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Immunohistochemistry in Cancer Diagnosis: A Review

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ABSTRACT

Immunohistochemistry in cancer diagnosis holds great potential to improve patient's outcomes through enhanced diagnostic accuracy and more effective treatment strategies. Antigen-antibody interactions is one of its main objectives that utilizes the specific binding of antibodies to cellular antigens allowing for the precise identification and localization of specific proteins within tissue samples. However, there exist practical hitches in the form of tissue fixation, epitope retrieval, and antibody quality. It is crucial to continue streamlining the techniques and scoring systems to guarantee their reliability in various contexts. Understanding the interactions is pivotal for the accurate diagnosis, prognosis, and future perspectives. As technology continues to advance and our understanding of cancer biology deepens, immunohistochemistry will remain an invaluable tool for precision in cancer diagnosis.

KEYWORDS: Principle of Immunohistochemistry, Cancer diagnosis, Diagnostic Biomarkers

INTRODUCTION

With millions of new instances being diagnosed each year, cancer continues to be a major problem for world health. In order to create effective treatment strategies, a precise cancer diagnosis is essential, and Immunohistochemistry (IHC) has emerged as a resourceful technique in the field of oncology, playing a pivotal role in the diagnosis and treatment of various cancers. [1] In this challenging setting, Immunohistochemistry (IHC) shines as a ground-breaking and revolutionary force. With the accuracy of a surgeon's scalpel, it cuts through the darkness of cancer to uncover hidden complexity within the damaged tissues enabling the classification of cancers into various subtypes and assisting in the selection of effective treatment approaches, this technique also offers insightful information about the molecular properties of tumors. [2]

The significance of IHC in cancer diagnosis becomes evident in its multifaceted applications. By profiling the expression of receptors such as estrogen and progesterone receptors in breast [3], HER2/neu in breast cancer [4], Quantitative assessment of the heterogeneity of PD-L1 expression in non–small-cell lung cancer [5], IHC empowers clinicians to make informed decisions regarding the choice of targeted therapies, hormone therapy, or immunotherapy. In addition, IHC is a utility in assessing the effectiveness of chemotherapy. [6]Furthermore, IHC holds promise for individualized cancer therapy which adapts therapeutic regimens to a person's particular molecular profile. Moreover, the technique identified prospective therapeutic targets by detecting particular protein biomarkers, such as the over expression of the EGFR in non-small cell lung cancer (Lindeman et al., 2008). Oncologists may now choose the best medications and therapeutic modalities for each patient thanks to this method which cleared the path for the development of precision medicine. [2]

However, the true extent of IHC's contributions in cancer detection and treatment continues to change despite its extraordinary promise. The area of oncology is poised to provide patients with more individualized and efficient cancer treatment as researchers identify new biomarkers and perfect the technique. Consequently, the present study examined immunohistochemistry and its future prospect in the detection and management of cancer, diving into how it would aid in uncovering important markers and targets within cancerous tissues, emphasizing its fundamental ideas, practical uses, and implications for patient care.

HISTORICAL OVERVIEW

Immunohistochemistry is a pivotal technique in the field of pathology and oncology that enables the visualization of specific proteins or antigens within tissue specimens. This section provides an overview of IHC, its principles, applications, and significance in diagnosing and characterizing cancer. Taylor et al. [2] emphasized the transition from visual scores to objective grading systems with the introduction of quantitative immunohistochemistry which plays a crucial role in pathology.

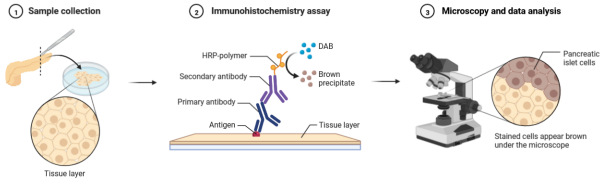

Figure 1: llustrates the Immunohistochemistry technique

The development of immunohistochemistry in the detection and treatment of cancer is evidence of the tremendous progress of medical research and its profound influence on oncology. This section offers an examination of the evolution of IHC over time, highlighting the critical turning points that have influenced its relevance today. Immunohistochemistry originated in the late 19th century and is a branch of the larger science of immunology. Albert Coons and associates first proposed the idea of employing antibodies to identify particular antigens in the 1940s. [7] Their groundbreaking study showed that antibodies could be used to localize antigens within tissue specimens which lay the groundwork for the creation of IHC techniques. However, it was not until the 1970s that this groundbreaking work began to be effectively applied in the context of cancer diagnosis. The application of IHC to cancer diagnostics gained momentum with the discovery of monoclonal antibodies. In 1975, Georges Köhler and César Milstein developed a method for producing monoclonal antibodies, allowing for the generation of highly specific antibodies that could target cancer-related antigens. [8] This marked a significant leap forward in the field of IHC, enabling the development of more precise and reliable assays for detecting cancer biomarkers.

Over the course of the 1980s and 1990s, scientists improved IHC methods and discovered an increasing number of protein markers linked to cancer. For instance, IHC proved helpful in determining the expression of the estrogen and progesterone receptors in tumor tissues, which have been recognized as important biomarkers in breast cancer. [1] Another significant development was the identification of HER2/neu overexpression in gastric and breast malignancies, which opened the door for targeted treatments like trastuzumab.

In the 21st century, IHC continues to evolve, and its role in personalized cancer treatment has become increasingly significant. The discovery of new biomarkers, such as programmed death-ligand 1 (PD-L1), has revolutionized immunotherapy for various cancers. [5] In addition, advances in digital pathology and image analysis have streamlined the interpretation of IHC results, making it an even more accessible and powerful tool for pathologists.

PRINCIPLE OF IMMUNOHISTOCHEMISTRY

IHC relies on the principle of antigen-antibody binding. Tissue sections, usually obtained through biopsies, are fixed on slides and treated to preserve the structural integrity of the tissue.Figure 1 These specimens are then subjected to a series of steps involving deparaffinization, antigen retrieval, and blocking of nonspecific binding sites.Figure 2 Primary antibodies, highly specific to the target protein, are applied to the tissue sections. Subsequently, secondary antibodies, conjugated to a visible marker such as an enzyme or a fluorochrome, are introduced. If the primary antibody binds to the target protein, the secondary antibody will also bind, allowing the visualization of the protein of interest. [5, 9]

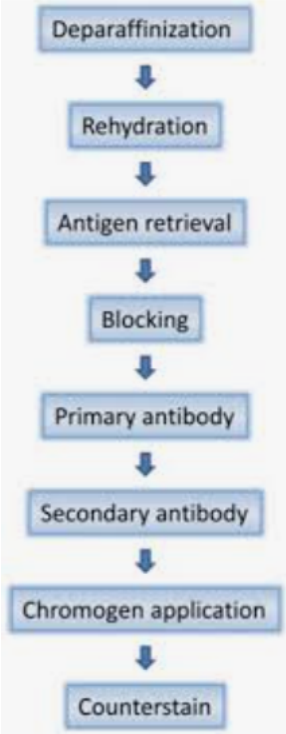

Figure 2: mmunohistochemistry flow chart. [10]

ANTIGEN-ANTIBODY INTERACTIONS IN IMMUNOHISTOCHEMISTRY

At the heart of IHC is the crucial interaction between antigens and antibodies forming the basis for its success in various medical and research applications. In IHC, antigens, which are proteins of interest, are targeted using antibodies. These antibodies, designed to bind selectively

to their corresponding antigens, play a pivotal role. [11]The basis for IHC's ability to locate and visualize particular proteins within tissue samples is antigen-antibody binding. An immunocomplex, which can be identified and seen, is created when an antibody attaches to its target antigen in the tissue slice.Figure 3 IHC is distinguished by the specificity of antigen-antibody interactions. The method can yield very specific and accurate findings by choosing antibodies that accurately detect the protein of interest. [7] For instance, the exact binding of antibodies to these particular protein targets is necessary for the evaluation of hormone receptor status in breast cancer, including the ER and HER2 receptors. [2]

Furthermore, antigen-antibody interactions are central to the ability of IHC to discriminate between different cell types and identify pathological changes in tissues. [12] This capability has far-reaching implications, particularly in the diagnosis, prognosis, and treatment of diseases, such as cancer. Essentially, the specificity of antigen-antibody interactions determines how well IHC works. Researchers and pathologists can investigate the complex molecular landscape of tissues and diseases thanks to the interaction between antigens and antibodies. This study ultimately yields important insights into the underlying mechanisms of a variety of pathological situations. [5] Consequently, the antigen-antibody interaction in immunohistochemistry (IHC) is a fundamental concept in pathology that propels improvements in the precision of diagnosis and customized treatment.

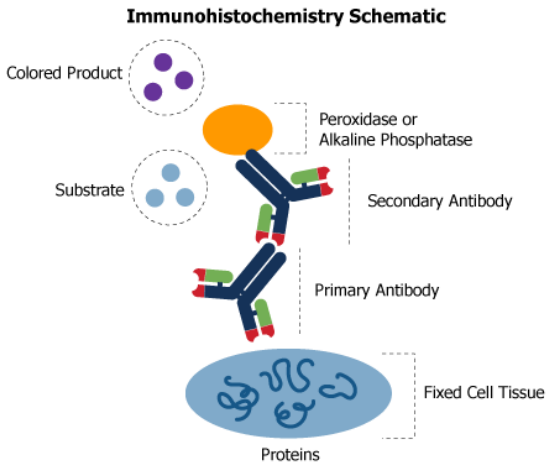

Figure 3: Imunohistochemistry schematic diagram

IMPORTANCE OF ANTIGEN-ANTIBODY INTERACTIONS

The antigen-antibody interactions in IHC are the cornerstone of this powerful technique, enabling the specific and sensitive detection of proteins within tissue samples. Understanding the significance of these interactions is pivotal for the accurate diagnosis, prognosis, and research of various diseases, especially in the context of cancer. Some importance of this interaction includes:

- **Specificity and Selectivity**: Antibodies used in IHC are designed to specifically recognize and bind to a particular antigen. This exquisite specificity ensures that only the target protein is detected within the tissue sample. Without this high specificity, cross-reactivity with unrelated proteins could lead to misleading results. [5]
- **Signal Amplification:** In immunohistochemistry, signal amplification is based on the interaction of antibodies with antigens. A single antibody-antigen contact can provide a detectable signal by a variety of labeling approaches, such as enzyme-linked antibodies or fluorescent tags, increasing the assay's sensitivity. [11]
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- **Localization of Proteins**: Antigen-antibody interactions enable the precise localization of proteins within tissue sections. This spatial information is crucial for understanding the distribution of specific biomarkers, aiding in the diagnosis and prognosis of diseases, including cancer. [1]
- **Quantification**: Accurate quantification of protein expression levels is achievable due to the specificity of antigen-antibody interactions. Researchers and pathologists can assess not only the presence of the target antigen but also its relative abundance. [13]
- **Research and Clinical Applications**: The ability to perform IHC with high specificity transformed the field of cancer research and clinical diagnostics. It allows for the identification of tumor markers, determination of receptor status (e.g., HER2 in breast cancer), and the classification of different cancer subtypes. [11, 14]

NAVIGATING THE INTRICATE STEPS INVOLVED IN IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) is the multifaceted technique that allows us to peer into the microscopic world of tissues and glean vital information about their composition. This investigative method, akin to following a carefully crafted roadmap, involves a series of intricate steps, each essential in unraveling the cellular mysteries that hold the key to disease diagnosis and understanding. This technique involves a series of expertly planned steps that culminate in a stunning visual work of art; think of it like a trail of clues leading to the discovery of buried treasure. The following steps are involved in performing an IHC test:

1. **Tissue preservation:** Human and animal biopsies, or whole organs, are collected for preservation and

IHC analysis, depending on the requirements of the researcher. Tissue must be rapidly preserved to prevent the breakdown of cellular protein and degradation of the normal tissue architecture. Often, the tissue is perfused in vivo or in vitro, or simply rinsed free of blood, prior to fixation/preservation. [10]

2. **Tissue sectioning**: Thin sections of tissues are attached to individual glass slides. Multiple small sections can be arranged on a single slide for comparative analysis, a format referred to as a tissue microarray. [10]
3. **Blocking:** To reduce background staining in IHC, samples are incubated with a buffer that blocks the non-specific sites to which the primary or secondary antibodies may otherwise bind. [10]
4. **Primary antibody incubation**: The primary antibody is added to the sample and allowed to bind to the target antigen. [10]
5. **Secondary antibody incubation:** A secondary antibody, which is conjugated to an enzyme or fluorophore, is added to the sample and allowed to bind to the primary antibody. [10]
6. **Detection:** The target antigen is detected through either chromogenic or fluorescent means, depending on the experimental design. [10]

CANCER BIOMARKERS

Cancer biomarkers are molecules or genetic alterations that can be objectively measured and evaluated as indicators of normal or pathological processes within an individual. These biomarkers play a crucial role in the diagnosis, prognosis, and treatment of cancer. In recent years, the identification and characterization of cancer biomarkers revolutionized the field of oncology, leading to more personalized and effective approaches to cancer management.Figure 4

Diagnostic Biomarkers

Diagnostic biomarkers are utilized to detect the presence of cancer. They aid in early cancer diagnosis, allowing for timely intervention and improved treatment outcomes. For instance, prostate-specific antigen (PSA) is a widely known diagnostic biomarker for prostate cancer. [16] Its measurement in blood helps identify prostate cancer at an early stage.

Prognostic Biomarkers

Prognostic biomarkers are indicators that provide information about a patient's overall cancer outcome, independent of therapy. IHC has played a pivotal role in identifying various prognostic markers in different cancer types. For instance, in breast cancer, the assessment of Ki-67, a proliferation marker, through IHC has been associated with prognosis. [17]Similarly, the expression of programmed death-ligand 1 (PD-L1) in IHC has been recognized as a prognostic factor in multiple cancers, including non-small cell lung cancer (NSCLC) and melanoma. [18]

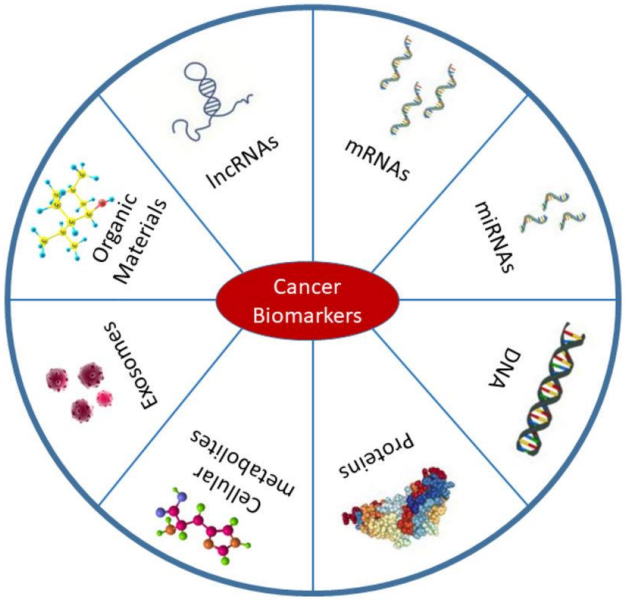

Figure 4: Cancer biomarkers by Wu et al. [15]

Predictive Biomarkers

Predictive biomarkers help determine the likelihood of responding to a specific treatment. In the era of targeted therapies and immunotherapies, the role of IHC in identifying predictive biomarkers is vital. EGFR expression in IHC is predictive of the response to EGFR inhibitors in NSCLC. [19]Likewise, the presence of hormone receptors in breast cancer tissues, as determined by IHC, predicts the potential benefit of hormonal therapy. [20]

IMPORTANCE OF IMMUNOHISTOCHEMISTRY

Immunohistochemistry (IHC) in the field of oncology and cancer research, offers several critical advantages in the diagnosis, prognosis, and treatment of cancer patients. IHC is a technique that utilizes the specific binding of antibodies to cellular antigens, allowing for the precise identification and localization of specific proteins within tissue samples. [21] Its importance includes:

Diagnosis and Subtyping:

IHC aids pathologists and oncologists in accurately diagnosing cancers by identifying key markers that distinguish various cancer types. For instance, the presence or absence of hormone receptors in breast cancer, such as estrogen and progesterone receptors, is crucial for tailoring therapy. [20] Additionally, IHC can help differentiate subtypes of lymphomas, a group of hematological malignancies that require distinct treatment strategies. [22]

Prognostic and Predictive Value:

Beyond diagnosis, IHC also provides critical prognostic and predictive information. Overexpression or absence of specific markers can indicate the aggressiveness of the cancer and its potential to respond to targeted therapies. For example, the assessment of human epidermal growth factor receptor 2 (HER2) status in breast cancer through IHC informs treatment decisions with drugs like trastuzumab. [23]

Personalized Medicine:

With the rise of personalized medicine, IHC has become integral to tailoring therapies. It assists in selecting the most effective treatment modalities by identifying biomarkers. In lung cancer, IHC is used to determine epidermal growth factor receptor (EGFR) mutations, guiding the use of EGFR tyrosine kinase inhibitors. [24]

Research and Drug Development:

IHC also fuels cancer research and drug development. It helps elucidate the molecular underpinnings of cancer, enabling the discovery of new drug targets and the evaluation of treatment responses in preclinical and clinical trials. [25]

SIGNIFICANCE OF BIOMARKERS IN CANCER

Biomarkers play a pivotal role in the field of oncology due to their multifaceted significance. They offer valuable insights into the detection, diagnosis, prognosis, treatment, and monitoring of cancer. [26]The significance of biomarkers in cancer can be summarized as follows:

Early Detection and Diagnosis: Biomarkers enable the early detection of cancer, often before clinical symptoms manifest. This early detection can significantly improve patient outcomes by allowing for timely intervention and treatment initiation. [27]

Precision Medicine: Biomarkers facilitate the era of precision medicine, where treatment decisions are tailored to an individual's unique genetic and molecular profile. This approach maximizes treatment effectiveness while minimizing side effects. [28]

Prognostication: Biomarkers help in predicting the likely course of a cancer, aiding clinicians in determining the prognosis. Patients with poor prognosis may require more aggressive treatments, while those with favorable prognosis can opt for less intensive therapies. [29]

Treatment Selection: Predictive biomarkers are instrumental in treatment selection which provide insights into how a patient is likely to respond to a particular treatment. This ensures advising therapies that are most likely to benefit them. [30]

Monitoring Response: Biomarkers assist in monitoring a patient's response to treatment. Changes in biomarker levels can indicate whether a therapy is effective, allowing for treatment adjustments when necessary. [31]

Minimizing Overtreatment: Through precise diagnosis and prognosis, biomarkers help in avoiding overtreatment. Patients can be spared from unnecessary aggressive treatments when their prognosis is favorable. [32]

Clinical Trials and Drug Development: Biomarkers are essential in the development of new cancer therapies and the design of clinical trials. They help identify suitable patient populations for experimental treatments. [33]

Patient Empowerment: Knowledge of one's biomarker profile empowers patients by involving them in treatment decisions. Informed patients can actively participate in their care. [34]

Cost-Effective Healthcare: By ensuring that treatments are directed towards those who are likely to benefit, biomarkers contribute to cost-effective healthcare by reducing the use of ineffective therapies. [35]

IMMUNOHISTOCHEMISTRY IN CANCER DIAGNOSIS

IHC is an important tool in distinguishing cancer from non-cancerous tissue, as well as providing information on tumor classification, staging, and prognosis. [11]

1. **Tumor Classification**: IHC is instrumental in classifying tumors based on their cellular origins. For instance, the presence of cytokeratins, such as CK7 and CK20, can differentiate between various types of carcinomas, helping to determine the primary site of a metastatic tumor. [36]

2. **Receptor Status**: IHC is crucial in determining the hormone receptor status of breast cancer, such as estrogen receptor (ER) and progesterone receptor (PR), which guides treatment decisions. HER2/neu protein expression is another critical marker, influencing the use of targeted therapies like trastuzumab (Herceptin). [37]

3. **Grading and Staging**: Tumor grade and stage are key factors in prognosis and treatment planning. IHC can assess proliferation markers, like Ki-67, to determine tumor aggressiveness and cell proliferation rates, thus influencing therapeutic strategies. [38]

4. **Mutation Analysis**: In certain cancers, such as non-small cell lung cancer, IHC is employed to identify specific mutations, like EGFR mutations, which have implications for targeted therapy using tyrosine kinase inhibitors. [24]

5. **Metastatic Workup**: When the primary site of a metastatic tumor is unclear, IHC can be employed to identify the tissue of origin. It is particularly useful in distinguishing between primary and metastatic malignancies. [39]

6. **Treatment Response Monitoring**: IHC can monitor changes in protein expression during cancer treatment. For example, monitoring HER2 expression in breast cancer can help in adjusting therapy based on changes in receptor

status. [4]

CONCLUSION

Immunohistochemistry in cancer diagnosis holds great potential to improve patient's outcomes through precision medicine, enhanced diagnostic accuracy, and more effective treatment strategies. As technology continues to advance and our understanding of cancer biology deepens, IHC will remain an invaluable tool in the fight against cancer.

AUTHOR'S CONTRIBUTIONS:

SMG and LF conceptualized and wrote the original draft, edited the manuscript as well as performed the critical literature search and SMG supervised the manuscript. All authors read and approved the final manuscript.

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