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REVIEW

Immunohistochemistry in Dermatopathology: A Review of the Most Commonly Used Antibodies (Part I)☆

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Abstract Dermatopathology includes a long list of disorders, some of which have very similar histopathology. Immunohistochemistry is an important auxiliary tool for diagnosis and differential diagnosis, and for predicting the outcome of many skin tumors. It is also the main technique for determining the origin of a tissue or the differentiation of neoplastic cells. In many cases, immunohistochemistry provides a more accurate diagnosis of the different processes that infiltrate the skin. This review examines the role of immunohistochemistry in studying the differentiation and biological behavior of the majority of tumors that can involve the skin. We review the immunoperoxidase techniques, discuss the utility of the most commonly used antibodies, and highlight a number of diagnostic problems in which immunohistochemistry may be very useful. In each case, the goal is to reach a specific and definitive diagnosis. In the first part of this review, we examine the antibodies that determine the different cell-differentiation profiles of skin tumors.

PALABRAS CLAVE
Dermatopatología;
Inmunohistoquímica;
Citoqueratinas;
Marcadores musculares;
Endoteliales;
Neurales;
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Inmunohistoquímica en dermatopatología: revisión de los anticuerpos utilizados con mayor frecuencia (parte I)

Resumen La dermatopatología incluye una larga lista de entidades, algunas con una histopatología muy similar. La inmunohistoquímica representa una importante herramienta de ayuda en el diagnóstico, diagnóstico diferencial y pronóstico de muchas de las neoplasias cutáneas. La inmunohistoquímica es también la mejor técnica para determinar el origen de un tejido o la diferenciación de las células neoplásicas. En muchos casos la inmunohistoquímica permite un diagnóstico más preciso de los distintos procesos infiltrando la piel. Este artículo revisa el papel de la inmunohistoquímica en el estudio de la diferenciación y el comportamiento biológico de la mayoría de las neoplasias que pueden afectar a la piel. Se revisan las técnicas de inmunoperoxidasa, se discute la utilidad de los anticuerpos utilizados con mayor frecuencia y se presentan una serie de problemas diagnósticos en los que la inmunohistoquímica puede resultar muy útil.

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En cada caso, la finalidad es llegar a un diagnóstico concreto y definitivo. En la primera parte de esta revisión se estudian los anticuerpos que exploran las distintas líneas de diferenciación de las neoplasias cutáneas.

Introduction

Immunohistochemistry has become an essential diagnostic tool in dermatopathology. The term covers a group of immunostaining techniques in which labeled antibodies are used to detect the presence of antigens in cells or tissues. The principle of immunohistochemistry lies in the ability of antibodies to bind specifically to their respective antigens. The resulting reaction can only be visualized when the antibody is labeled with a substance that absorbs or emits light or produces color.

Immunofluorescence techniques rely on the use of fluorescein-labeled markers, which, when exposed to ultraviolet light, emit visible light of varying wavelengths depending on the nature of the compound used. Direct immunofluorescence is used widely in the diagnosis of skin diseases, a field in which it has very specific indications. In particular it is used to diagnose bullous diseases, vasculitis, and certain types of tumors. Although it is more sensitive than immunostaining, immunofluorescence has certain disadvantages, including loss of fluorescence over time, the need for a specialized light microscope, and poor visualization of morphologic features. Furthermore, the resulting reactions need to be photographed each time for documentation purposes.

Immunoperoxidase techniques involve the use of enzyme labels that convert a colorless substrate into a colored one. The most widely used enzymes are peroxidase and alkaline phosphatase, and the most widely used substrates are diaminobenzidine, amino ethylcarbazole, and nitroblue tetrazolium, which, respectively, produce a brown, red, and blue color. These markers can be attached, or conjugated, directly to the primary antibody, or indirectly using secondary antibodies or substances such as biotin and protein A. The range of commercially available antibodies is growing daily and it is now possible to find markers for a broad spectrum of antigens.

Immunohistochemistry has become an increasingly important histopathologic tool over the past 20 years and is now a key part of routine practice. In particular, it is becoming increasingly important for the diagnosis and classification of a growing list of tumors.

Below is a summary of the main applications of immunohistochemistry techniques today:

1 Determination of the origin or degree of differentiation of a tumor
2 Refinement of prognosis
3 Differentiation between benign and malignant tumors
4 Determination of the molecular architecture of a tissue
5 Detection of infectious agents in cells or tissues

Table 1 shows the most common immunohistochemical markers used in dermatopathology, classified by the type of differentiation they are used to detect.

Epithelial Differentiation Markers

Cytokeratins

Cytokeratins are the largest group of intermediate filaments. They are filamentous proteins which, together with other filaments, form the eukaryotic cytoskeleton. They have numerous functions, including maintenance of epithelial structure, protection from injury, and communication with other cytoplasmic components. They are expressed in pairs, with expression patterns varying according to location, and classified numerically from 1 to 20 according to their molecular weight and isoelectric point.

There are 2 major groups of cytokeratins: simple epithelial cytokeratins (CK7, CK8, CK18, CK19, and CK20) and more complex epithelial cytokeratins, such as those found in the skin (CK5/6, CK10, CK14, and CK15). A second classification system distinguishes between acidic (or type I) cytokeratins, which generally correspond to low-molecular-weight cytokeratins (CK9-CK20) and basic (type II) cytokeratins (CK1-CK8), which generally have a high molecular weight. Monoclonal antibodies, with different levels of specificity, have been developed for these different cytokeratins[1] (Table 2).

The pan cytokeratin AE1/AE3 is a cocktail of antibodies that recognizes a wide range of cytokeratins of different molecular weights. It is very useful for identifying epithelial tumors, classifying these by degree of differentiation, and detecting micrometastases. In the skin, AE1/AE3 labels the epidermis, the eccrine glands, and the folliculosebaceous-apocrine unit. It has high diagnostic sensitivity as it is capable of identifying most carcinomas (Fig. 1), even poorly differentiated ones. It also recognizes several epithelial mesenchymal tumors formed by epithelioid cells (e.g., mesothelioma, synovial sarcoma, and epithelioid sarcoma), as these all have cells containing large quantities of intermediate filaments in their cytoplasm. Cytokeratin AE1 recognizes acidic cytokeratins (CK10, CK15, CK16, CK19). It is a characteristic simple epithelial cytokeratin and in the skin the cytokines it recognizes are expressed only in the basal layer of the epidermis.[1,2] Cytokeratin AE3, in turn, recognizes basic cytokeratins (CK1-CK8) and is characteristic of transitional epithelial cells and squamous cell carcinomas. The cytokines are expressed throughout the epidermis.[1,2]

CAM 5.2 recognizes low-molecular-weight cytokeratins in glandular tumors.[3] There are conflicting data in the literature regarding the cytokeratins recognized by CAM 5.2. In early reports, CAM 5.2 was considered to react with CK8, CK18, and CK19.[4] It is now known, however, that it reacts with CK8 and, less strongly but more specifically, with CK7 and also that it does not react with CK18.[5–7] In healthy skin, CAM 5.2 labels the eccrine and apocrine units, but not all the layers of normal epidermis. It can be used to demonstrate the epithelial origin of highly undifferentiated tumors