



Tumor markers

Cytokeratins

Analyte Information





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Cytokeratins

Introduction

Cytokeratins (newly called keratins) are proteins from the family of fibrous structural proteins, found in the intracytoplasmic cytoskeleton of epithelial tissue. They maintain the structure of epithelial cells and prevent them from damage or mechanical stress. Cytokeratin monomers assemble into bundles and form tough intermediate filaments.

There are two categories of epithelial cytokeratins: the acidic type I cytokeratins (K9-28) and the basic or neutral type II cytokeratins (K1-8, K71-80). They create heterodimeric pairs of acidic and basic subunits of similar size. Cytokeratins 8, 18, and 19 are the most abundant.

Although the cytokeratin intermediate filament structures are extremely insoluble in water and organic solvents, smaller cytokeratin fragments are soluble and can be found in circulation. Cytokeratin fragments are markers of cell proliferation and their release into circulation is in relation with proliferation and apoptotic cell activity. As they are also present in neoplastic cells, they can be used as tumor markers reflecting activity of epithelial malignancies.

Expression of the cytokeratins within epithelial cells is, at certain extent, specific for particular organs or tissues. Tumors that express cytokeratins include carcinomas, thymomas, sarcomas and trophoblastic neoplasms.



There are several assays that determine cytokeratin fragments:

TPA (tissue polypeptide antigen)	First generation assay, based on polyclonal antibody and directed against cytokeratins 8, 18, and 19
TPS[®] (tissue polypeptide antigen specific)	Based on monoclonal antibodies, determine M3 epitope of cytokeratin 18
Cytokeratin 19 fragment (known also as Cyfra 21-1 – trade mark of company Roche)	Based on monoclonal antibodies, directed against cytokeratin 19
MonoTotal[®]	Based on monoclonal antibodies, directed against cytokeratins 19, 8 and, partially, cytokeratin 18
TPAcyk[™]	Based on monoclonal antibodies, directed predominantly against cytokeratins 8 and 18
UBC[®]	Based on monoclonal antibodies, directed predominantly against cytokeratins 8 and 18 - designed for determination in urine

Cytokeratins – physiological function

Cytokeratins are present in cell fibres called intermediate filaments. The proteins that form intermediate filaments are present in various tissues and can be subcategorized into six types according to similarities in amino acid sequence and protein structure. Acidic cytokeratins (type I) and basic cytokeratins (type II) create the intermediate filaments that are typical for epithelial cells. Acidic and basic cytokeratins associate in a 1:1 ratio to form heterodimers, which assemble into heteropolymeric filaments.

The organization of intermediate filaments and their association with plasma membranes suggest that their principal function is structural - to reinforce cells and to organize cells into tissues. Their name is derived from their 10-nm diameter, what is a size between two other cell fibres - microtubules (24 nm) and microfilaments (7 nm).



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Intermediate filaments are extremely stable. Even after extraction with solutions containing detergents and high concentrations of salts, most intermediate filaments in a cell remain intact, in contrast to microfilaments and microtubules which depolymerize into their soluble subunits.

Assembly of intermediate filaments proceeds through several transitional structures, which associate by lateral and end-to-end interactions. Intermediate filaments are organized into networks and adhere to plasma and nuclear membranes, microtubules, and microfilaments via their binding to proteins (so called intermediate filament - associated proteins).

Cytokeratins – Clinical application

Cytokeratin fragments are produced by both normal and cancerous cells.

Enhanced proliferation activity and turnover of cells results in increased release of soluble cytokeatin fragments into circulation. Thus, in contrast to classical tumor markers reflecting tumor burden, cytokeatins are markers of tumor activity.

Increased levels of cytokeatin fragments can be found also in general infections, pneumonia, liver disease, renal failure, diabetes and other conditions, what limits their use for diagnosis. They are useful particularly in monitoring of treatment and follow-up of different epithelial carcinomas. Combined determination of tumor burden markers and cytokeatins as markers of disease activity provides earlier and more efficient information about the disease status and its changes.

Although their main use is to monitor treatment and evaluate response to therapy, early prognostic information particularly on tumor progression and metastasis formation is also provided for several types of cancers. Cytokeatin tumor markers can accurately predict disease status before conventional methods and offer a simple, non-invasive, cheap, and reliable tool for more efficient management.



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TPS®

Characteristics:

TPS® – tissue polypeptide antigen specific assay determines soluble fragments of Cytokeratin 18, containing defined epitope recognized by antibody M3, in human serum. The size of the determined cytokeratin fragments is in the range of 10-500 kDa.

Cytokeratin 18 is an acidic protein with molecular weight of 45 kDa.

Occurrence:

Cytokeratin 18 occurs in digestive, respiratory, and urogenital tracts, endocrine and exocrine cells and mesothelial cells.

Expected values: <80 U/L

Clinical interest

It is used as a marker of tumor activity reflecting malignant tissue degradation and cell necrosis in epithelial cell carcinomas.

- Breast cancer (in combination with CA 15-3)
 - Prognostic factor
 - Monitoring of treatment
 - Follow-up
- Prostate cancer (in combination with PSA)
 - Prognostic factor
 - Monitoring of treatment
 - Follow-up
- Ovarian cancer (in combination with CA125)
 - Prognostic factor
 - Monitoring of treatment

Increased levels in benign conditions

- Liver cirrhosis
- Chronic renal failure
- General infections
- Pregnancy



Cytokeratin 19 Fragment

Characteristics:

Cytokeratin 19 fragment assay (known also as Cyfra 21-1 – trade mark of company Roche) determines specific fragments of cytokeratin 19 subunits of intermediate filaments in human serum.

Cytokeratin 19 is an acidic protein with molecular weight of 40 kDa.

Occurrence:

Cytokeratin 19 occurs in glandular-type epithelia cells of the lung, uterus and gastrointestinal tract.

Biological half-life: 2 days

Clinical interest

It is used as a marker of tumor activity reflecting malignant tissue degradation and cell necrosis in epithelial cell carcinomas.

- Non-small cell lung cancer (NSCLC)
 - Differential diagnostics (especially if biopsy is not possible)
 - Prognostic factor for NSCLC (SCLC)
 - Monitoring of treatment
 - Follow-up
- Monitoring of uterine cancer (mainly cervical cancer)
- Monitoring of urinary bladder cancer
- Monitoring of head and neck cancer

Increased levels in benign conditions

- Liver cirrhosis
- Chronic renal failure
- Asthma
- Tuberculosis
- General infections
- Pregnancy



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MonoTotal®

Characteristics:

MonoTotal® assay determines soluble fragments of cytokeratin 19, 8 and, at certain extent, cytokeratin 18 in serum. The size of the determined cytokeratin fragments is in the range of 10-500 kDa.

Cytokeratin 19 is an acidic protein with molecular weight of 40 kDa.

Cytokeratin 8 is a basic protein with molecular weight of 52 kDa.

Cytokeratin 18 is an acidic protein with molecular weight of 45 kDa.

Occurrence:

Cytokeratin 19 occurs in glandular-type epithelia cells of the lung, uterus and gastrointestinal tract.

Cytokeratins 8 and 18 occur in digestive, respiratory, and urogenital tracts, endocrine and exocrine cells and mesothelial cells.

Expected values: <75 U/L

Biological half-life: <24 hours

Clinical interest

It is used as a marker of tumor activity reflecting malignant tissue degradation and cell necrosis in epithelial cell carcinomas.

- Non-small cell lung cancer (NSCLC)
 - Differential diagnostics (especially if biopsy is not possible)
 - Prognostic factor for NSCLC (SCLC)
 - Monitoring of treatment
 - Follow-up

Increased levels in benign conditions

- Liver cirrhosis
- Chronic renal failure
- Asthma
- Tuberculosis
- General infections
- Pregnancy



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TPAcyk™

Characteristics:

TPAcyk™ - tissue polypeptide antigen assay determines predominantly soluble fragments of cytokeratin 8 and 18, in serum.

Cytokeratin 8 is a basic protein with molecular weight of 52 kDa.

Cytokeratin 18 is an acidic protein with molecular weight of 45 kDa.

Occurrence:

Cytokeratins 8 and 18 occur in digestive, respiratory, and urogenital tracts, endocrine and exocrine cells and mesothelial cells.

Expected values: <1.0 ng/mL

Clinical interest

It is used as a marker of tumor activity reflecting malignant tissue degradation and cell necrosis in epithelial cell carcinomas.

- General Epithelial Cancers
 - Monitoring of treatment
 - Follow-up

Increased levels in benign conditions

- Liver cirrhosis
- Chronic renal failure
- General infections
- Pneumonia
- Pregnancy



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UBC[®]

Characteristics:

UBC[®] – Urinary Bladder Cancer assay determines predominantly soluble fragments of cytokeratin 8 and 18, in urine.

Cytokeratin 8 is a basic protein with molecular weight of 52 kDa.

Cytokeratin 18 is an acidic protein with molecular weight of 45 kDa.

Occurrence:

Cytokeratins 8 and 18 occur in digestive, respiratory, and urogenital tracts, endocrine and exocrine cells and mesothelial cells.

Expected values: <35 µg/L

Clinical interest

It is used as a marker of tumor activity reflecting malignant tissue degradation and cell necrosis in bladder cancer.

- Urinary bladder cancer
 - aid in diagnosis
 - follow-up checks for recurrent disease in patients with suspected or earlier diagnosed bladder cancer

Increased levels in benign conditions

- After surgery and cancer treatment
- Infections of the genitourinary tract
- Semen contamination
- Renal or bladder calculi
- Benign prostate hyperplasia
- Renal dysfunction
- Pregnancy



References

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