LETTER TO EDITOR

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Biomarkers in cancer: is 'omices' the way to go

Biomarkers, as indicators of normal biological or pathogenic processes or pharmacological responses to a therapeutic intervention (1), have been reported to be useful prognostic and predictive markers of cancer diseases (1, 2). The past decade has witnessed major advances toward biomarker discovery; however, only a few biomarkers have made their way into clinical routine such as estrogen receptor (ER) and human epidermal growth factor receptor 2 (HER2) (2). The ER-positive patients with breast cancer respond to ER antagonist, Tamoxifen; whereas ER-negative patients do not benefit from Tamoxifen treatment. HER2-positive patients respond well to a humanized monoclonal antibody against the extracellular domain of HER2, Herceptin, whereas HER2-negative patients do not.

The study of biomarkers has gained impetus in part due to advances in high-throughput technologies such as microarray-based genomics, mass spectrometry-based proteomics, and next generation sequencing concomitant with the development of advanced bioinformatics tools. These high-throughput techniques commonly referred as 'omices' have been vital in our understanding of the molecular regulatory pathways and networks involved in specific disease pathogenesis and in examining complete complements of genes or proteins. Other potential areas in 'omics' include transcriptomics, metabolomics, metabonomics glycomics, interactomics, kinomics, and microRNAomics.

The global high-throughput techniques have been actively applied to the molecular analysis of various human cancers such as bladder, colorectal, breast, stomach, and liver cancers and leukemias. However, high-throughput genotyping or proteomic studies have not been reported comprehensively from the Arab world including Libya. In order to maximize progress in research with a vision to improve the health standards nationwide, we need to move forward in a collective and dedicated manner and push for the development and application of innovative technologies in national research institutions. The goal is to implement those technologies in obtaining the disease-relevant knowledge that can be tailored for specific diagnostic or therapeutic purposes. Once this has been achieved, the research findings may be translated into clinical applications, for example, by providing new biomarkers for early disease detection (diagnostic markers), survival outcome (prognostic markers), treatment responses (predictive markers), and disease recurrence (monitoring markers) specific for the population (3, 4).

In the days of 'personalized medical care', identification of population-specific biomarkers constitutes a road-map that may be harnessed for achieving short-term and long-term goals of personalized medicine. We recently showed significant differences at the genomic and protein level when the comparison was made between Saudi and non-Saudi populations at the Center of Excellence in Genomic Medicine (CEGMR), Jeddah, Saudi Arabia (5, 6). These studies warrant investigation in other parts of the Arab world. Currently, only a few clinical biomarkers and specific diagnostic tests are available across the globe pointing to the need, in general, for the development of novel biomarkers in many areas of health care. Without specific and reliable biomarkers, diseases such as cancer will remain undetected early-on that will in turn affect therapeutic response in the cancer patients (7).

Measurement of the expression of genes (mRNA expression) such as microarray and quantitative polymerase chain reaction (PCR) have been well developed and extensively used in genomics approaches of biomarker studies. Affymetrix and Agilent-based microarray platforms are widely used for expression analysis. Array-based comparative genomic hybridization (aCGH) is now accepted technology to determine copy-number variations of the whole genome in a single experiment. It is presumed that a CGH will replace conventional cytogenetics (karyotyping and fluorescent in situ hybridization, FISH) for diagnostic purposes. Massively parallel sequencing or next generation sequencing (NGS) technology is another addition to genomic approaches. Mass spectrometry (MS) is the major technology used in proteomics approaches of biomarker studies. Label-free or labeling approaches such as those based on SILAC can be utilized for quantification followed by multidimensional liquid chromatography (LC) coupled to mass spectrometry (MS) based on electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI) ion sources. In addition to genomics and proteomics approaches, pharmacogenomics and metabonomics can address studies in response to a variety of stimuli including drugs. It may be important to mention here that all these methods are incomplete in identifying novel biomarkers without powerful supercomputing analysis methods, artificial intelligence-based tools, and statistical tools.

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The question we should be addressing is: which technologies are we going to adopt to get the best results in terms of biomarkers? Mass spectrometry-based clinical proteomics has an advantage of enabling researchers to work on the level of gene products, the proteins, which are more dynamic and complex than genome. The studies based on DNA or RNA becomes equally important for molecular diagnostics when dealing with clinical samples. In this direction, high-throughput sequencing technologies (next generation sequencing or NGS) are currently being utilized for targeted sequencing of candidate genes or genomic intervals to perform sequence-based association studies since they are able to generate three to four orders of magnitude more sequence than the previous methodologies. Furthermore, detection of single nucleotide polymorphisms (SNPs) and other novel variants that have been reported as essential to predispose individuals to neoplasms gives NGS technologies an added advantage. Genome-wide SNP arrays can be utilized to investigate chromosomal defects and molecular abnormalities and address the issues of clonality in human cancers that may be of familial type (e.g. familial breast cancer or familial myeloproliferative neoplasms). While these technologies may work at the individual level in addressing certain problems, integrative approaches seem more feasible in terms of biomarker discovery.

In the above context with rapid developments in the high-throughput technologies, the other question is: are we able to bridge the gap between the 'bench and the bed-side' by enhancing cooperation among clinicians, research scientists and computational biologists? This becomes entirely essential in particular, with a massive scale of data generated using high-throughput technologies along with the number of different protocols, platforms, and analysis methods that make these studies difficult for clinicians to comprehend. Another essential factor that will have a direct impact on the specificity and sensitivity of a biomarker is proper and adequate sample handling procedures. Clear-cut policies and protocols need to be formulated for sample handling and storage among various collaborative centers in order to achieve reliable and reproducible results.

In summary, we strongly believe that emphasis on research innovation toward biomarker discovery and education will continue to alleviate human suffering from common diseases thereby providing better health care.

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