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Mini-review

Strategies in functional proteomics: Unveiling the pathways to precision oncology

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ABSTRACT

Personalised strategies in cancer care are required to overcome the therapeutic challenges posed by variability between patients and disease subsets. To this end, enhanced precision tools must be developed to describe the molecular drivers of malignant proliferation. Such tools must also identify druggable targets and biomarkers in order to provide essential information regarding drug development and therapeutic outcome. Here we discuss how proteomics-based approaches provide a set of viable methodologies capable of delivering quantitative information throughout the main stages of personalised oncology and a ratiometric platform that delivers systems-wide methods for drug evaluation.

Introduction: a new era for precision oncology

With a clear message from Barack Obama on the Precision Medicine Initiative (PMI), quoting 'innovation and risk-taking' as necessary requirements for medical breakthrough, we are entering into a new era of health care [1]. Encouragingly, the latest developments in *-omic* databases are delivering powerful approaches for stratifying diseases and patients. The integration of genomics, proteomics, metabolomics, as well as formidable bioinformatics tools for the analysis of large sets of data has enhanced the prospects for precision medicine [1]. One of the two main components of the proposed initiative is a near-term focus on cancers. According to the American Society of Clinical Oncology (ASCO) 2015 report on the state of care in the US [2], 68.5% of cancer patients now survive beyond five years after diagnosis, an improvement of 20%, spanning 40 years of research and development, making oncology the most exciting field for applying a personalised approach. Cancers occur often and targeted therapeutics, including immunotherapy, have so far improved overall survival rates in some disease subtypes. The strategy for precision medicine in oncology aims at overcoming the limitations imposed by the inadequate understanding of biological function. With the combination of pan-*omic* data on one hand and the growing panels of tailored drugs, designed to eradicate and oppose oncogenic driver mechanisms on the other hand [3], the information obtained from individual patients will be important in the design of truly personalised theranostic profiles.

Tailoring cancer care

One of most pressing issues in cancer research today is the identification of reliable biomarkers that accurately depict the molecular phenotype(s) of a cancer and guide treatment. This information is necessary to fully understand the impact of gene and protein functions on malignant phenotype. As outlined recently, a reclassification of cancers is needed to stratify patients according to their molecular mechanisms. Bridging *-omics* data with phenotype will help overcome the complications posed by tumour heterogeneity and the inadequate approaches for monitoring therapeutic responses. In turn, this will help standardise protocols for big data analyses and eventually improve therapeutic outcome [1,3–5]. Clinical implementation of biomarker-based therapies is limited by the accuracy of the laboratory platforms used for biomarker identification, heterogeneity of biospecimens [6], and lack of standardised methods for targeted drug development. Here, we will outline some of the benefits of effective molecular characterisation of malignancies through *-omic* approaches [4,6,7]. We will focus on the use of proteomics methodologies and discuss their ability of identifying oncogenic signalling pathways, pinpointing the mechanisms of action of pharmacological compounds and evaluating drug response, thus overcoming in part the difficulties in bench-to-bedside translation of personalised therapeutics. To meet the emerging requirements in translational oncology, current strategies must include a significant amount of feedback between stages of therapeutic development (Fig. 1). Proteomics tools can help streamline this feedback and provide a range of complementary methodologies. Probably the best

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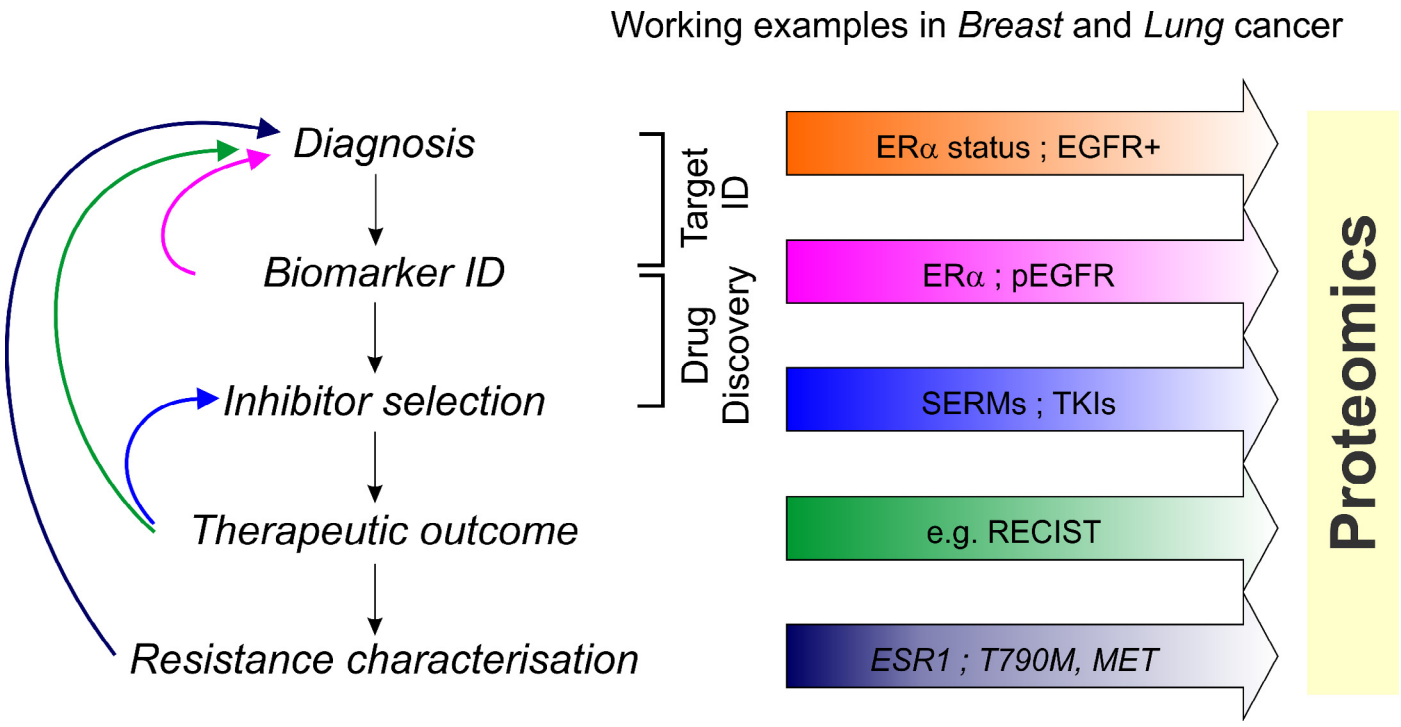

Fig. 1. Rationale for designing and testing proteomics-based personalised therapeutic strategies. An initial cohort of cases needs to be classified according to its molecular characteristics, or biotype. A range of biomarkers need to be identified and validated that represent the said biotypes, to this point feedback between the two stages is required. A drug discovery platform then leads to synthesis and validates a range of inhibitor compounds that require testing. Proteomic analysis of therapeutic outcome can further help in the classification of the diagnostic biomarkers where sensitive and resistant biotypes can be distinguished.

understood examples of successful targeted therapeutics can be found in lung and breast cancers, where disease subtypes [8] have been successfully linked to the expression of cell surface receptor tyrosine kinase biomarkers belonging to the ErbB family such as the epidermal growth factor receptor (EGFR) [9,10], the human epidermal growth factor (HER2) and the nuclear receptor superfamily member estrogen receptor α (ERα) [11,12].

Understanding signalling in breast cancer

Successful design strategies have to benefit from previous learning experiences because the landscape of molecular phenotyping is constantly evolving. On a positive note this means decision making can now happen faster and increase efficiency in drug development. Breast cancer provides a good example because the molecular basis of the ERa positive subset is reasonably well understood and a range of targeted compounds are available. ER expression at low levels is a feature of healthy breast tissue and estrogen signalling is key to normal breast development [13]. Two human genes, *ESR1* and *ESR2*, encode the two known subtypes of ER, namely ERα and ERβ respectively. In the normal breast, both isoforms are equally expressed. Estradiol (E2) binding to ERα in the normal breast results in increased proliferation and reduced apoptosis, whilst E2 binding to ERβ has opposing effects [14]. Recent findings have highlighted the interactome of unbound ERα and ERb, suggesting new roles for nongenomic ER signalling [15]. Over three quarters of diagnosed breast cancers are ERα-positive, characterised by an overexpression of ERα, with significantly lowered expression of ERβ [16–18] and estrogen-dependent proliferation [17], with removal of estrogen leading to tumour regression [18]. The mitogenic role of ERα activity has been established to occur via several mechanisms, both at genomic and non-genomic levels. Successful therapeutic strategy, however, is often a compromise between a clearly defined function required by cancer cells and the synthesis of inhibitor molecules that target it. Breast cancer patients diagnosed at a primary stage with no evidence of metastasis undergo surgery. Despite this, 50% of women die as a result of metastatic disease, even after surgical removal [19]. Successful therapy for breast cancer, with good Overall Survival (OS) and Progression-Free Survival (PFS), is largely reflected by the response to hormonal therapy, where the mechanisms of action of estrogen modulators are fairly well understood. Different methods of estrogen deprivation were demonstrated as potential ways to treat ERα-positive cancers [16]. Because of this, ERα expression has been long established as a good prognostic factor in patients [20]. The current accepted anti-estrogenic therapies fall into three main categories: Estrogen Selective ER Modulators (SERMs) bind to ERα and induce conformational changes differing from those induced by estrogen-binding [16]. The most well-known example of a SERM is Tamoxifen [18], clinically used postoperatively in women having surgical resection [19]. The E2-ERα interactome has been recently described to include myosin and pyruvate dehydrogenase alpha, where SERM treatment significantly affects ERα nuclear interacting proteins [21]. Selective ER down-regulators (SERDs) are pure anti-estrogens, binding to ERα and inhibiting its activity [18]. Aromatase Inhibitors (AIs) block the peripheral conversion of androgens to estrogen, and therefore reduce overall circulating estrogen levels. Due to the nature of their mechanism, AIs are much more effective in postmenopausal patients than premenopausal patients [16]. Almost two thirds of patients with ERα-positive metastatic breast cancer respond well to anti-estrogenic therapy as a first-line treatment and have a period of 6-12 months disease progression-free survival [11]. The principal failure of estrogen-deprivation therapy is 'innate resistance' occurring in one third of cases, and up to one quarter of initial responders develop 'acquired resistance' [11]. Interestingly, genomic analysis points to an increase in *ESR1* copy number as a reflection of clonal selection induced by the treatment, pointing to expansion of an ancestral clonogenic population as a mechanism of resistance [22]. Therefore, it is necessary to develop new targeted therapies to tackle resistance mechanisms and identify biomarkers linked to innate resistance.