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Review Article

VALIDATION OF SCREENING MODEL OF CANCER: A REVIEW

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ABSTRACT

Cancers are characterized by uncontrolled cell division and the development of metastatic qualities. The reason for the cause of cancer can be intrinsic factors like oncogenes, external factors like radiation, certain chemical exposure, etc., or biological like infection from certain viruses, bacteria. Hence, because of these factors, 200 different forms of cancer exist making cancer a leading of death and major health problem even in the present world. However, the lack of a comprehensive understanding of cancer biology in the modern period is a significant impediment to studying cancer tumour formation, invasion, and metastasis. Hence, cancer models can be crucial in removing that impediment and can give us a better understanding of the cancers because even in the 21st-century cancer is still an unsolved puzzle and with cancer models like in vivo models, In-vitro models and computerized models a better understanding can be achieved.

Keywords: Cancer, Screening Model, Tumour, Metastasis

INTRODUCTION

Cancers are generally characterized by uncontrolled cell proliferation and the development of metastatic qualities. In most situations, oncogene activation and/or tumour suppressor gene deactivation results in uncontrolled cell cycle progression and apoptotic mechanism inactivation.[1] However, these changes are not always because of internal factors, sometimes the person's genetic factor interacts with external factors like physical carcinogens (UV and ionizing radiation), chemical carcinogens (asbestos, component of tobacco etc.) and biological carcinogens (infection from certain virus, bacteria or parasites.[2] In today's world cancer has been a widespread and major public health problem. There are about 200 different forms of cancer, which are often called by the tissue where the disease was discovered for the first time. Cancer is one of the leading causes of death in the twenty-first century and the most serious impediment to increasing global life expectancy.[3] According to WHO data approximately 10 million deaths were accounted in 2020. [2,4] The lack of a comprehensive understanding of cancer biology in the modern period is a significant impediment to studying cancer tumor formation, invasion, and metastasis.[5]

Oncology research, like other illness research, is heavily reliant on an accurate and representative model framework. Nonetheless, cancer cannot be defined as a single characterized tumor, but rather as a complex and highly fluctuating system. As a result, selecting the most appropriate model to effectively portray a certain tumor system is one of the most difficult aspects of cancer analysis.[6]

Cancer models whether found naturally or artificially created, have characteristics with human tumors. In vitro cancer models' have the inability to simulate the variety of human cancer cells, their microenvironment, and the stromal compartment has hampered research into tumor development, treatment responses, and adverse effects.[7]

To quantify clinical feedback in patients using the model, it is necessary to achieve a confirmed "response" to therapy and to use clinically acceptable dosages of curative drugs to observe survival. Furthermore, it is critical to determine whether tumor regeneration occurs after medication is stopped, and if so, whether redevelopment is rapid when treatment is delayed compared to before treatment began. All cancer models attempt to simulate at least some aspects of human cancer, but we will never have a flawless model. Nonetheless, we must figure out how to intercept our data within the structure of the test's restrictions.[8] Hence, in this article we will discuss about different cancer models like in-vitro models, in-vivo models, computational models and will also throw some light on some novel cancer models.

In vitro models

Cancer cell lines

The cancer cell line is an in vitro tumor model that is widely used in oncology since it exhibits several intrinsic cancer characteristics and gene expression patterns. [10,11] Cancer cell lines have genomic abnormalities comparable to actual human cancers as measured by copy number alteration (CNA) and transcriptional profile. Due to their simplicity of use, low cost, immortality, little cellular heterogeneity, and high proliferation rates, cell lines are the most often used preclinical cancer model. Cancer cell lines are created by isolating cancer cells from patient-specific tissues and cultivating them in artificial culture conditions, which eventually lead to the production of cancer cell line xenografts when transplanted into immunocompetent mice.[9]

Mislabeling, replacement, and contamination of cell lines originated from various tissues, animals, and patients have been a severe quality control concern for the scientific community for over 50 years. [12] Cancer cell lines are useful for in vitro and in vivo human cancer models, but they also have significant drawbacks. Existing cell lines do not display all tumor subtypes. The absence of stromal components such as lymphatic vessels, complex extracellular matrix, related immune cells, blood, and fibroblasts is another disadvantage of using cancer cell lines.[11] High passaging causes changes in chromosomal configurations, differentiation markers, gene expression, karyotype, and cell line growth rates. Due to the composition of culture medium and the presence of fetal bovine serum in conventional culture, cancer cell lines have been unable to perfectly imitate the properties of tumor cell proliferation in vivo. [13]

Organoids

During the last decade, the introduction of organoids as an ex vivo model system has transformed primary and clinical cancer research. Organoids are the tiniest of human organs and tissues, and they efficiently reflect the functional properties and structures of a single organ. Tumor cells extracted from cancer patient tissue are placed in the extracellular matrix of specialized culture medium, resulting in the development of a cancer organoid.[7] Organoids are susceptible to molecular and cellular characterization and modification using a variety of genetic methods, and they aid in the discovery of cancer-causing mechanisms. Organoids are matrix-embedded colonies of primary epithelial cells that proliferate continuously in response to Wnt signaling and mitogens. The establishment of tissue-derived stem cells embedded in three-dimensional matrix organoids as self-sustaining structures.[14]

Despite the huge change that organoids have brought to cancer research, they nevertheless have certain limits. Organoids are imperfect replicas since they are only an epithelial layer without an inherent microenvironment. Organoids grown mostly from the epithelium have been the focus of current study, therefore further work on non-epithelial organoids production is needed. Growth stimulators and inhibitors have a significant influence on drug sensitivity, gene expression, and signaling pathways. [15] Organoids are not effectively created from every specimen therefore further work is needed on the techniques of organoid culture and matrix compositions. [16]

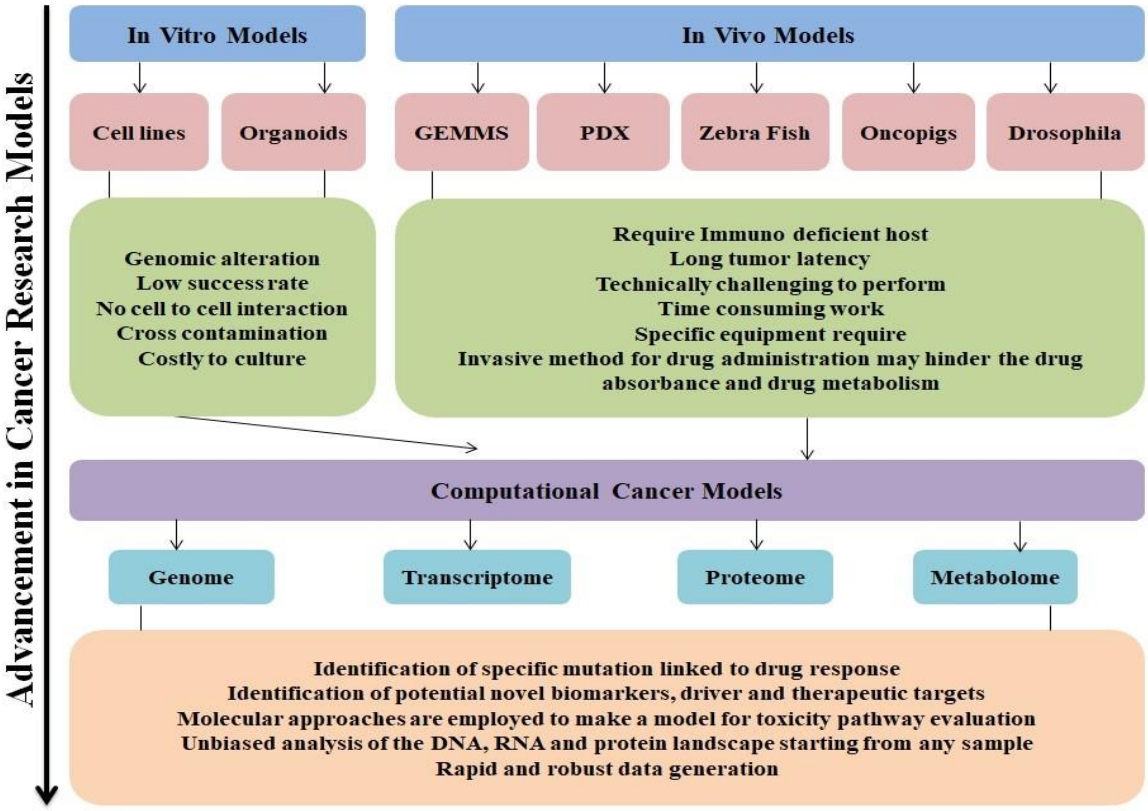

Fig. 1: Evolution in Cancer Models.[9]

***In Vivo* models**

GEMMS

The genetically edited mouse models (GEMMs) were created since the intrinsic features and physiology of xenografts do not delineate the genetic characteristics of a human tumor. [17] Researchers have been able to create changes in the genomes of mice that conditionally or constitutively affect the expression of critical genes that lead to the formation of particular cancers thanks to technological advancements in recent decades. GEMMs have aided oncogenesis by removing molecular pathways and controlling the genome to achieve loss or gain of oncogene or tumour suppressor gene activity, which is expressed in the tumour phenotype, and have proved useful for treatment by validating important genes as targets. [18-19]

GEMMs have been used to assess carcinogenicity for more than 20 years.[17] For a variety of reasons, the European Commission believes that the mouse appears to be a generally accepted animal for genetic alteration in order to explore improved pharmacological therapies for healing various diseases. First, the mouse genome is 99 percent identical to the human genome. Second, a rich molecular toolset is available, and their small size

allows for high throughput/large-scale research, making it a cost-effective model. Preclinical safety assessment and screening models using transgenic modified mice might be useful for lead optimization and identification. GEMMs' broad phenotyping can help researchers better understand gene activity in relation to human illness and health. The use of GEMM in clinical research has proven to be effective in many circumstances, including the amount of drug, technique, or process for advanced therapy. [20]

However, the fundamental disadvantage of GEMMs is that they only target a few copies of a gene, which does not account for the complex heterogeneity of real tumor cells. The creation of GEMMs is time-consuming and costly, and it typically necessitates extensive periods of labor before certification. Animal tumor evolution is unpredictable and sluggish. In comparison to humans, they have different biochemistry, physiology, and anatomy. [9]

PDX (PATIENT – DERIVED XENOGRAFT)

The term xenograft comes from the Greek word Xenos, which means "foreign." It's extracted from one creature and transplanted into another. Organs, tissue, or live cells are inserted into immunocompetent mice in the majority of cases. In the field of cancer research, xenografts are used to answer fundamental questions in which it is critical to rely on animal models that closely resemble the course of the tumor in human patients. [17] To preserve the original or primary tumor features, xenograft models containing primary carcinoma tissue taken from the patient's tumor tissue are built up at very low transit numbers; for example, less than 10 passes ejected from human patients.[21] Cell heterogeneity, clinical biomolecular markers, malignant genotypes and phenotypes, tumor shape, and vasculature are among these features.[17] The notion that these PDX models would show enhanced preclinical testing and are predictive of molecular cancer biology that is relevant to human cancer and how patients respond to cancer therapy is the foundation for developing PDX models.[22]

Patient-derived xenografts, on the other hand, have drawbacks in terms of tumor microenvironment, genetic alteration, and immune system inclusion since they are created in immunodeficient mice and do not mimic the host immune system's commitment. In xenografts, the bacterial flora for carcinogenesis that is required for early cancer diagnosis does not persist. Immunomodulatory testing for cancer prevention, onsets, and progression of genetics cancer models, along with low throughput drug screening, are not appropriate. Their biobanking is impossible, and their genetic variability and epigenomic instability are evident.[23]

Zebrafish

The zebrafish (Danio rerio) is a new potential model for studying human cancer. [24]Transgenesis was used to show a few typical human tumor forms in zebrafish, confirming that the molecular processes that promote mammalian cancer also apply to zebrafish.[25] The zebrafish is an appealing model for cancer researchers due to a number of aspects, including fast development, chemical screening, accessible genetics, and its suitability for in vivo imaging.[26] The zebrafish has a lot of potential as a cancer model system because of its forward genetics and vertebrate biology.[27] Chemical carcinogenesis, mutant lines, xenotransplantation, and transgenic lines are all methods that can be utilized to cause tumor growth in zebrafish. The alternating nucleotide sequence of DNA, bioinformatics investigation of -omics data, tumorigenesis evaluation, or PDXs technique may all be applied in cancer research using zebrafish. The majority of zebrafish studies on cancer formation come from transgenic zebrafish that express mammalian oncogenes. The transgenesis approach takes use of one of the benefits of zebrafish as a laboratory animal: the simplicity with which foreign DNA can be introduced into zebrafish cells and this DNA strand may then be expressed by injecting it into one-cell embryos. [27]

However, the main drawback of zebrafish is the difficulty in examining fixed tissue since sectioning embryos or larvae is difficult owing to their tiny size.[28] There is also a low tumor incidence, despite the fact that cancers in various mutants are equivalent, and tumors form in life at a later stage.[24] Zebrafish, on the other hand, is uniquely suited to contribute insights into cancer biology and to serve as a "whole-organism test tube" for the rapid identification of novel markers, their functions, and capacities, as well as the investigation of host reactions and the development of anti-cancer drugs.[26]

Oncopigs

The morphological, physiological, and genetic parallels to humans, including chromosomal synteny and epigenetic homology, as well as the lower cost of swine modelling, make this model ideal for representing the growth and development of cancer in humans.[29] Leukemia, lymphoma, soft tissue sarcoma, pancreatic ductal adenocarcinoma, HCC, and other hematological malignancies have all been successfully modelled using it. [29-30] Pig herds have phenotypic and genomic variability due to their outbred origin, which means that genes important for cellular transformation are more prevalent in pigs. In swine, chromosomal translocations, which are frequent in cancer, are convincingly illustrated. The Oncopig cancer model (OCM) is ideal for identifying potential biomarkers because of its inducible nature.[9]

The disadvantages of OCM include their inability to exhibit tumor-stroma interaction and inefficiency in incorporating the immune system, as well as their larger housing requirements compared to smaller animals, longer generation intervals, lower genome quality, and fewer genomic tools than mice and humans. Because pigs are kept in enclosures, biosafety is a bigger concern when working with them.[31]

Drosophila

Drosophila melanogaster has made significant contributions to understanding the molecular foundation of cancer biology by revealing the action mechanisms of cancer-related proteins. The cancer model D. melanogaster is created by inducing mutations in larvae using ethyl methanesulfonate (EMS). The outer proliferative center (OPC) and central brain (CB) portions of the larval brain contain tumorous tissue. The larval brain is then transplanted into the abdomens of adult female flies, where it continues to multiply. After few days, the host's ovaries are removed and immunofluorescence analyzed to discover tagged tumor cells that have metastasized. D. melanogaster strains that have been genetically modified serve an important role in therapeutic drug development and provide a platform for drug testing. For genomic investigations and functional testing, the amount of detail and speed achieved with Drosophila is unrivalled by other mammalian cancer models. Asymmetric division, centrosome malfunction, genomic instability, metabolism, and unscheduled gene expression all contributed to tumor start and development in D. melanogaster. The genome of Drosophila is analogous to that of humans, since proteins that cause cancer in humans are determined to be more than 50% orthologous in Drosophila.[32] Cell polarity mutations have been discovered in Drosophila, with implications in human cancers.[33]

However, In comparison to other model systems, homologous recombination in flies is time-consuming, and flies cannot be held frozen. Because flies only have four chromosomal pairs, aneuploidy is not an effective mechanism in them, and only a few models with single chromosome loss or gain are viable.[32, 34] It is difficult to represent in Drosophila before a secondary tumor develops and colonizes local tissue malignant cells that are undergoing metastasis penetrate the local blood vessel or lymph vessel, as flies have primitive hematopoietic systems and a different lymphatic system than humans. When compared to human malignancies, tumors produced in Drosophila have a far lower metastatic potential.[35]

Computational cancer model

Certain risk variables (tumor heterogeneity, illness complexity, suboptimal clinical identification of disease), genetic composition, pharmacokinetic properties, and other special traits unique to each afflicted individual would allow for a tailored therapeutic strategy to manage tumor severity. Personalized medicine, in this context, is adapting a treatment strategy to each patient's genetic genotype and is expected to become the paradigm of future medical care. The most advanced research in system biology and the rapid advancement of high-throughput technologies, as well as the portrayal of various -omics, have all significantly contributed to a shift in advanced medical and biological research from traditional hypothesis-driven structures to data-driven studies, and have aided the development of personalized or precision medications for more complex diseases like cancer.[36]

The phrase "computational cancer model" refers to computer-based modelling that is linked to cancer treatment and tumor physiology.[37] Computer-based researches have been widely used to diagnose, track, and forecast the progression of cancer. Tumors or tissue, for example, can be visualized using 3D microscopic imaging and computer simulation models. When compared to in vitro cellular cancer models, numerical or computational models are most typically associated with algorithms and other computational software packages, resulting in a lack of comparability and reproducibility.[38]

To explore the signal transduction pathways in human cells, large-scale computer models are now being built. For the design, modelling, and simulation of various cell systems, researchers are currently employing PyBioS3, an integrated programming platform. The current model includes roughly 50 cancer-related signalling pathways and relies on data derived from functional results of genetic variants and medication mechanistic action.[39, 40]

Computational methods provide the possibility of discovering new biomarkers in signaling pathways as well as promising targets for anticancer treatment. On the basis of time course experiments monitoring protein expression and activity, cancer signaling network models have been developed and are being used to validate simulation prediction and drug target efficacy.[41] The outcomes of experimental cancer models should be compared to the predictions generated by computational modelling to improve the translational achievement from cancer models to persons.[40]

Computational systems also aid picture analysis and interpretation in the realm of cancer research and therapy. Image analysis using computerized tomography has recently been presented as a method for studying specific cancer responses. A sophisticated computational model allows the experimental research to be redesigned, reducing the number of animal models needed for trials, lowering expenses, and, most importantly, boosting the translational value of the data provided. Computational models provide for a better understanding of molecular changes in disease-related pathways, as well as a more efficient prescreening process for the identification of essential candidates. It has the potential to increase our understanding of disease progression and therapeutic response.[40]

It is evident that present computational models do not capture the full complexity of biological simulations. The validity of prediction is a critical criterion for using such models in developmental and therapeutic settings. A different approach is to disentangle the model and use model reduction techniques to minimize the number of parameters. [40, 42]

CONCLUSION

Even in 21st century the lack of a comprehensive understanding of cancer biology is a significant impediment to studying cancer tumor formation, invasion, and metastasis. Hence, challenging scientists across the world in making a most effective treatment with fewer side effects. However, to cross this impediment cancer models like In-vivo models, In-vitro models and computational models were used which give better insights in understanding the biology of the cancer. As with these models without risking the human life a better and deep understanding can be achieved which ultimately helped scientists across the globe to in making more effective medications and treatment methods. Hence, in future more advance cancer models which overcomes the present cancer models limitations can help the whole scientist community in discovering more specific and better medication and treatments for cancer.

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