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CHANGES IN THE COMPOSITION OF BIOLOGICAL FLUIDS IN ONCOLOGICAL DISEASES

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Abstract: Oncological diseases are associated with complex molecular, metabolic, biochemical, and immunological alterations that may be reflected in the composition of biological fluids. Blood, urine, saliva, and cerebrospinal fluid contain numerous molecules capable of reflecting pathological processes associated with tumor development and progression. These include circulating tumor DNA, cell-free DNA, circulating tumor cells, proteins, cytokines, metabolites, microRNAs, and extracellular vesicles. The analysis of such components has become an important area of modern oncology because biological fluids can be collected with considerably less invasiveness than tissue biopsies. The present article reviews the principal changes occurring in biological fluids during malignant diseases and discusses their potential diagnostic and monitoring significance. Particular attention is given to biochemical changes in blood, molecular and metabolic alterations in urine, and the emerging role of salivary biomarkers. The integration of conventional biochemical parameters with molecular biomarkers may contribute to the development of more informative and minimally invasive approaches to cancer assessment. [1–5]

Keywords: oncological diseases, cancer, biological fluids, biomarkers, blood, urine, saliva, circulating tumor DNA, liquid biopsy, metabolites.

Introduction

Cancer represents a heterogeneous group of diseases characterized by uncontrolled cellular proliferation, accumulation of genetic and epigenetic alterations, invasion of surrounding tissues, and potential metastatic dissemination. The development of a malignant tumor is accompanied not only by local structural changes but also by systemic metabolic, inflammatory, and immunological responses. As a result, tumor-associated molecular alterations may become detectable outside the primary tumor, including in circulating biological fluids. This has increased interest in biological fluids as potential sources of biomarkers for cancer diagnosis, prognosis, treatment monitoring, and detection of residual disease. [1,2]

The concept of liquid biopsy has become particularly important in modern oncology. Unlike conventional tissue biopsy, liquid biopsy uses biological fluids, most commonly blood, to obtain molecular information associated with a tumor. Circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), cell-free RNA, proteins, metabolites, and extracellular vesicles may provide information about tumor biology and molecular heterogeneity. ctDNA is released into the circulation mainly as a consequence of tumor-cell death and can contain tumor-specific mutations, copy-number changes, and epigenetic alterations. These characteristics have made ctDNA one of the most intensively investigated components of liquid biopsy. [3–6]

Blood is the most extensively studied biological fluid in cancer research because it provides access to both systemic biochemical changes and tumor-derived molecular material. Malignant disease can affect protein metabolism, inflammatory responses, cellular turnover, and energy metabolism. Changes in circulating proteins and enzymes may therefore accompany tumor progression, although many conventional biochemical markers are not cancer-specific and can also be influenced by infection, inflammation, tissue injury, nutritional status, or organ dysfunction. [7–10]

Inflammation is an important component of the interaction between a tumor and its host. Tumor-associated inflammatory responses can alter circulating cytokines, acute-phase proteins, and other

mediators. C-reactive protein, albumin, interleukin-6, tumor necrosis factor-alpha, and other inflammatory parameters have consequently been investigated in relation to cancer progression and prognosis. However, these markers should be interpreted in the context of the patient's clinical condition because systemic inflammation is not specific to malignant disease. [8–11]

Cancer is also characterized by metabolic reprogramming. Malignant cells frequently alter glucose utilization, amino-acid metabolism, lipid metabolism, and nucleotide synthesis to support rapid proliferation. The resulting metabolic changes may influence the concentration of metabolites in blood and other biological fluids. Metabolomic studies have therefore become an important research area for identifying patterns that may distinguish malignant disease from non-malignant conditions. [12,13]

Urine represents another important biological fluid for cancer biomarker research because it can be collected repeatedly using a non-invasive procedure. Urine contains proteins, DNA, RNA, extracellular vesicles, exfoliated cells, and numerous small metabolites. Studies have investigated urinary biomarkers in bladder, prostate, kidney, breast, lung, pancreatic, liver, and other cancers. Urinary metabolomics has also identified alterations in several metabolic pathways and candidate biomarkers associated with cancer development and progression. [14–18]

Saliva has attracted increasing attention as another non-invasive source of cancer-associated biomarkers. Saliva contains proteins, messenger RNA, microRNA, DNA, metabolites, cytokines, and extracellular vesicles. Because it can be collected easily and repeatedly, salivary analysis has been investigated particularly in oral and head-and-neck cancers, although potential applications have also been studied for systemic malignancies. [19–22]

The aim of the present study was to characterize changes in the composition of biological fluids associated with oncological diseases and to summarize their potential diagnostic and clinical significance. Particular attention was given to biochemical alterations in blood, molecular and metabolic changes in urine, and emerging biomarkers identified in saliva.

Materials and Methods

The study was designed as a comparative observational investigation of biological-fluid parameters in patients with oncological diseases and individuals without a documented malignant disease. The study population should include patients with histologically or otherwise clinically confirmed malignant disease and an appropriate control group. Participants should be selected according to predefined inclusion and exclusion criteria in order to reduce the influence of acute infections, severe organ dysfunction, and other conditions capable of substantially altering biochemical parameters.

Venous blood samples should be collected under standardized pre-analytical conditions. Serum or plasma should subsequently be separated according to established laboratory procedures. The biochemical assessment may include total protein, albumin, C-reactive protein, glucose, lactate dehydrogenase, creatinine, and urea. These parameters were selected because they reflect different aspects of systemic inflammation, protein metabolism, tissue injury, energy metabolism, and renal function. [7–11]

Urine samples should be collected using standardized procedures, preferably with documentation of collection time, hydration status, and relevant pre-analytical factors. Depending on the study resources, urinary protein, metabolites, nucleic acids, and extracellular vesicles may be investigated. Pre-analytical standardization is particularly important in urinary biomarker research because collection, storage, processing, and normalization procedures can substantially influence measured biomarker concentrations. [15,17,18]

If molecular analysis is available, circulating tumor DNA, cell-free DNA, microRNAs, or extracellular-vesicle-associated molecules may additionally be evaluated. Such analyses can provide information that is complementary to conventional biochemical testing and may be particularly useful for investigating tumor-specific molecular alterations. [3–6]

Quantitative variables should be assessed for distribution before statistical analysis. Normally distributed variables should be presented as mean ± standard deviation, whereas non-normally distributed variables should be expressed as median and interquartile range. Categorical variables should be presented as absolute numbers and percentages. Comparisons between groups should be performed using

appropriate parametric or non-parametric statistical tests. A p-value below 0.05 should be considered statistically significant.

Results

The analysis of biological-fluid composition should be performed by comparing the oncological group with the control group. The primary outcome measures should include biochemical parameters of blood and urine, while secondary analyses may include molecular biomarkers where available. The following table represents the structure that should be used for the actual laboratory dataset.

Table 1. Biochemical characteristics of biological fluids in patients with oncological diseases compared with controls

Parameter	Oncological group (n=__)	Control group (n=__)	Difference	p-value
Total protein, g/L	__	__	__	__
Albumin, g/L	__	__	__	__
C-reactive protein, mg/L	__	__	__	__
Lactate dehydrogenase, U/L	__	__	__	__
Glucose, mmol/L	__	__	__	__
Creatinine, µmol/L	__	__	__	__
Urea, mmol/L	__	__	__	__
Urinary protein, mg/L	__	__	__	__

Changes in serum protein parameters should be interpreted in relation to systemic inflammation, nutritional status, hepatic protein synthesis, and the metabolic requirements of malignant disease. Albumin may decrease in association with systemic inflammation and altered nutritional status, while changes in total protein may reflect alterations in protein synthesis, catabolism, hydration, and disease-related metabolic processes. [8–11]

The inflammatory profile should be evaluated separately because systemic inflammatory responses can accompany many malignant diseases. Increased concentrations of inflammatory markers such as C-reactive protein may reflect activation of the acute-phase response, while cytokines including IL-6 and TNF-α can participate in tumor–host interactions. Nevertheless, these parameters should not be interpreted as cancer-specific markers because similar changes may occur in infectious and inflammatory diseases. [8–11]

Lactate dehydrogenase may also demonstrate alterations in patients with malignant disease. Because LDH is involved in cellular energy metabolism and is released during tissue injury or cellular destruction, increased activity can occur in conditions characterized by high cellular turnover. In oncology, LDH has been investigated as a marker associated with tumor burden and prognosis in several malignancies, although its lack of specificity remains an important limitation. [9,12]

Urinary analysis may demonstrate changes in proteins and metabolites associated with malignant disease. Urine is particularly attractive for biomarker research because it can be obtained non-invasively and contains a wide range of molecular components, including proteins, nucleic acids, extracellular vesicles, and small metabolites. Research in urinary metabolomics has identified alterations in metabolic pathways involving amino acids, nucleotides, lipids, and other metabolic products in different cancers. [14–18]

If salivary analysis is incorporated into the study, the results may include alterations in proteins, inflammatory mediators, microRNAs, messenger RNAs, and metabolites. Research on oral cancer has identified several candidate salivary biomarkers, including IL-6, IL-8, TNF-α, LDH, and MMP-9, although their clinical utility requires further validation in larger populations. [19–22]

Discussion

The observed or expected changes in biological-fluid composition can be explained by the complex interaction between tumor cells and the host organism. Malignant cells undergo metabolic reprogramming to support rapid proliferation and survival, while the tumor microenvironment contains

immune cells, fibroblasts, endothelial cells, and extracellular matrix components that contribute to tumor progression. These processes can collectively influence circulating proteins, metabolites, nucleic acids, and inflammatory mediators. [1,12,13]

One of the most important developments in this field is the use of ctDNA as a component of liquid biopsy. ctDNA can contain molecular alterations derived from tumor cells and may therefore provide information about tumor genotype. Serial analysis may also allow changes in tumor-derived DNA to be evaluated during treatment or after therapy. Nevertheless, ctDNA concentrations can be particularly low in early-stage disease, making highly sensitive analytical methods necessary. [3–6]

Extracellular vesicles represent another promising component of biological fluids. These membrane-bound particles can carry proteins, lipids, DNA, mRNA, and microRNA between cells. Tumor-derived extracellular vesicles may participate in communication within the tumor microenvironment and may contribute to processes such as angiogenesis, immune modulation, invasion, and metastasis. Their molecular cargo is therefore being investigated as a potential source of cancer biomarkers. [23,24]

Urinary biomarkers provide an additional opportunity for non-invasive cancer assessment. Current research demonstrates that urine can contain tumor-associated DNA, RNA, proteins, extracellular vesicles, and metabolites. However, the translation of promising urinary biomarkers into routine clinical practice remains challenging because biomarker concentrations may vary according to sample collection, hydration, processing, tumor stage, and patient characteristics. [15–18]

Saliva is similarly attractive because of its accessibility and non-invasive collection. A meta-analysis of salivary biomarkers for malignant non-oral tumors found promising overall diagnostic performance, but substantial heterogeneity between studies remains. Therefore, salivary biomarkers should currently be regarded primarily as research candidates rather than universal replacements for established diagnostic methods. [20–22]

An important limitation of biological-fluid biomarkers is their lack of absolute specificity. A change in a protein, metabolite, cytokine, or enzyme may result from malignancy, but it may also occur because of infection, inflammation, medication, nutritional status, organ dysfunction, or other physiological and pathological conditions. Consequently, the clinical interpretation of biological-fluid biomarkers should involve integration with clinical findings, imaging, histopathology, and other laboratory parameters. [3,15,18]

Conclusion

Oncological diseases can produce substantial alterations in the composition of biological fluids through metabolic reprogramming, systemic inflammation, tissue injury, altered protein metabolism, immune responses, and tumor–host interactions. Blood may demonstrate changes in proteins, inflammatory markers, enzymes, and circulating tumor-derived molecules, while urine can provide information through altered proteins, metabolites, nucleic acids, and extracellular vesicles. Saliva also represents a promising non-invasive source of molecular biomarkers, particularly in oral and head-and-neck malignancies. [1–24]

The combination of conventional biochemical parameters with molecular approaches such as ctDNA analysis, metabolomics, microRNA profiling, and extracellular-vesicle analysis may improve the ability to characterize malignant disease and monitor its dynamics. However, further prospective studies with standardized sampling procedures, sufficiently large cohorts, appropriate control groups, and independent validation are required before many candidate biomarkers can be routinely implemented in clinical oncology. [3–6,15,18]

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