cancer demonstrate a complex network. Therefore it is of utmost importance to understand such diseases to lay the foundational basis for better treatment opportunities.

3. Physics and biophysics of cancer

Today physics, mathematics, and engineering are used widely to interpret complex problems occurring in cancer biology. Physical science acts as a tool to understand the concepts that could help deal with this incredibly complex disease [49]. Molecular biology has provided a rich history of cancer research and treatment. Regardless of these spectacular achievements, the fight against cancer has still been disappointing. Thus by applying a multidisciplinary approach that combines biological sciences with physics, provide better ways to understand cancer [50]. The collaborations among the biologist and the physicists have shown that cancer is no more restricted to a genetic disease but the physical forces exerted on the cells control the cancer progression as well. In this review, we will focus on the role that physics plays in the field of cancer research and we will look at the various advances that physics has contributed in the field of cancer research [51]. For instance concepts like computer modeling provide a simulating experience of the interaction between genetic and physical facets of cancer. Mathematical modeling helps in forecasting cancer that leads to an enhanced prediction of tumor evolution and effective course of drug therapy which are beyond the scope of the article [52]. Newer technologies are making use of carriers that can carry drugs to their targets precisely and develop diagnostic tools for the detection of cancer at earlier phases.

Physics has been used in cancer for years in diagnosis, imaging techniques like X-rays, MRI. When the question arises about what physics has to with cancer? The physics of cancer has been a real challenge in identifying this disease. Certain deep-rooted questions might be essential: What is the relationship between physics and biology? Is physics necessary in cancer research? To answer this in this article we will be briefly dealing with the physicist's attempts to solve problems linked with cancer research. The biological viewpoint showcases cancer growth and proliferation perceptive. To collaborate with this NCI formed a network of Physical Sciences –Oncology Centre's (PSOCs) and the main vision lies in identifying problems related to cancer and observe them from various perspectives and scrutinize the physical principles underlying them [53]. This will provide a foundation step to enhance the oncology treatment, help in the diagnosis of metastasis, and find the physical interactions in malignant cells and microenvironment as well as control of exterior mechanical forces. This trending approach is known as the Physics of Cancer. The main objective of this perspective comprises of quantitative description of

cancer development and progression using tools and models from physics [54]. Tackling this problem in an interdisciplinary way could lead to an enhanced understanding of cancer.

Physicists offer a special approach to cancer research and treatment. Peter Kuhn, a physicist in his research said that the life expectancy of lung cancer patients can be improved by applying mathematical modeling to the clinical data obtained. Blagoev noted that the theoretical-physics approaches can be useful in finding fundamental principles in human cancer that will in a way help us to improve our understanding of this complex disease [55]. Thus, the linkage of physics with biology would break barriers in facing these challenges. Putting together the aspects in an appropriate way will work wonders in the cancer research field. Enhanced treatments and superior diagnostics would be possible by collaborating physical scientists with biologists and oncologists to gain knowledge about the latest advancements in this field [56].

There is a very beautiful set of equations that physics uses in determining its role to understand the mechanism of force production and propagation by the cancer cells. The application of physic in determining the mechanical properties of the tumor tissue and the significance of the spatial tissue arrangement in which the tumor growth occurred is being explored [57]. The evolution of investigative means in advancements and the effectiveness of cancer therapy take into account the concepts of physics. This approach is quite beyond a usual biologist's area of expertise.

Looking at the physical perspective that has contributed to tackling cancer is needed. The mechanisms of tumor opening, progression, and treatment response and drug resistance have been reported using the rationale of evolutionary biology [58]. For instance, the evolutionary approach was used with genomic data sets to envisage the temporal sequence in somatic events occurring in the period of tumorigenesis which facilitates to direct the production of the accurate genomic framework in animal cancer models and assists in validating the targets for drugs. The altered behavior of cells helps in the detection of cancerous lesion that phenomenon is referred to as “field effect”. This effect is made use by partial wave spectroscopy to detect cancers in the tissue which are difficult to locate [59].

Application of concepts of physics allows for better management of the extraordinary complex disease. Onco-Physics perspective on cancer considering it as a multigene phenomenon of mass transfer deregulation were used to examine tissue mass transfer characteristics that were used as vectors for localized and better drug release in tumors. Transport oncophysics is the interrelationship of physical mass transfer processes with the progression and therapy of cancer which provides a foundation in the cancer treatment. These examples from different sections on cancer mechanic, evolutionary approach to cancer, transfer, and release indicate interface of physical sciences with cancer biology that has worked wonders in cancer research [60].

The observation that tumors are being rigid than neighboring tissue brought into picture the term oncology which helps in the detection of cancer. Mechanics have shown biological function from the studies of organ development and by the use of various imaging tools. Tensile forces have emerged through the connection of cells and cell-matrix. It also involves surface stress and intracellular molecules involved in signal transduction within a cell and the components of the cytoskeleton [61]. When equilibrium forces characterizing the cell shape are disturbed, change in the cell shape, organization and mechanics are altered. Mechanical forces alter the communications between cell surface receptors in the signal transduction pathways that consecutively activate or inactivate the genes. The integration of physical sciences with biology is exemplified here showing the surface mechanics that intervened pattern formation in Drosophila malanogaster melanogaster the equation used here is right from the elasticity theory from the physics textbook and the N-cadherins and E-cadherins [62].

The biophysics deals with the aspects of the cell mechanics of normal cells differ from that of cancer cells and the areas of tumor are stiffer than the adjacent area that's where the cell mechanics play a role and it deals with the surrounding extracellular matrix and the microenvironment. Extracellular matrix plays a major role to maintain tumor cell behavior and any changes provide an idea of alterations in cancerous cell matrix [54]. The microenvironment of the tumor is dynamic consisting of cancer cells enclosing the blood vessels, signaling molecules and the extracellular matrix (ECM). Throughout the malignant transformation of normal tissue there is a striking in the physical context of the tumor. These changes are influenced by the increased tumor size and rapid tumor cell invasion along with changes in extracellular matrix features [55]. The ECM rigidness and architecture reflect the cell behavior changes and eventually tissue organization and function. Mechanotransduction is a vital process in cancer pathology, by which the cells can sense and act as per mechanical indications by transforming mechanical signals into biochemical signals. Cancer cells show variations in focal adhesion dynamics. Focal adhesions are protein complexes that are in the physical contact among cell-ECM and adjoining cells through integrins. By such an approach, ECM inelasticity alters cellular stress that affects tissue stiffness and morphology [56].

The tumor microenvironment is an active portion that plays a vital role in providing the physical characteristic of cancer progression. Additionally, the endothelial microenvironment of tumor masses provides cancer cell invasion into extracellular masses. The tumor microenvironment properties can be linked physically with the stiffness of the matrix, fiber composition, cross -linking proteins and spatial arrangement that play a role in governing migratory and metastatic behaviors. A clear conception of the physical interactions and the forces will provide a novel approach to fight the deadly disease and will prove new areas of growth in the therapeutic segment. The metastasis process is accountable for the majority of cancer linked deaths [57]. Davies stated that variation in Young's modulus plays a key role in the whole metastatic process. He also noted that, along with the chemical microenvironment, the physical microenvironment too plays a considerable role in cell behavior and is chief players in the metastatic process [58]. Similar to pressure forces, even shear stresses can affect gene expression was stated by Davies. In metastasis, cancer cells migrate through diverse microenvironments, comprising of blood vessels, endothelium, and tissues at the secondary site (shown in Fig. 5).

It is a complex multistep process that begins from the progression of the primary tumors to the development of the secondary tumor. The physical interactions linking the cell to the extracellular matrix plays a chief function in the migration of tumor cells surrounding blood vessels [59]. In the invasion and outward movement of cancer cells, they undergo elastic deformations to gain entry into intercellular junctions. Association of cell velocity and adhesion in vascular system persuades

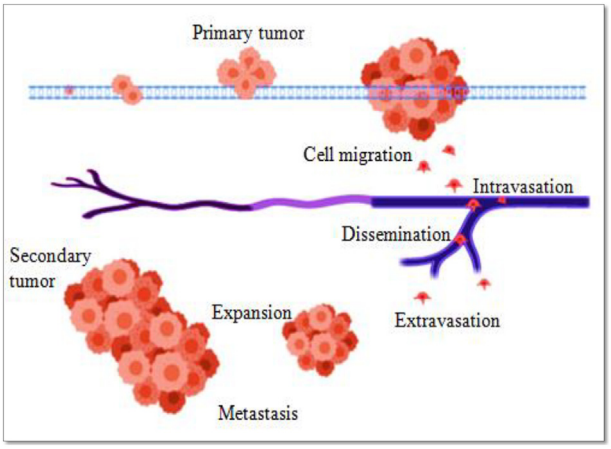

Fig. 5. The metastatic cascade.
The stages of cancer progression as it transforms from the primary tumor to a malignant tumor undergoing cell migration to intravasation to dissemination and extravasation and expansion leading to metastasis.

the binding of cancer cells to blood vessel walls. At these sites, primary tumor has the potential to develop into a secondary tumor. A better understanding of these forces will bring a new approach cancer succession and possibly will offer a new platform for better therapeutic advancement [60].

Epigenetic and genetics transitions lead to malignancy. Scientists now are identifying the mechanical changes in the phenotype of the cell that comprises modifications in cell tissue architecture, a forced journey of changes in the environment and ECM and metastasis. This force-dependent transformation in the tumor offers new trends in cancer therapeutics. These changes in the cell are characterized by mechanical stress and strain. Young's modulus or elasticity is directly proportional to the stiffness of the material and is a measure to enumerate mechanical differences among the tissues. The knowledge regarding cell mechanics and integrating it with the cancer cell biology has made it possible to recognize the key drivers and the signaling sequences in cancer [61]. We have seen this briefly in an example of Rho GTPase. Rho GTPase plays a role of a molecular switch in cancer propagation at different stages. As explained earlier the GTP bound form is active and GDP is the inactive form. This switching is stimulated by GEF AND GTPase.

Metastasis is triggered by tumor propagation, angiogenesis, genetic alterations and stimulation of signaling routes. As carcinoma cells leave the epithelium, the stroma gets invaded that resembles the epithelial-to-mesenchymal transition (EMT). EMT function is rapidly being examined in cancer metastasis [62]. Remarkable changes are observed in the physical and mechanical properties of cells like the reduction of intercellular adhesion and structural transformations from cuboidal epithelial to mesenchymal due to loss of adhesion molecules like E-cadherin and cytokeratins as shown in Fig. 6. As a result of their detachment from the primary tumor they acquire a motile phenotype. In the mammary tumor, the matrix is rigid than the normal tissue due to high collagen deposits and cross linkage of lysyl-oxidase of the collagen fibres by tumor fibroblasts. This increases signaling via integrin and collection of specific fibres. Therefore, enhancing cell propagation and intravasation into a right feedback loop [63]. Throughout the passage through the circulatory system, in which tumor cells undergo different stresses like hemodynamic forces, immunological stress and host cell collisions [64]. Only CTCs that are the circulating tumor cells that surmount the fluid shear effect hold on to the endothelium layer of outlying organs. Insignificant proportions of CTCs continue to produce metastasis and the majority of which pass away [65]. EMT gives an excellent illustration of cellular plasticity in cancer succession. In complete EMT the epithelial cells lack any indication of their epithelial source and attain mesenchymal phenotype. In cancer progression during EMT, cancer cells from epithelial source display mesenchymal as well as epithelial traits and attain fusion of E/M phenotype. This phenomenon is known as partial EMT. Partial EMT has seen to play a role in the invasion, producing circulatory tumor cell clusters and enhancing tumor cell migration [66].

Several of physical and mechanical factors influence the path of a tumor cell on entering the circulatory system. These parameters include the blood flow pattern, blood vessels diameter, interaction between shear flow and intercellular adhesion. Shear stress (τ) is the result of fluid viscosity (μ) and shear rate and is developed among fluid layers of viscosity [67].

The circulating tumor cell departs the circulatory system after binding to a blood vessel by using different means of capture like physical occlusion and cell adhesion [68]. In physical occlusion, the arrest is by mechanical trapping. In the case of adhesion, adherence is by the creation of definite bonds. The possibility of arrest is given by probability (P) where P $\propto$ft, and f denotes the collision frequency between membrane-bound receptors and endothelial ligands and t is the residence time [69,70].

Dating back to the history from the discovery of DNA mechanism and understand the gene functions and complexities from a molecular biological point of view, the discovery of oncogenes, identification of the hallmarks but still the struggle is not in favor of cancer. 'We Fought Cancer and Cancer Won' a story titled in Newsweek gave us the real picture of the status of cancer in the current scenario. Therefore scientists, physicists, engineers from various disciplines started contributing to cancer research in different ways [71]. These contributions applying the knowledge of physics have led to developments that make use of m imaging techniques and rays' treatment to detect tumors. Secondly the use of bioinformatics to understand the properties of complex biological systems in the handling genome sequence. Thirdly use of quantitative applications of the physical processes in tumorigenesis.

Focusing on the physics of cancer we look at its recent advances that it has contributed to cancer research. Firstly, let us see the significance of the spatial constitution in cancer evolution. Martens et al. showed the effect of spatial tissue structure in which metastasis occurs due to

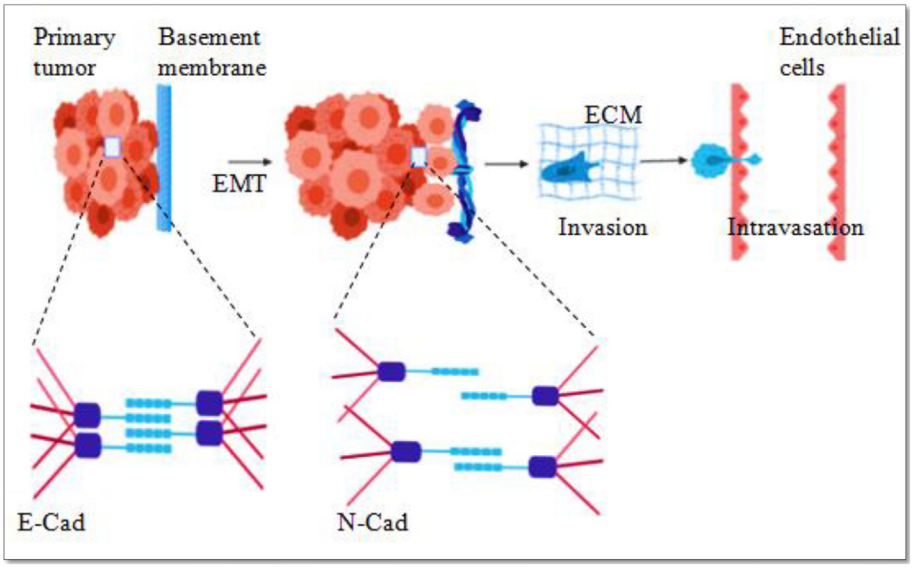

Fig. 6. Physics of invasion.
The epithelial to mesenchymal transition (EMT) related to lack of E-cadherin. Invasion by tumor cells of neighboring tissue changes the physicochemical properties of the extracellular matrix (ECM). Further through squeezing effect they enter the vascular system.

mutations [72]. Mutations occur successively over time develop into monoclonal cell population. As soon as pre tumorous cells begin to multiply, the mutations occur at different locations. Authors have applied the clonal adaptation model to the human colon, where crypt bifurcation plays a role in the clonal expansion. A mutation arising in waveform was shown which gain potential for tumourous growth by Fisher [73]. The significance of mechanical characteristics on the tumor mass or microenvironment that affects tumor growth was understood by applying the physical sciences. Drasdo and Hoehme explored the biomechanical influence on the cell cycle entry and cell migration considering the tumor microenvironment on tumor growth [74]. Sciumè et al. investigated tumor growth is multiphasic which consisted of the following different components [75].

The potential of the physical perspective of cancer provides insights about the cancer disease. The process of cancer progression is a mechanically driven course that influences the signaling pathways, for instance, the signal transduction pathway is induced by changes in cell mechanics. This is not clearly understood but requires a thorough understanding of it [76]. Cancer physics presents a promising field of research. Advancements in the field of biological sciences showed an amazing chance to analyze the mechanics of cells with cellular functions. Major progress is seen in the accessibility of techniques to measure the force vs. displacement signature of living cells through a variety of biomechanical assays [77]. These mechanical, chemical, biological and genetic routes, offer the unique perception that lays the mechanistic foundation of human wellbeing at the molecular stage that can be better comprehended. Getting a link between cell mechanics with chemical and biology in human health provides promising developments in the field of cancer diagnostics, prophylactics and therapeutics [78]. The background of cancer research has brought the advent of cross-disciplinary collaborations this has enabled us to get an idea of the disease mechanisms at spatial and temporal scales. Thus, physics contributes effectively.

4. The perspicacity of biology and physics in cancer treatment

Cancer is one of the most complex diseases. It is a collection of extraordinary multi-gene diseases having the potential to metastasize. These features along with a bunch of others make cancer drug delivery and treatment a challenging one. The treatment for cancer depends on location, risk factors, severity and kind of tumor. Various methods for the management of cancer include surgical removal of tumor, chemotherapy and radiation therapy [79].

Surgery includes the removal of a tumor. Radiation utilizes high energy rays to destroy cancer cells. Chemotherapy drugs are toxic drugs which hamper the DNA replication and in the cell cycle. Existing therapies utilize the lack of cell cycle control and genetic instability of cancer cells. Anticancer treatment exploits the properties of cancer cells that differentiate them from normal cells. Genetic instability is a consequence of loss of DNA repair systems [80]. The conventional anticancer therapies work on maintaining chromosomal integrity. Comparing the normal cells with that of the cancerous cells using radiation therapy on normal cells will damage their DNA but then repair mechanisms will hold their the cell cycle until they have restored. On the other hand cancer cells have cell cycle checkpoint defects lose the capability of arresting cell cycle and continue with rapid growth. Our rising knowledge of cancer cell biology and tumor progression is emerging new ways to treat cancer and by targeting cell division cycle arrest and DNA repair defects [81].

The advent of complementary therapies in cancer has bought a new era in cancer treatment. These include immunotherapy, apoptosis and angiogenesis regulators, signal transduction therapy and other molecular therapies [82]. Researchers have focused this idea of the molecular biological concepts towards targeted therapy in cancer treatment. This treatment works by targeting different mechanisms to showcase its anticancer effects like blocking of proliferative capacity, apoptosis induction and angiogenesis and metastasis inhibition, immunotherapy, a reversal of MDR [83]. A better understanding of the biology lead to the rise of efficient targeted therapeutic agents. Researchers have developed anticancer drugs showing potential for molecular targeting and these targets are useful in the cancer treatment as shown in the table.

In the case of breast cancer the Human epidermal receptor 2 (HER2) is highly expressed therefore shutting down the HER 2 function might reduce the growth of breast tumors and this approach was used in clinical trials using a monoclonal antibody that identifies HER 2 [84]. Overexpression of Erb-B is seen in breast cancer which acts as a potential for tumor propogation [85]. Thus this antibody Herceptin is used as a potential therapeutic agent against the target Erb—B. Even MYC is a successful target for the treatment of many types of cancer. For the treatment of HER 2, therapeutic agents like monoclonal antibodies, tyrosine kinase inhibitors (TKIs) and other anti-HER2 agents. Trastuzumab (Herceptin) is the first approved monoclonal antibody for tyrosine kinase [86].

In this context, we have demonstrated the significance of molecular biology in the diagnosis and treatment of cancer. Cancer biology can act as tools to detect any changes in tumor cells linked to malignancy. Here will take the example of chronic myeloid leukemia (CML) and see the use of molecular biology as a therapeutic tool for its treatment. The main feature of CML is the presence of the Philadelphia chromosome that gives rise to BCR-ABL in chromosome 22. These transitions lead to a reduction in programmed cell death and gives rise to oncoprotein which has a domain that adds a phosphate group to tyrosine amino acid residue activating surge of reactions [87]. The presence of a phosphate group has the capability of regulation of cell cycle, inhibition of DNA repair leading to genetic instabilities. Now the choice of treatment depends on the specific targets. The therapy of TKIs is given like imatinib, nilotinib, dasatinib and has shown potential for inhibition of BCR-ABL oncoprotein [88].

Therapies are developed to attack cells deficient in p53, considering the case of the adenovirus they encode proteins that inactivate the host cells p53 that allow them to freely replicate their genome and infect the surrounding [89]. Therefore, adenovirus lacking gene making p53 blocking protein was developed and this faulty virus will replicate only in cells in which p53 was already inactivated. This modified adenovirus when injected into a tumor, the virus may replicate inside and only kill the specific cancer cells lacking p53 not arming the normal cells and this approach is also in clinical trials. Mutant p53 contributes to a broad network of oncogenic processes thus developing drug therapies to target mutant p53 tumors is challenging and need in-depth knowledge of the signaling pathways. However, researcher's expertise work on it will provide efficient therapies ahead.

Another therapy that blocks angiogenesis can be used to treat cancer [84]. The growth of the tumor can be blocked by depriving the supply of blood to the cancer cells. Endothelial cells in the process of new blood vessel formation express distinct cell-surface markers giving a potential way to treat cancer without damaging the blood vessels in non-cancerous tissues. The understanding of cancer cell biology at different paths like DNA repair, cell cycle checkpoints, and apoptosis has provided innovative ways in designing, diagnosing and treating cancer [85]. Anticancer therapies work by destroying the cancer cells by using properties that differentiate them from normal cells. Understanding cancer biology has provided promising ways to find out which genes are mutated in tumor cells, hence we can determine drugs targeting cancer more accurately [86].

Angiogenesis is another promising target for cancer treatment. Compounds like angiostatin and endostatin have an advantage over other drugs as they do not target the cancerous cells directly, therefore, lesser chances of drug resistance and these drugs prevent tumor growth and metastasis [87]. Another target in cancer can be the failure of the immune system to act on the destruction of the cancerous cells. That is the immunological approach that uses antibodies to inactivate cancer-specific proteins [88]. For example, many breast cancer cells

Table 1
Anticancer drug, their mechanism of action and examples.

Anti-cancer drug classes	Mechanism of action	Examples of drugs used	References
Anthracyclines	They act as DNA and RNA synthesis inhibitors and topoisomerase II inhibitors, therefore block DNA transcription and replication	Doxorubicin, epirubicin, and daunorubicin	[92]
Alkylating agents	Addition of an alkyl group to DNA guanine base resulting in DNA strand breaks thus interferes with the multiplication of cancer cells acting agent.	Carboplatin, cisplatin and cyclophosphamide	[99]
Taxanes	They act as mitotic inhibitors by disrupting microtubule function, in this manner inhibit the cell division.	Paclitaxel and docetaxel	[94]
Platinum-based chemotherapy	These results in crosslinking of DNA and thereby inhibits DNA repair and synthesis n cancer cells.	Carboplatin and oxaliplatin	[101]
Antimetabolites	They stimulate cell death in the S phase or blocks enzymes essential for nucleic acid production.	They include folic acid antagonists, purine, pyrimidine analogs	
a) Folic acid antagonists	Inhibits dihydrofolate reductase, by preventing the reduction of dihydrofolate to tetrahydrofolate	Methotrexate	
Purine analogs	Acts as ucleotide biosynthesis inhibitors by direct inclusion into DNA	6-Mercaptopurine,azathioprine	
Pyrimidine analogs	Acts as nucleic acids synthesis inhibitor, works by inhibition of enzymes essential in DNA synthesis	5-Fluorouracil, Gemcitabine	
SERM (Slective estrogen receptor modulators)	Blocks the estrogen binding site	Tamoxifen and raloxifene	[102]
SARM (Selective androgen receptor modulators)	Blocks the binding site for testosterone	Enzalutamide	[103]
Farnesyl tranferase inhibitors	Blocks addition of a farnesyl group to RAS preventing its replication.	Chaetomellic acid A	[104]
Angiogenesis inhibitors	Prevent angiogenesis by inhibiting blood vessel growth	Endostatin, Angiostatin	
Immunostimulants	Stimulate normal immune response	Interlukin 2,alpha interferon	

overexpress a receptor protein called HER2. An antibody Herceptin that binds to HER2 inhibits tumor growth by avoiding the binding of growth factors to the cells. Azacitidine, decitabine, romidepsin are potential chemotherapeutic agents which are inhibitors of DNMTs are proven treatment agents for such malignancies. Several other compounds are been reported that target epigenetic constituents as well as the genetic factors [89]. The presence of these genetic and epigenetic abnormalities has shown beneficial outcomes in cancer therapy. The bromodomain inhibitor inhibits transcription by MYC that is overexpressed in many cancers [90].

Non small cell lung cancer accounts for a high mortality rate. RAS mutations are frequently observed in majority of the cancer and the alterations in RAS mutations due to codon 12 are linked to the incidence of cancerous cells [91]. Gefitinib and Erlotinib are a regimen n NSCLC if there is resistance to standard chemotherapy which is indicated for mutations in the RAS gene and imatinib in case of chronic myeloid leukemia [92]. Farnesyl inhibitors are a novel class of biologically active anticancer drugs that inhibits cell growth [93]. Cell checkpoints have a promising role as a target in cancer therapy. The cell cycle vital checkpoints help to improve time for the DNA repair. The G1-S, S and G2/M points consist of sensor proteins that sense the DNA damaged signals and improve the process of DNA repair. Advanced chemotherapeutic drugs target particular proteins, genes or processes in cancer cell signal transduction cascade. The oncogene RAS is activated by the addition of a chemical entity and scientists are discovering drugs that inhibit the addition of the chemical group to RAS. These have shown promising outcomes in cancer treatment [94]. Like for instance the drug Gleevac has the potential to inhibit cancer cell growth leading the cancer cells to undergo apoptosis. It is a standard treatment for chronic myeloid leukemia and also shows positive results in other cancers.

Molecular therapy in renal cell carcinoma (RCC) holds 2–3% of all malignant diseases. The treatment here aims at inhibiting the activity of vascular endothelial growth factor (VEGF) is involved in the RCC [95]. Sorafenib, sunitinib are the TKIs (Tyrosine kinase inhibitors) and bevacizumab one of the anti-VEGF antibody used. Sunitinib is the standard of care in the metastatic RCC. VEGF a primary stimulus binds to the vascular endothelial growth factor receptor (VEGFR) and induces angiogenesis and rapid cell growth leading to the activation of the MAPK pathway. Sorafenib is an approved agent and is an inhibitor of VEGFR and showed amazing antiangiogenic potential in RCC and hepatocellular carcinoma (HCC) [96]. Oncogenes are a potential target to treat cancer. Like an instance, Imatinib (ABL kinase inhibitor) used in the treatment of BCR-ABL. Gefitinib and Erlotinib used for targeting EGFR. VEGF oncogenes are targeted by bevacizumab or sorafenib.

Hormone therapy is used to treat cancer as certain cancer cells require hormones for growth. This process is initiated by blocking the activity or synthesis required for the hormones. Like selective estrogen receptor modulators (SERMs) and selective androgen modulators (SARMs) are drugs that block the hormones required and prevent cancer from forming. Another area where the biology of cancer can be used in treatment of neoplasia which includes an epigenetic mechanism [97]. Temozolomide an alkylating agent used as the first line of treatment in multiforme glioblastoma. The epigenetic silencing of the O6-methylguanine-DNA methyltransferase (MGMT) helps in DNA repair and provides improved therapy. MGMT removes the methyl group and prevent methyl group degradation. Thus it can be said that molecular biology, genetics, epigenetic pathways are vital in the diagnosis and therapeutic tools for cancer treatment [98].

Many anticancer drugs are available for the treatment of different cancers. These can be classified into taxanes, anthracyclines and antimetabolites, hormonal drug therapy and platinum analogs [99]. Many chemotherapeutic drugs use cell cycle checkpoints as targets. The underlying principle is that the cancerous cells are expected to duplicate than normal cells and the mechanisms of the cancer chemotherapy can be better understood with the help of understanding tumor biology and cellular kinetics [100]. Having discussed the application of this in the treatment of cancer it is important to summarize few drugs that have the application of the biology and physics concepts to have a clear understanding. To demonstrate this we have provided a few examples and a summary in Table 1. The premise of targeted therapy in oncology is inhibiting the biological pathways of tumor cells. Here, we also provide an overview of these potential mechanisms that can facilitate the further improvement of anticancer.

The discovery of target-based drugs was a boon due to the advancements in molecular biology for the treatment of cancer. HER1/EGFR is a striking target for anticancer therapy. Cetuximab is an anti-HER1/EGFR monoclonal antibody that was recently approved for metastatic colorectal cancer in patients noncompliant to irinotecan [105]. Folfirinox a cytotoxic combinational chemotherapy regime comprising of irinotecan hydrochloride, folinic acid, fluorouracil, oxaliplatin was used for metastasized pancreatic cancer treatment.

Advanced understanding of cancer cell biology has provided novel opportunities for the treatment of cancer. For instance, the researches on the molecular pathology of cancer have provided a wide-ranging theoretical outline within which new approaches to therapy are been convinced [106]. Also, tumor pathology studies offer potential approaches in the therapeutic field. The chief aim is to switch insights at the molecular level into new pharmaceuticals that can be clinically used.

The drug delivery approach has shifted towards a technological approach for better patient compliance [107]. The novel and smart delivery systems have shown great impact in cancer therapy [108–111]. This includes some stimuli like biological signals, pH, temperature and pathological changes [112]. This field of interest is the electronic drug delivery that makes use of electrical signals as stimuli for the drug release. Devices in this range include electric devices to those that make use of polymer triggering the electric stimuli. Microelectromechanical systems (MEMS) as devices can be used in cancer therapy by effectively loading the anticancer drugs like doxorubicin with use of polydimethylsiloxane [113]. Novel opportunities are seen in areas where there are remarkable alterations in cell biology and molecular genetics giving rise to better treatment strategies in cancer. Cancer is a heterogeneous disease that develops over the years due to the accumulation of malignancies. It was possible due to research in this field that could identify genes contributing to carcinogenesis. These genes and the pathways in which they act therefore have become the focus of researchers to develop newer strategies in treating and detecting cancer at earlier stages.

5. Conclusion

Until we investigate cancer's fundamental principles, the fight can only step forward in inches, rather than in miles. It is very well said that first understand the disease than treat it. This statement helps us understand the application of biological and physical concepts in treating the disease. Thus, superior therapy and precautionary strategies can be applied only if the disease is understood well. A better understanding of this has provided a shift from the traditional therapeutic approach towards a more of a tailored treatment approach targeting specific events. Enough research on cancer has disclosed the genetic basis of tumors. It is time that cancer physics with information on physical interactions in cells and tumor growth is joined to biology to provide the well needed targeted cancer therapy. The delivery of anticancer drugs to their appropriate targets with the help of cancer biology will bring rapid advances in the diagnosis and treatment of cancer with the application of concepts from physics. Understanding of the cellular mechanisms underlying cancer has shown the rationale for the development of cancer therapies and this has been a proficient therapeutic approach for many cancer patients.

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