Phage Display Libraries in Sequelization of Autoantibody Signature Analyses in Cancer Immunomics

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Editorial

In current researches in clinical chemistry, an increasing number of projects are utilizing autoantibody signatures to test their diagnostic and prognostic values for cancer. For various types of cancer, it has been established or suggested that circulating immunoglobulins from the sera of cancer patients contain a repertoire of antibodies elicited against the tumor [1]. Interest of researchers toward this topic has been ignited partly by the findings that production of autoantibodies against tumor-associated antigens may precede clinical confirmation of tumors by several months or years [1]. Beyond their potential usefulness for cancer diagnosis, autoantibody signatures may show usefulness in occasions where a fine discriminatory power is required, such as inference of cancer stages. In the present issue of our journal, Partin et al report the performance of the panel of ten phage-peptides recognized by autoantibodies from prostate cancer patients in discriminating patients with prostate cancer of advanced stages (Gleason score 7 or greater) from those with Gleason score 6 [2].

Phage display strategy can enrich autoantibody-binding peptides from a pool of peptides derived from cDNA as well as from a pool of combinatorial peptides [3]. Of note, the phage cDNA library used in Partin et al was the same as the one used in Wang et al [4] and Schipper et al [5]. Wang et al conducted iterative biopanning followed by phage-peptide microarray analyses and identified autoantibody biomarkers that can be used for screen of prostate cancer [4]. The 22-phage peptide panel performed well to discriminate patients with an intermediate range of PSA (4-10 ng/mL) from healthy controls. Intriguingly, of the 22 selected peptides, 17 were untranslated region or out of frame in the coding sequences of known genes. In Schipper et al [5], biopanning and subsequent analyses led to 62 peptides, but the authors’ training analyses led to a logistic regression model based on eight peptides that are totally different from those selected in Wang et al [4]. Three of the eight peptides were from the products of androgen response genes or their regulators. The panel of the eight clones discriminated the PCA patients from healthy controls with area under the curve (AUC) of 0.69. Of note, the phage display strategy typically translates to beads-based microarray approaches usually lead the authors to focus only on ~10-20 candidates autoantibody-binding peptides. Several rounds of biopanning allows enrichment of autoantibody-binding peptides.

It is of clinical interest to consider overall usefulness of phage display in comparison with protein microarray strategies. For both strategies, typical sensitivities of individual autoantibody biomarkers are not high (~10-25%) although their specificities are high. Both approaches usually lead the authors to focus only on ~10-20 candidates TAAs or peptides. To my knowledge, phage-display and protein microarray performance have not been directly compared in terms of the performance. Once a panel of useful clones is established, the phage display strategy typically translates to beads-based microarray strategies. So, this comparison is not about their running costs in large-
scale studies, but about the costs for obtaining a good panel of auto-
antity-binding peptides.

Of note, while it takes one or two weeks to prepare a phage library
from tissues or cells, the same library can be shared by related studies.
So, it is understandable that one library can serve many analyses that
utilize diverse combinations of sera from patients and controls. For
example, Zhang et al recently used the sera from patients of HBV and/
or HCV infection as controls in the analysis of hepatocellular carcinoma
serum biomarker screening based on a random phage display strategy
[10]. Thus, phage display strategies seem to expedite researchers to
try to see the performance of the panel of peptides in various related
settings at low cost.

It is of interest to compare performance of combinatorial peptide
phage libraries as opposed to cDNA phage libraries. In theory, a
recombinant peptide library can cover more diverse sequences in an
unbiased manner than cDNA library, but an epitope may consist of
peptide portions separated in sequence or its recognition may depend
on protein folding stabilized by flanking sequences. Future studies may
focus on comparison among various phage display strategies.

By way of the random peptides approaches, my personal question
is directed to the fact that the peptide clones that are enriched by a
phage-display method and show diagnostic usefulness often include
protein products of untranslated region of genes and out-of-frame
cDNA fragments [4]. Somehow, such apparently meaningless peptides
work well as autoantibody-binding antigens, so it would be interesting
to envisage that the repertoire of autoantibodies generated in cancer
patients could have amazingly high complexity possibly due to
anomalous ways of protein degradations that may lead to autoantibody
generation against epitopes that are normally hidden.

It is also important to recognize that such high-throughput analyses
are enabled by a number of supports including organization and
management of bioresources. For future retrospective cohort analyses
on earlier stages of cancers, it is crucial to obtain and reserve serum
samples not only from cancer patients but also from healthy subjects.

I am often impressed with frequent revisions of textbooks of
clinical chemistry compared to those of biochemistry and physiology,
and reason that this reflects the multidisciplinary nature of clinical
chemistry encompassing practical importance as well as biomedical
understanding. Until a decade ago, however, we had little need to talk
about autoantibody cancer markers other than anti-p53 in the classes
on clinical chemistry [11]. Given the recent findings signifying an
extraordinarily rich source of information in autoantibody signatures,
high-throughput analyses of autoantibody signatures may become a
basic knowledge of future students.

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