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Novel Genomics and Proteomics Based Biomarkers to Predict Radiation Response and Normal Radiotoxicity in Cancer Patients for Personalized Medicine

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Introduction

Radiation therapy (RT) is one of the highly effective treatments option for clinically advanced tumor, and plays a prominent role in cancer therapy and prognosis. It is estimated that 62% of newly diagnosed cancer patients are treated with radiation therapy [1]. The efficacious radiation therapy depends upon the homogenous delivery of total dose which could eliminate tumor cells while protecting surrounding normal healthy tissues and avoid ancillary toxic effects [2,3]. Further, the tumor radioresistance and radiation-induced late toxicity can considerably limit treatment regularity, and cause hindrance in effective tumor control. In addition, late radiation-induced toxicity negatively impacts the quality of life of radiation treated patients and long term cancer survivors [4]. There are many latent side effects of radiation induced toxicity such as late toxicity response, epithelial tissue degeneration, infection, fibrosis and vascular lesions [5,6]. It is clinically well established that a significant number of patients develop radiation-induced toxic effects and currently, there is dearth of available technology which could precisely predict and monitor radiation induced side effects. Therefore, one of the major bottlenecks in radiation oncology is to deliver the effective targeted dose of radiation which could efficiently kill all the tumor cells, and at the same time ensure minimum normal tissue damage [4]. Nevertheless, in numerous clinical cases, the survival of cancer cells after radiotherapy can result in recurrence and disease progression. The global data have shown that up to 60% of prostate cancer patients receiving radiation therapy experience recurrence of the disease within 5 years of treatment [7]. Moreover, patients undergoing radiation therapy may exhibit radiation-induced resistance, fibrosis, and erectile dysfunction [8].

Few studies have identified biomarkers which have shown patient response to radiation, and drug treatment [9,10]. The discovery of promising diagnostic and prognostic biomarkers for radiation resistance in tumor is presently one of the main challenges of radiation oncology. Although handful of predictive assays exists, none has demonstrated highly significant results that are promising in clinical setting. Hence, proteogenomics represents a promising approach for discovering new relevant predictive biomarkers. The advancement in high-dimensional and high-throughput Omics technologies has provided an opportunity to address the development of sensitive biomarkers from a clinical perspective [11-15]. Previously, the use of individual biomarker have also demonstrated the effectiveness of this approach and the proteo-genomic analysis of some tumors have identified *APEX1* gene involved in the repair of DNA damage, and its deletion enhanced the radiosensitivity in radioresistant cell lines [16-18]. Recently, three stage genome-wide study in prostate cancer have identified *TANC1* locus implicated in radiation induced toxicity [4]. In addition, many genetic variants have also been found to be associated with radiation toxicity. In another elegant study the GRP78 and Mn-SOD were upregulated in the radioresistant CNE2-IR nasopharyngeal carcinoma cell line as compared to sensitive control cells. [19]. Further, in breast cancer cell lines radiation-induced cathepsin D and peroxiredoxin-5 has been reported to be upregulated [20]. Recently, CXCR4 has been identified and validated as biomarker for radiation resistance in cancer stem cells [21].

In the past decade several research reports have been published on identification of few individual proteomic biomarkers to predict radiation resistance [1]. However, it has been observed that the individual proteomic biomarkers are not precise enough to accurately predict normal tissue response and at the same time radiotherapy effectiveness [3,4,22]. Therefore, clinical validity of a multigene expression model or cascade of proteomic biomarkers expressed in entire irradiated tumors, exhibiting both normal tissue radiosensitivity, and effective radiotherapy are extremely important. Recently, in a novel approach, panel of multi-gene expression has been used to identify biomarkers for radiation resistance and radiosensitization in prostate cancer patients [23]. Similar approach has been employed to identify panel of genes as biomarkers for radiation resistance in breast and head-and-neck cancers [24,25]. The panel of genomic signatures have been shown to be prognostic markers in breast, lung, and head-and-neck (HNC) cancers [12-14]. Interestingly, some unique genomic signatures have also been integrated to predict intrinsic radiosensitivity in some cancer patients. Correspondingly, combination of proteomic signatures have also been used to reliably predict the tumor radio resistance and normal tissue radiosensitivity in some cancers, which could also be deployed to monitor the clinical outcomes [5,6,15].

Interestingly, in recent years individualized medicine have shown tremendous promise in diagnosis, prevention, and treatment of cancer [26,27]. The cancer radiation treatment plans based on individual patient genomic and proteomic profile could reduce morbidity and potentially improve survival by avoiding treatment failures. Thus, better insight of the tumor's biological landscape, as measured in the patient's biopsies will efficiently guide for precise patient-specific treatment strategies and best clinical outcome. Currently, in most of the cases RT is recommended without considering the possible individual genomic variations in tumor and patient radioresponse. Consequently, individualized treatment decisions based on genomic and proteomic biomarkers profile would give more precise picture of cancer stages and minimize treatment failures.

The accurate clinical diagnosis and prognosis of cancer is achievable when panel of genomic and proteomic signatures and high-throughput

genomic tools are used in clinical laboratories. The recent TCGA based study have identified multi-cancer gene expression biomarker based on *ESR1*, *PRKACA*, *LRP1*, *JUN* and *SMAD2* which are being used to predict the clinical outcome in 12 types of cancer. The genomic signature of this biomarker has been corroborated by published literature and prognostic power in other cancers [28]. Recently, the comparative genomic molecular signatures have been employed as a prognostic biomarker gene set that could potentially be used to help guide clinical trials in Squamous cell carcinoma of the head and neck cancer [29]. Using the samilar approach panel of genes such as *CDKN2A*, *RPRM*, *CDKN1C*, *TP73*, *RUNX3*, *CHFR*, *MGMT*, *TIMP3* and *HPP1* have shown diminished methylation in Radiation Treatment response in esophageal cancer patients and [30]. This panel of biomarkers have the potential to serve as clinical biomarker for esophageal cancer. Further, in another report the hypermethylation of *SERPINB5*, *S100A6*, *CAT* and *BNCI* genes has been been linked to radioresistance in the tumor of lung cancer patients [31]. The similar genomic approach is also being used to identify HGF dependent expression of 20 genes in targeted therapy for glioblastoma patients [32]. Thus, in clinical care settings genomics and proteomics based signatures are sensitive and precise which has the potential to predict accurate clinical outcome.

Proteomics and genomics based cascades of biomarkers has the promise to successfully guide radiation therapy in individual patients and predicting treatment outcome. This approach will allow developing individual therapeutic programs. The biomarker based approach will minimize the failure of RT and will be more effective to ensure extended survivability of cancer patents. Thus, proteo-genomic based study of radiation response in cancer patients may unravel the mechanism and pathways of radiation resistance, which will help in developing radiosensitizers for successful radiation therapy.

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