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The importance of arylsulfatase A and B, correlated with other molecular markers, in the evolution and prognosis of colorectal carcinoma

PhD thesis summary

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Arylsulfatases are lysosomal enzymes catalyzing the desulfation of a phenol sulfate. The best-known arylsulfatases are arylsulfatase A (ARSA - cerebroside-sulfatase), arylsulfatase B (ARSB - N-acetylgalactosamine-4-sulfatase) and arylsulfatase C (ARSC - steroid sulfatase). In the early 1990s, the investigation of ARSA expression began in cancers of the gastrointestinal, breast, lung, renal, central nervous system and female genital tract. It has been observed that ARSA and ARSB may play key roles in carcinogenesis and metastatic potential of tumor cells. In normal conditions ARSB metabolism requires oxygen, while in malignant transformation, it is described low ARSB expression, which suggests intense anaerobic glycolysis in malignant cells.

In the present paper, we proposed to examine the clinico-pathological and molecular aspects of colorectal cancer, from a prognostic and predictive perspective, with special interest in the role of ARSA and ARSB in the evolution and prognosis of this type of cancer.

Because molecular examination requires a standardization of the working techniques, the first step was the validation and optimization of DNA extraction from paraffin-embedded tissues, respectively of RNA extraction from blood of patients with colorectal cancer. Thus, in chapter 3 of Personal contributions, we presented how to optimize the DNA isolation from the colorectal cancer tissue included in paraffin. We aimed to establish a working protocol, usable in daily practice, for DNA extraction with adequate purity (OD: 1.8-2.0).

In Chapter 4, we presented how to optimize RNA isolation from blood, respectively to quantify the circulatory expression of ARSB gene. After optimization, within the thesis, these techniques are currently used in the Molecular Pathology Laboratory of the Pathology Department of the Mures County Emergency Hospital in Târgu Mureș. The determinations have been made, after obtaining the agreement of the Hospitals and the University of Medicine, Pharmacy, Science and Technology 'George Emil Palade' of Târgu Mureș Ethical Committee, for the retro- and prospective processing of the cases included in the study.

In Chapter 4, we detailed the techniques for examining the molecular and immunohistochemical (IHC) profile of colorectal cancer, focusing on a less-understood mechanism of tumor invasiveness and metastasis, respectively the possible role of arylsulfatases in the evolution and prognosis of colorectal cancer. We hypothesized that ARSA and ARSB might be involved in the evolution of colorectal cancer and we tried to identify the mechanism behind tumor cell behavior of these proteins. We subsequently examined the relationship between circulatory gene expression and protein expression in tumor tissue of ARSB.

In Chapter 5, we identified, in clinical practice, a rare but aggressive subtype of gastrointestinal carcinoma, with plasmacytoid phenotype. We hypothesized that arylsulfatases could play a role in epithelial-mesenchymal transition of tumor cells and

could be responsible for the aggressiveness of this type of carcinoma. To prove the hypothesis, we carried out the detailed immune profile of the tumor cells.

There is a relatively small number of publications that refer to the role of arylsulfatases in the genesis and evolution of colorectal cancer, so the thesis has outstanding scientific value, including an original study, in which we correlated the IHC expression of ARSA and ARSB with ARSB gene expression in patients with colorectal cancer.

For the first time in the literature, we tried to establish a correlation between the epithelial-mesenchymal transition of the tumor cells, the expression of ARSA / ARSB and the expression of Maspin.

The series of cases of gastrointestinal carcinomas with plasmacytoid phenotype has a note of originality. The results highlight the possible interactions of epithelial-mesenchymal transition with the Wnt pathway and ARSA / ARSB pathways, proven to play a role in tumor differentiation. Thus, by highlighting a particular, aberrant subtype of epithelial-mesenchymal transition, the result of which is the appearance of the plasmacytoid phenotype, has an original aspect.

Following the results obtained, we tried to synthesize some hypotheses that give a new interpretation of the epithelial-mesenchymal transition in colorectal cancer, correlated with ARSA/ARSB for the first time in scientific literature.

Regarding the technical part, an important aspect is the optimization of the isolation and quantification protocols of the DNA from paraffin blocks, by modifying the doses of the digestion and purification solutions during isolation.

These aspects prove the originality of the research but also the clinical and practical aspect of it, respectively the potential of continuing the exploration of colorectal cancer through molecular biology examinations.

Therefore, based on the assumptions made, the achieved objectives and the standardized working protocols, this Ph.D. thesis has an obvious character of originality and practical importance.