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A Gold Key to Open the Door to Archival Biomedical Tissue Treasure

Editorial

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Formalin-fixed, paraffin-embedded (FFPE) tissue sections have widely been adopted for more than a century as the standard method for morphological study, particularly in the field of diagnostic pathology, most of the criteria for pathological diagnosis are established by the observation of FFPE tissue sections. With remarkable achievements in morphologic research field during the past one more century, FFPE tissue samples have been accumulated worldwide that are accompanied with complete clinical data including follow-up results of treatment, or, experimental data collected previously, resulted in an invaluable resource of research. Three more decades ago, immunohistochemistry (IHC) started to show its power and beauty in the field of histopathology, however, at the early stage it was largely limited on frozen tissue sections only. Formalin fixation masks the proteins (antigen) in the tissue sections that unfortunately become inaccessible for antibody in IHC. Numerous scientists urged to find a way to apply IHC staining on FFPE tissue sections based on a dream that formalin-modified proteins may be retrievable.

The dream became true in 1991 when antigen retrieval (AR) technique was invented [1]. AR is so simple that it just needs to boil the archival FFPE tissue sections in water with microwave oven or any conventional heating methods prior to IHC staining procedure, while it is so effective to achieve excellent IHC staining results. Since then, hundreds and thousands articles all over the world have been published to demonstrate the great impacts of AR technique in the field of morphology [2-5]. It has been recognized that the AR technique provides a gold key to open the door of an invaluable treasure for biomedical research based on a great number of FFPE tissue blocks, accompanied by known patients' follow-up data as mentioned above, providing an extremely valuable approach for translational clinical research and basic research that cannot easily be reproduced. Therefore, the AR technique has been credited as a revolutionary breakthrough in pathology and a milestone in IHC [5-7].

Following the wide application of AR in immunohistochemistry (IHC), AR was also adopted in immunoelectron microscopy (IEM), in situ hybridization (ISH), TUNEL, etc., It can also be used as a blocking procedure to avoid cross antigen/antibody reaction during multiple IHC staining process [2-5]. Wide application of AR-IHC in histology, pathology, veterinary medicine as well as other fields with respect to morphology have led to several critical issues in further study along the line in terms of quantitative IHC as well as optimal condition for combined application of IHC and other histochemical staining methods [3, 4, 8].

Based on the similarity of formalin-induced chemical modification between proteins and nuclei acids [9], a serial studies performed at our laboratory have demonstrated the successful application of AR technique in extraction of protein, DNA/RNA from FFPE tissue sections [10-12]. These studies have indicated that AR technique may be a necessary step in any new techniques of molecular biology whenever they involve FFPE tissues. Therefore, we believe that AR is the gold key for the FFPE tissue resource worldwide. Exactly as pointed out by Taylor that the AR technique is "A huge bonus, literally unlocking the riches of a resource, that otherwise was simply discarded following diagnostic use" [13]. This "bonus" has increasingly been extended following a serial of novel molecular techniques that are rapidly explored day-by-day. Interestingly, at the beginning of application of these novel molecular techniques, exactly through an approach just as that happened in IHC from limited use in frozen tissue sections and gradually extending the use on FFPE tissue sections based on a simple and effective AR technique [3, 4, 14, 15], all new techniques are used in fresh tissue samples at the beginning, then shifted to use FFPE tissue samples based on the test battery approach to create an optimal protocol of AR principle. The reasons why most, if not all, novel techniques requiring extending use for FFPE tissue are based upon not only the above-mentioned archival FFPE tissues being invaluable resource in basic and clinical research, but also numerous difficulties and limitations while using fresh or frozen tissue samples [16]. Recent successful application of AR technique in imaging mass spectrometry (IMS) on FFPE tissue section has provided an excellent example showing the process of shifting IMS from fresh to FFPE tissue section. First of all, the Experts of IMS are attracted by great achievements in AR-IHC, and have recognized that FFPE tissue is an irreplaceable research source for current personalized medicine. Scientists are gradually aware of the significance of heat-induced AR that is the key to open the door to FFPE tissue samples for application of

any new techniques. Recently, several investigators documented their successful application of IMS in FFPE tissue sections based on numerous experiments mimicking the approach of test battery used in AR-IHC in the past two decades. In the Caprioli's Laboratory, they emphasized the critical meaning of two basic factors, heating condition and the pH value of AR solution for the AR technique in the IMS when used to achieve a satisfactory IMS map of proteins distributed in FFPE tissue section [7]. Gustafsson et al [18] compared two solutions, Tris-EDTA and citric acid, as the retrieval solution for IMS analysis of FFPE ovarian cancer tissue sections, and found that their method using citric acid buffer at pH 6.0 with boiling heating condition gave better results based on careful comparison among matched fresh and FFPE ovarian cancer tissue sections, and FFPE tissue sections with heating or without heating treatment. They emphasized that this heat-induced AR protocol for IMS is still in developing. Obviously, it needs more experimental work in achieving satisfactory results when testing a new technique on FFPE tissue sections based on using AR technique. Since the ongoing IMS technique that has been credited as a new tool for tomorrow's morphology in a molecular age [19-21], successful application of AR in IMS provides a valuable research future for FFPE tissue treasure [22].

Today, the gold key to open the door for FFPE tissues has been holding in all scientists' hands who are going to practice new techniques on FFPE tissues. With successful application of AR technique, there have been a twin of major achievements in AR-based techniques in protein science: IHC and tissue proteomics. In consideration of advantages and disadvantages for IHC and tissue proteomics, abundant publications have demonstrated that combining use of IHC and tissue proteomics is the most powerful way to discover biomarkers to reach the goal of personalized target treatment currently [4, 23, 24]. With the unique advantage of morphological analysis based on microscopy, IHC can be used to compensate for lack of cellular localization of proteins indicated by tissue proteomics, although thousands proteins being identified by proteomics that has been a convincible demonstration to indicate proteomics being high throughput sensitive method. Focusing on this combining use of two techniques, a philosophy with respect to development of modern morphology will be established based on combining several modern techniques to create radical changes in traditional morphology. Although prediction of future is difficult, at a foreseeable future, morphology will continue to play a critical role in biomedical science. The sharp localization characterized by morphology is irreplaceable. Thus, morphology will be revolutionized by combining with other molecular techniques continuously to become modernized molecular morphology.

Conclusion

AR technique, as a gold key to open the door for FFPE tissue treasure for modern techniques, will start a new field in the future side-by-sidely with progression of modern molecular morphology.

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