ROLE OF PATIENT DERIVED CELL LINES AND XENOGRAFT IN CANCER RESEARCH

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ABSTRACT

Cancer is now epidemic in both developed and developing countries. Most of the anticancer drugs passed rigorous preclinical pharmacology evaluation but only a small fraction of drugs showed significant antitumor activities in the clinic. Tumor cells have undergone different genetic and epigenetic modification as compared to normal cells. The success of in cancer research depends on closeness of preclinical cancer models to that of patients cancer cells. Immortal cancer cell lines have been used in cancer research from decades. However, low clinical predictability is a main reason for the unusually high clinical failure rates of therapeutic compounds in cancer research. Therefore, refinement in the preclinical immortal cancer lines and use of patient derived primary cancer cell lines for clinical outcome holds great promise to reduce the clinical attrition rates of anticancer compounds. Recent scientific reports suggest that preclinical anticancer studies using patient derived cell lines are more predictive for clinical outcome as compared to immortal cell line. In this mini review we have discussed the role of patient derived cell line in the cancer research, personalized cancer therapy and discussed the advantages and limitations of patient derived cancer cell lines as preclinical research models of anticancer therapies.

KEY WORDS: Primary cell line, Immortal, Breast cancer, Patient derived xenograft, Personalized therapy.

INTRODUCTION

Cancer is the leading cause of death worldwide and ranks 1st followed by cardiovascular disease in morbidity and mortality (Mathers et al., 2008). It is a group of disease causes growth of the cell without any intrinsic control. Most types of cancer cells eventually form a lump or mass called a tumor, and are named after the part of the body where the tumor originate. It is the leading cause of death both in economically developed countries and developing countries (Jemal et al., 2011). The burden of cancer is increasing in economically developing countries as a result of population aging and growth as well as, increasingly, an adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and ‘‘westernized’’ diets (Jemal et al., 2011). The total numbers of cancer deaths by country are collected annually and are made

available by the World Health Organization (WHO) (Calys-Tagoe et al., 2014). Based on the GLOBOCAN 2008 estimates, about 12.7 million cancer cases and 7.6 million cancer deaths were estimated to have occurred in 2008; of these, 56% of the cases and 64% of the deaths occurred in the economically developing world (Jemal et al., 2011). Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females, accounting for 23% of the total cancer cases and 14% of the cancer deaths. Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths (Jemal et al., 2011).

Surgery, radiotherapy, and chemotherapy are the only available treatments for cancer. However, reoccurrence of cancer after surgery, radio-toxicity, drug toxicity and drug resistance are the limitations of current treatment strategy. Administration of chemotherapeutic drugs to cancer patients also produces undesired side effects such as bone marrow depression, alopecia, retching, stomatitis and normal cell apoptosis. These drawbacks of current available treatment strategies have further promoted the search for alternative drugs or adjuvants that confer maximum effect and are less harmful to cancer treatment (Fabricant et al., 2001). In the era of advanced technology our understanding of various aspects of cancer initiation, progression, metastasis and tumor microenvironment have increased but we have achieved limited clinical success. After investment of billions of dollars in the drug discovery and clinical trials very few drugs are in market for clinical use due to lack of objective clinical response or toxicities (Zhou et al., 2009; Zou et al., 2014).

Immortal cancer cell lines have been used for decades in cancer studies, these cells are easily accessible and usable set of biological models to investigate the cancer biology and explore the potential efficacy of anticancer drugs (Mitra et al., 2013). However, due to various boundaries these stable cancer cell lines are fails to show better scientific results and success in clinical trials. Due to these limitations there is an urgent need of precise tumor models which are more relevant to the in vivo patient's cancer cells and helps in clinical translation of drugs and better understanding of tumor biology. Patient derived cancer cell lines or primary cancer cell lines are more clinically relevant cancer models, useful in the drug discovery, identification of novel biological therapeutic targets and personalized cancer therapy (Halvorsen, 2016).

In this review we focused on the role of patient-derived cancer cell lines in the cancer research, their advantage over immortal cancer cell lines and use of these cancer cell lines in personalized cancer therapy.

IMMORTAL CANCER CELL LINES

Commercially available Immortal cell lines are used to study cancer biology, genomic alterations against drug response and better understanding of molecular mechanism of cancer treatment (Shoemaker, 2006). Cell lines provide an important experimental tool for cancer research with major benefit of the infinite supply of a relatively homogeneous cell population that is capable of self-replication which can be widely distributed to facilitate comparative studies (Pandrangi et al., 2014). Immortal cell lines are often used in research in place of primary cells because they offer several advantages, such as cost effective, easy to use, provide an unlimited supply of material and bypass ethical concerns associated with the use of animal and human tissue (Kaur et al., 2012). However, the reliability of such cell lines has provoked considerable debates due to

the high failure rate of newly developed targeted agents in subsequent clinical trials (Kerbel, 2003).

Since cell lines are genetically manipulated and become immortal which may change the phenotype and native functions of the cells. Moreover, serial passage of cell lines may result in genotypic and phenotypic variation over an extended period of time (Roschke et al., 2003). In addition, due to lack of interaction with other non-tumor components such as vascular, inflammation tumor cells lose their clinical relevancy (Kaur et al., 2012). Earlier studies also suggest that these cell lines poorly represent the diversity, heterogeneity and drug-resistant tumors occurring in patient (Mitra et al., 2013). Though cancer is now an epidemic disease, there is a need of robust pre-clinical cancer models so that efficacy identified in the pre-clinical studies can be translated to clinical trials and beyond.

PATIENT DERIVED CANCER CELLS AND PATIENT DERIVED XENOGRAFT MODELS

Preclinical drug development has traditionally relied on established human cancer cell lines which cultured in serum-containing media in adherent conditions for extended periods of time. But due to lack of translating ability in clinical trials these cell lines open the door for other models.

Genetically altered cancer cell lines under in vitro conditions do not truly represent clinical scenarios (Kirk, 2012). There is a wide range of variability in patient response towards the same drugs because of their genetic aberration (Lima et al., 2010; Toyota et al., 2005). Thus it may be difficult to comprehend the genetic and epigenetic diversities of millions of patient dependent tumor variability are the driving force behind personalized medicine and provide the impetus to develop method of generating and culturing primary tumors cell from patients that will enable effective bench to bed side translation (Mitsiades et al., 2011; Schilsky, 2010; Trusheim et al., 2011). In the era of personalized therapy, researchers need a repertoire of patient-derived primary tumors cells that can generate high-fidelity data for translating in vitro findings to in vivo models and ultimately to clinical settings (Mitra et al., 2013) (Figure 1). Primary cancer cell lines are isolated from tumor slices derived directly from patient, cultured in vitro for only the first couple of passages to avoid cellular adaptation and possess more predictive validity. However, isolation and culture of solid tumor cells under in vitro conditions similar to the microenvironment of the original tumor is a major challenge for the researchers (Chopra et al., 1981; McCallum et al., 1996; Skrbo et al., 2014). These primary cell lines retain the tumor property. On the other hand, xenograft derived from cell lines shows a homogeneous histology with a lack of human stroma (fibroblast) and immune cells, which are important for tumor growth and metastatic processes (Baiocchi et al., 2010; De Wever et al., 2003). However, xenograft directly derived from patient biopsies or surgical specimens with minimal in vitro manipulations appear to possess better retention of the morphologic and molecular characteristics of the original tumors (Rubio-Viqueira et al., 2009; Rubio-Viqueira et al., 2006).

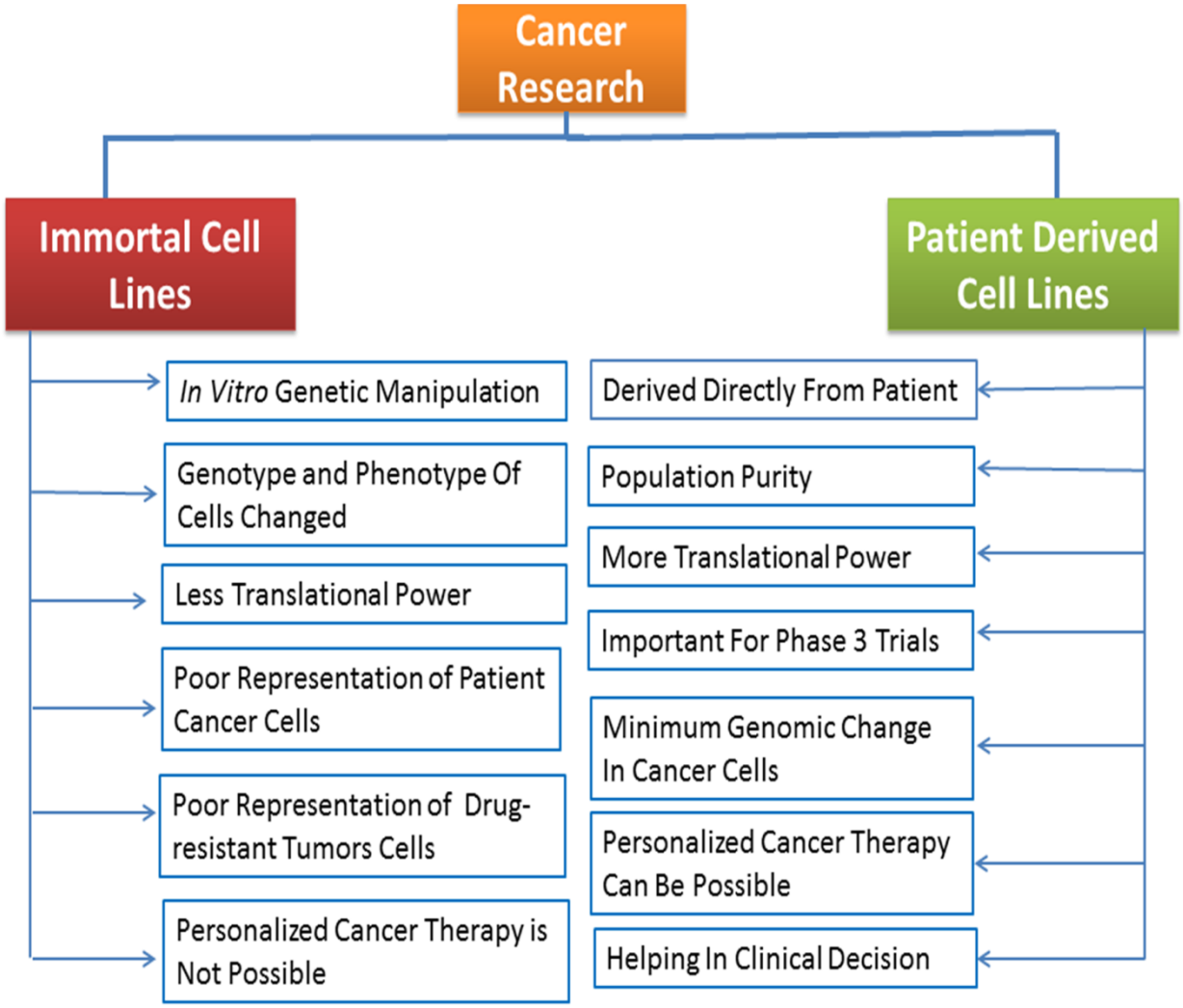

Figure 1. Depicting the advantages of patient derived cell lines and disadvantages of immortal cell lines in cancer research.

Therefore, patient derived xenograft may be an informative preclinical model for the development of novel therapeutics as they can more accurately predict the subsequent clinical success and allow various mechanistic studies that are not possible in patients (Kummar et al., 2010; Lee et al., 2015; Rubio-Viqueira et al., 2006). The elucidation of target populations is a prerequisite for the clinical success of molecularly targeted agents. Because of the limited intra-and inter tumoral heterogeneity of conventional cell lines, it is very difficult to develop reliable personalized strategies in the preclinical stage. Combining PDXs with high-throughput drug screening technologies would be a promising solution because PDXs recapitulate the functional properties of corresponding individual tumors and a PDX library would represent heterogeneous patient populations (Tonekaboni et al., 2016).

Advantages

- It is possible to generate cell lines from individual patients to pursue numerous

high throughput drug screenings (Mitra *et al.*, 2013).

- Patient derived cell cultures have advantage of population purity in long term culture and little stromal cell contamination which make possible the genomic sequencing, transcriptomic, proteomic and metabolomic studies (Mitra *et al.*, 2013).
- Patient derived cell lines and PDX models have more translation power then immortal cell lines (Hidalgo *et al.*, 2011).
- These cell lines have direct impact on clinical decisions, and helps in conducting prospective, properly powered, phase 3 trials (Aparicio *et al.*, 2015).
- These approaches would allow for more direct studies of tumor biology (Garralda *et al.*, 2014).
- PDX models are well established for both solid and hematological malignancies (Hidalgo *et al.*, 2014; Lock *et al.*, 2005).
- These cell line can also used in the cancer biomarker development, understanding of mechanisms of drug resistance and drug screening (Bertotti *et al.*, 2011).
- Patient derived primary tumor cells can generate high-fidelity data for bench to bed translation of anticancer drugs and personalized cancer therapy (Mitra *et al.*, 2013).

Limitations

- The complexity of culture medium such as use of various nutrients and growth factors for sustaining their phenotype of the primary cells make it more sophisticated technique (Gazdar *et al.*, 1998; Mitra *et al.*, 2013).
- Isolation and culture of solid tumor cells under *in vitro* environment to that of microenvironment of the original tumor is a major challenge and requires specialized techniques (Mitra *et al.*, 2013).
- In case of PDX the necessity for immune deficient hosts is the main hurdle (DeRose *et al.*, 2011; Garrido-Laguna *et al.*, 2011; Julien *et al.*, 2012).
- Some cancers such as breast tumor tissue xenografting are unpredictable and expensive, as well as hard to align to the timescales of clinical decision making and treatment (Aparicio *et al.*, 2015).
- In some cases, the time needed to develop a PDX model is too long for clinical decision making, particularly in diseases such as pancreatic ductal adenocarcinoma that have an aggressive behavior (Crystal *et al.*, 2014).
- PDX models are in many cases more replicative of the pace of tumor growth in humans and specifically grow to terminal size over the course of several months, not weeks. With PDX models, there are examples of both positive and negative correlations with clinical results, and differences in drug pharmacokinetics remain a concern (Bertotti *et al.*, 2011; Boven *et al.*, 1992; Hammer *et al.*, 2010; Hidalgo *et al.*, 2011; Peterson *et al.*, 2004).

CONCLUSION

Current developments including high-throughput technologies for screening drugs, aberrant signaling pathways, and extensive tumor microenvironment analysis have yielded various therapeutic strategies such as monoclonal antibodies, radiotherapy, chemotherapy, small molecule inhibitors, targeted therapies, or combinations of the above. However, complete eradication of cancer has eluded researchers for several reasons such as drug toxicity, clinical trial failures, and tumor relapses. One major

obstacle may be the extensive use of stable cancer cell lines in cancer research. From the literatures it is clear that these stable cancer cell lines are not exactly mimicking the in-vivo tumor biology. For limiting the high failure rate clinical trials one strategy can be use of patient derived cell lines instead of stable cell lines. The patient derived cell line offers several advantages over stable cancer cell lines. Moreover, primary cell lines are capable in determination of novel cancer biomarkers, which is utmost step of personalized cancer therapy (Mitra *et al.*, 2013).

In a conclusion re derivation of tumors as primary cell lines offer great advantages for promising clinical strategies. The generation of primary cell lines from individual patients may help in cancer research via high-throughput drug screenings, better understanding of tumor biology, drug mechanism and personalized cancer therapy. Hopefully, this review will strengthen the existing knowledge on the role of patient derived cell line in the cancer research among researchers and helps in bringing newer drug in the market for cancers patients.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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