



Commonly Used Immunohistochemical Stains and Their Diagnostic, Theranostic, and Prognostic Utilities

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Objective

- Learn the importance of immunohistochemistry as an adjunct study in surgical pathology.

Introduction

Immunohistochemistry is a technique based on antigen–antibody binding reaction. It visualizes the distribution and localization of specific antigen or cellular components in tissue sections.

Based on the affinity of mono- or polyclonal antibodies produced in variable species (mostly mouse, rabbit, or goat) to specifically recognize protein epitopes, it helps in recognizing tissue- or cell-specific proteins and can be applied as a direct, an indirect, or a multistep assay. Most of the time a combination of antibodies (“immunohistochemical profile”) is used to confirm a diagnosis.

Diagnostic Use

Organ Diagnosis

- Intestinal differentiation
CDX2
- Thyroid and lung
TTF-1

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- Prostate
PSA, PSA-P
- Lymphoid cells
CD45
- Melanocytic cells
Melan-A, HMB45, S-100
- Germ cells and liver
Alpha-fetoprotein
- Thyroid gland, parathyroid glands, C-cells, beta-islets of the pancreas
Hormones, hormone receptors and secretory vesicles of neuroendocrine (respectively *thyroglobulin, parathormone, calcitonin, insulin, glucagon...*).
- Syncytiotrophoblast
Beta-HCG

Differentiation

- Epithelial
Cytokeratin (*CK1 to CK20*, numerated inversely depending on their molecular weight and basic or acidic character). A combination of CK of low- and high-molecular weight will give an idea on the organ systems from where a tumor might come from (e.g., *CK7- and CK20+*: gastrointestinal tract or *CK7+ and CK20-*: endometrial origin, biliary tract, mesothelioma).
- Hematopoietic
Cluster of differentiation (CD): broadly present types of antigen at the surface of different hematopoietic cells or subtypes of lymphoproliferative disorders (e.g., *CD45* is the common marker of leukocytes). A profile of cluster of differentiation is specific to certain subtypes of leukocytes; Pan-T-cells antigens: *CD3, CD5*; Pan-B-cells antigens: *CD20, CD79a*. Clonality of B-cells: *kappa and lambda light-chains*. Clusters of differentiation are not only present in hematopoietic cells (e.g., *CD56 (or NCAM)* is expressed in some lymphomas but also neuroendocrine tumor cells).
- Mesenchymal
Vimentin: a common marker of mesenchymal differentiation. It can be encountered in other neoplasms such as melanoma, renal cell carcinoma, and mesothelioma.
- Neural
S-100, GFAP.
- Muscular
Smooth muscle actin; desmin (striated fibers).
- Vascular
Endothelial (*CD31, CD34, Factor VIII*).
- Melanocytic
Melan-A; HMB45 (naevus cells or melanoma).
- Neuroendocrine
Hormones, hormone receptors, and secretory vesicles of neuroendocrine organs or (sometimes secreting) tumors (*thyroglobulin, parathormone, calcitonin, insulin, glucagon, or ACTH ...*), tumors with neuroendocrine differentiation (*chromogranin A, synaptophysin, CD56*).

Inflammation

- Immune deposits
Immunoglobulins and complement in inflammatory diseases (e.g., *IgG4* in IgG4-associated inflammatory diseases).
- Subtyping of infiltrating leukocytes
CD3 or CD5: T-cells
CD20: B-cells
CD38 and CD138: plasma cells

Tumor Subtypes

- Mammary carcinoma
E-Cadherin (+: ductal; –: lobular).
- Lung/Pleura malignant tumor
CK7, napsin, EMA, Ber-EP4, TTF-1 (adenocarcinoma) versus *CK5/6, p63* (squamous cell carcinoma) versus *calretinin, CK5/6, mesothelin, thrombomodulin, WT-1* (mesothelioma).
- Ovarian carcinoma
CA125.
- Gastrointestinal and biliopancreatic carcinoma
CA19-9.
- Intestinal adenocarcinoma
CDX-2.
- Adenocarcinoma (vs. other carcinomas)
CEA.
- Squamous cell carcinoma
CK5/6, p63.
- Prostatic carcinoma
PSA, PSA-P.
- GIST
cKIT, DOG1.
- Adipocytic tumors
MDM2; CDK4 in well-differentiated and dedifferentiated liposarcoma.

Infections

- Bacterial
Helicobacter pylori; Mycobacterium tuberculosis; Tropheryma whipplei; rickettsia sp.; bartonella sp.; borellia sp.; Treponema pallidum; staphylococcus sp.; streptococcus sp.; clostridium sp.; Escherichia coli.
- Viral
HSV 1 and 2 (herpes simplex viruses); *CMV* (cytomegalovirus); *EBV* (Epstein–Barr virus); *BK-virus* (Polyomavirus); *HPV* (human papilloma viruses); *HHV* (human herpes viruses); *adenovirus, parvovirus B19; VZV* (varicella zoster virus); *Hepatitis B or C viruses*.
- Fungal and parasitic
Candida sp., Aspergillus sp.; Cryptococcus neoformans; Pneumocystis carinii

- Protozoan
Leishmania; *Toxoplasma gondii*; *trichomonas Vaginalis*; *Trypanosomia sp.*;
Entamoeba histolytica; *Giarda lamblia*

Theranostic Use

The immunohistochemical detection of the following proteins supports the decision for hormonal deprivation or targeted therapy.

- Lung adenocarcinoma
EGFR, ALK, cMET, ROS1, PD-L1
- Breast carcinoma
Estrogen and progesterone receptors, BRCA1&2, HER2, PI3K/AKT, androgen receptor
- Colon adenocarcinoma
EGFR, VEGF, VEGFR, KRAS, NRAS, BRAF
- Gastric adenocarcinoma
HER2, VEGF, VEGFR, EGFR, c-MET, mTOR
- Prostatic adenocarcinoma
PDGFR, HER2, VEGF
- Melanoma
BRAF V600E, NRAS, PD-L1
- Ovarian carcinoma
VEGFR, PDGFR, BRCA1&2, PD-L1
- Renal cell carcinoma
VEGFR, EGFR; PDGFR, HER2, PD-L1
- GIST
cKIT, PDGFR-A

Prognostic Use

- Proliferation marker
Ki-67 is in many tumors a marker of poor prognosis (gastric, pulmonary; prostatic adenocarcinoma)
- Cell cycle markers
Cyclin D-1, p16INK4 in melanoma
- Oncogenes
HER2 in mammary, pulmonary or colorectal carcinoma
Bcl-2 in melanoma
cKIT in GIST, lung adenocarcinoma, melanoma
BRAF in thyroid papillary carcinoma, melanoma, colorectal carcinoma, lung carcinoma
cMET and HGF in testicular tumors
- Tumor suppressors

- p53* is in many tumors a marker of poor prognosis (gastric carcinoma; lung adenocarcinoma; prostate carcinoma)
BRCA1 and 2 in breast carcinoma
PTEN in prostatic adenocarcinoma
- Vascular and lymphatic markers
CD31, CD34, podoplanin in melanoma (better detection of angio- or lymphangiogenesis)
 - DNA mismatch repair
 Microsatellite instability syndrome in colon carcinoma (*MSH6, MSH2, MLH1, PMS2*)
 - Neuroendocrine differentiation
 Worse prognosis for prostatic adenocarcinoma
 - Hormone receptors
Androgen receptor for prostatic carcinoma
Estrogen- or progesterone receptors in breast cancer

Further Reading

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