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Immunohistochemical analysis of the expression of ALCAM and ALDH1 markers in patients with colorectal adenocarcinoma and association with clinicopathological outcomes

Análise imunoistoquímica da expressão dos marcadores ALCAM e ALDH1 em pacientes com adenocarcinoma colorretal e associação com desfechos clinicopatológicos

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ABSTRACT

Introduction: Colorectal cancer has high global mortality, requiring investigations to be carried out to better understand this disease. Tumor markers have emerged as indicators of diagnosis, management and prognosis of neoplasms. New markers are studied in this scenario.

Objective: To verify whether there is a correlation between the immunohistochemical expression of ALCAM and ALDH1 proteins in tissue with colorectal adenocarcinoma with the epidemiological and clinicopathological characteristics, their impact on disease progression, and death.

Method: Narrative review based on publications selected from research on virtual platforms. Initially, a search was carried out for MESH descriptors related to the topic, being chosen: "colorectal cancer, ALCAM and ALDH1" with AND or OR search, first by title and abstract and, then, by reading in full those selected.

Result: 52 articles were included.

Conclusion: The immunohistochemical expression of the ALCAM and ALDH1 markers did not show any association with disease progression and death, nor was it possible to observe a correspondence relationship with the markers evaluated

KEYWORDS: Colorectal cancer. ALCAM. ALDH1.

RESUMO

Introdução: O câncer colorretal apresenta alta mortalidade global, requerendo que investigações sejam realizadas para melhor compreender esta enfermidade. Marcadores tumorais têm surgido como sinalizadores de diagnóstico, manejo e prognóstico das neoplasias. Novos marcadores são estudados neste cenário.

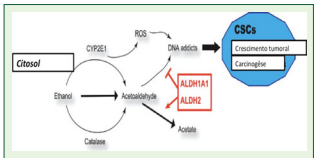
Objetivo: Verificar se há correlação da expressão por imunoistoquímica das proteínas ALCAM e ALDH1 em tecido com adenocarcinoma colorretal com as características epidemiológicas, clinicopatológicas, seu impacto na progressão de doença, e no óbito.

Método: Revisão narrativa com base em publicações selecionas a partir de pesquisa em plataformas virtuais. Inicialmente foi realizada busca por descritores DeCS relativos ao tema, sendo escolhidos: "câncer colorretal, ALCAM e ALDH1" com busca AND ou OR, primeiramente pelo título e resumo e, depois, por leitura na íntegra dos selecionados.

Resultado: Foram incluídos 52 artigos.

Conclusão: A expressão por imunoistoquímica dos marcadores ALCAM e ALDH1 não apresentou associação com a progressão de doença e ao evento óbito, também não foi possível observar relação de correspondência com os marcadores avaliados

PALAVRAS-CHAVE: Câncer colorretal. ALCAM. ALDH1.



ALDHs and ROS in carcinogenesis

Central Message

Tumor markers have emerged as diagnostic signs, management, and prognosis of neoplasms. New markers are studied in this scenario, verifying whether there is a correlation between immunohistochemical expression and disease evolution. Thus, to review the role of ALCAM and ALDH1 proteins in colorectal adenocarcinoma in their epidemiological, clinicopathological, and impact characteristics on disease progression and death. is pertinent to better support medical care in this cancer

Perspective

One of the strategies for understanding colorectal cancer is associated with tumor markers, which are molecules identified in one or more types of tissues, capable of indicating the presence of a certain neoplasm. The existence of tumor markers allows for earlier diagnosis, as well as, in some situations, serves as a form of population screening. Currently, its use is not restricted to diagnosis, but also to establish prognosis, follow-up, evaluation of therapeutic response, or even the detection of recurrence. Carcinoembryonic antigen is the most commonly used in this context, however, although its serum elevation suggests positivity of the disease, it is not able to confirm the diagnosis or the presence of metastasis.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer death in the world (mortality 8.9%).[1] The pillars of its treatment consist of surgical procedure, chemotherapy and radiotherapy. Although surgery can be potentially curative, less than 25% of cases are operable with recurrence rates of up to 70%. Inoperable tumors, relapses, or metastatic tumors are treated by palliative chemotherapy, although the prognosis remains poor.

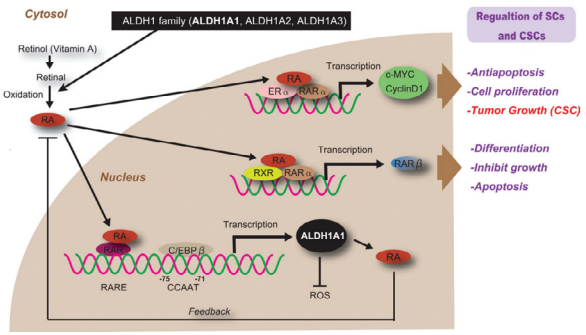
Determining the stage of progress, extent, and severity of a tumor at the time of diagnosis is essential to establish the treatment strategy and to estimate the evolution of the disease. The classifications used to define this stage are: degree of cell differentiation, clinical and pathological stages (TNM, Astler-Coller, Dukes), lymph node involvement, and presence of distant metastasis.[2]

Colorectal cancer restricted to the wall of the intestine (stages I and II) is potentially curable due to early detection and treatment. It has a 5-year survival between 70-90%; However, most countries do not have a screening program that allows for their early detection.[3] In contrast, the median 5-year survival in regional (stage III) and distant (metastatic and stage IV) stages is approximately 50-70% and 10-14%, respectively.[3] These rates are mainly attributed to the disruption of the intestinal wall by the tumor and its lymphatic dissemination to distant organs through the bloodstream. The incidence of CRC increases after 50 years of age, with 90% of cases being within this age group.[3]

The marker ALCAM (Activated leukocyte cell adhesion molecule) - or CD166, is present in several tissues and has several functions such as mediating cell adhesion. It is physiologically expressed in activated leukocytes, neural and epithelial cells, as well as hemotopoietic progenitors. It functions as a CD6 ligand and can mediate homophilic interactions (ALCAM-ALCAM).[2] It preserves protein cell adhesion in physiological processes such as leukocyte invasion through the blood-brain barrier, migration of monocytes through endothelial junction, angiogenesis, capillary formation, protection against apoptosis in breast neoplasia, and T cell activation by tumor cells and antigens presented.

Aldeidodehydrogenases (ALDHs) are a group of enzymes composed of nicotinamide adenine dinucleotide phosphate-positive, which catalyzes the oxidation of endogenous and exogenous aldehyde with their corresponding carboxylic acids as a product. This detoxification can protect stem cells from oxidative stress, in addition to modulating cell proliferation, acting in the regulation of healthy stem cells, as well as cancerous ones. This mechanism of regulation of stem cells is carried out by intracellular biochemical reactions. It begins with the oxidation of retinol by the ALDH 1 family and transforms it into retinoic acid (RA), still in the cell cytoplasm. This participates in 3 pathways in metabolism within the nucleus. The first is RA together with estrogen receptors and RA itself, capable of generating c-MYC and cyclin D1. Both products stimulate cell proliferation, inhibit apoptosis and favor cell tumor growth. The second leads to the formation of beta RAR (RA beta receptor), which stimulates cellular protection mechanisms such as apoptosis, differentiation and growth inhibition. The third ends with the formation of more AR, favoring the perpetuation of this chain.

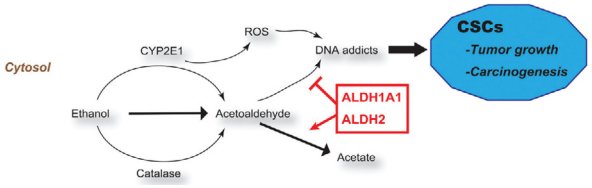
Figure 1 illustrates the regulation and function of ALDH1 in normal and cancerous stem cells. Several ALDHs metabolize RA, thereby regulating tumor self-renewal, differentiation, and resistance of stem cells and cancer stem cells. Retinol absorbed by cells is oxidized to the retinal. Retinal is oxidized to RA by the enzymes ALDH1, which binds to ARRa and RxRs dimers to induce the expression of its downstream target genes, excluding RARb. In ERa-expressing cells, RA can bind to RAR and ERa dimers, as well as induce c-MYC and cyclin D1 expression. RA (retinoic acid); RAR (retinoic acid receptor); RXR (retinoid x receptors); ER (estrogen receptor); ROS (Reactive Oxygen Species)



Source: Tomita (2016)[4]

FIGURE 1— Regulation and function of ALDH1

Another example of the action of the ALDH1 family occurs in acetoaldehyde, having as products: acetate and "addicted" DNA - the latter related to tumor growth and carcinogenesis. ALDHs reduce ROS and reactive aldehydes, thereby promoting tumor growth and initiating carcinogenesis in CSCs. Figure 2 illustrates ALDHs and ROS in carcinogenesis. ALDHs reduce ROS and reactive aldehydes, thereby promoting tumor growth and initiating carcinogenesis in CSCs, ROS, reactive oxygen species.



Source: Tomita (2016)[4]

FIGURE 2— ALDHs and ROS in carcinogenesis

North American data show a 5-year survival of 88.1% and 12.6% for stages I and IV of the disease, respectively. Diagnostic and therapeutic strategies are necessary, which requires a greater understanding of the molecular mechanisms of RCC and the use of biomarkers, in order to improve the prognosis through the early detection of these tumors.

The objective of this review was to verify the correlation between the immunohistochemical expression of the ALCAM and ALDH1 proteins in colorectal adenocarcinoma with the epidemiological and clinicopathologic characteristics, to verify their impact on the progression of disease and death, and also to verify whether there is increased expression in tissues with colonic adenocarcinoma when compared to healthy tissue that motivates the increase in tumor aggressiveness.

METHOD

The literature review was done through reading and analysis based on research in publishers and virtual platforms (SciELO, Virtual Health Library, Google Scholar, Pubmed and Scopus). We started with a search based on descriptors using the following terms: "colorectal cancer, markers, ALCAM, ALDH1" and its equivalents in English "colorectal cancer, biomarkers, ALCAM, ALDH1" with AND or OR search, considering the title and/or abstract and after reading the texts. A total of 52 articles were included.

DISCUSSION

According to data from the International Agency for Research on Cancer, through the Global Cancer Observatory, CRC ranked 2nd in causes of cancer death in Brazil (2018). Also, according to the same source, it is the 4th in number of new diagnoses in the world, with 19.7% incidence. In Brazil, its incidence is 19.5 new cases per 100,000 inhabitants. The prevalence is 48.2 per 100 thousand inhabitants and the mortality rate is 8.8%.

One of the strategies for understanding this disease is associated with tumor markers, which are molecules identified in 1 or several types of tissues, capable of indicating the presence of a certain neoplasm. The existence of 1 tumor marker allows for earlier diagnosis, as well as, in some situations, serves as a form of population screening.[5] Currently, its use is not restricted to diagnosis, but also to establish prognosis, follow-up, evaluation of therapeutic response, or even the detection of recurrence. Carcinoembryonic antigen is most commonly used in RCC; however, although his serum elevation suggests positivity of the disease, it is not able to confirm the diagnosis or the presence of metastasis.

The markers related to the present study were divided into 2 main topics. Each topic was concerned with reviewing studies that contributed to the foundation of knowledge, not only theoretical, but also to contrast with the results found.

ALCAM

The activated leukocyte cell adhesion molecule, known by its acronym ALCAM (activated leukocyte cell adhesion molecule), is part of a small subgroup of transmembrane glycoproteins expressed in immunoglobulins. Also known, in its systematized nomenclature, as CD166, these proteins are structurally characterized by the presence of 5 extracellular domains, followed by 1 transmembrane portion and then 1 small intracellular portion.

Because it follows a specific pattern of cell and tissue distribution, the first studies on this subgroup (at the time also represented by M-CAM and B-CAM) already showed strong evidence of the relationship between these glycoproteins and the development of tissue architecture, neurogenesis, hematopoiesis, immune response, and tumor progression.[6]

The gene responsible for expressing ALCAM is genetically located on chromosome 3, at position 13 of its long arm (3q13).[7] This expression is concentrated in proliferative and hematological cells but is not restricted to these sites.[8]

In functional terms, it is directly related to cell proliferation because it participates in chain reactions, which involve everything from the organization in the cytoskeleton to the adhesion itself between the cells, which can occur in a homophilic way (ALCAM-ALCAM) or even heterophilic (ALCAM-CD6 interaction). The fact of performing these 2 forms of adhesion shows less specificity in the role of this molecule, which would also allow a greater probability of errors in this chain.[9,10]

Some studies have shown that the loss of homophilic cell adhesion (especially due to aberrations in the cadherins) is associated with both neoplastic progression and the degree of tissue invasion by the tumor.[11] However, paradoxically, there is evidence of the conservation of homophilic cell adhesion mediated by ALCM in malignant tumors.[12]

The first evidence of the correlation between ALCAM and cancer was described in the late 1990s, showing expression of ALCAM in more invasive and deeper melanomas, associated with the absence of expression in tumors of less depth. Thus, ALCAM may be an important marker to assess melanoma progression and, later, this concept was extended to other types of cancers.[10]

Another important finding was the identification of ALCM expression in precursor lesions, such as dysplasia, reinforcing the relationship with tumor invasion and metastases. In oral squamous cell carcinomas, ALCAM overexpression was identified in preneoplastic stages, and was maintained during disease progression. However, neoplastic progression showed an association with even more significant expression and with a change in the pattern of ALCAM accumulation, from greater expression in the membrane to a majority cytoplasmic expression.[13]

This change in pattern could be seen in other tissues, such as epithelial ovarian cancer, where

decreased expression of ALCAM in the membrane was a marker of worse prognosis.[14]

In addition to the sites mentioned above, the association with other types of cancers of different lineages has been described in the literature. In the pancreatic system, ALCAM is characterized as an independent prognostic marker for poor survival and rapid progression. Regarding bladder tumors, the association was observed only with a worse prognosis in tumors of advanced staging, but strongly significant.[15,16]

Although most studies use the immunohistochemical expression of ALCAM, there are genetic analyses that show increased mRNA in both prostate and breast carcinomas. In both cases, the expression of ALCAM was also shown to be inversely proportional to the aggressiveness of the tumor, i.e., it is expressed in the early stages, and as the tumor acquires invasive characteristics, progressive reduction is observed.[17]

The pathophysiological mechanisms that could explain this association are not yet fully elucidated; however, some theories are well established. Because it is found specifically at the cellular junction of endothelial cells, some authors state that ALCM plays a role in tumor angiogenesis and may even be the target of future treatments. This mechanism shows that ALCAM facilitates the transendothelial migration of activated leukocytes, also exerting control over diapedesis.[18]

The first study to investigate the association between ALCAM expression and colorectal cancer was a case-control study using 111 patients. In this study, the difference between cytoplasmic and membranous expression of ALCAM was observed. Although the expression of both forms was significant, only membranous expression was statistically significant when compared with survival.[2]

The biological role of these 2 forms of expression is still uncertain; however, Tomita et al.[19] observed the presence of cytoplasmic expression in prostatic cell lines that lost αcatenin expression, concluding that membranous expression would be a physiological condition of ALCAM. However, this statement does not corroborate the association found in colorectal cancer, where cytoplasmic expression is found in normal mucous membranes. A possible explanation for this phenomenon is that ALCAM behaves differently in tissues.[2,19]

Although other studies corroborate the hypothesis of a risk association between ALCAM and CRC, 2 stand out for finding results that indicated an association of protection in relation to survival. Also noteworthy for the sample size were 1,574 patients analyzed in the 2 studies.[18,20]

The first systematic analysis of the prognostic value of CD166, as well as other markers, was performed by Lugli et al. (2010)20 with a sample of 1,274 patients. This analysis evidenced a significant association not between increased ALCAM expression, but rather the absence of this marker with more advanced disease, both clinically and histologically. There was also a possible confounding bias in other studies, because when performing univariate analysis, a significant correlation was found between the loss of membranous expression of CD166 and overall survival; however, in the multivariate analysis, there was no such association. These results indicate that the impact of this marker may be secondary to the association with other prognostic criteria.

Another significant study, with a sample of 300 patients with primary colorectal cancer, also showed the predominance of membranous expression of CD166. In addition, a significant correlation was found between the reduction of its expression in metastases, when compared with primary tumors. However, ALCAM positivity did not have a significant correspondence with the appearance of distant metastases or lymph node involvement.[18]

As previously mentioned, it is important to highlight that the clinical components analyzed exert a great influence on the results, especially in univariate analyses. Studies show that there is no significant direct correlation between ALCAM expression (both overexpression and absence) and clinical-epidemiological data, such as age, gender, and staging. However, an inversely proportional relationship is observed in relation to cytological staging, i.e., the higher the expression of ALCAM, the lower the degree in relation to cell differentiation (on a scale that 1 represents well-differentiated cells and, as it increases, the level of differentiation decreases).[18,21]

Regarding overall survival, in agreement with the univariate analysis performed by Lugli et al. (2010)20, a significant decrease in survival in patients with absence of ALCAM expression could be observed in other studies.[18,20,22]

After several studies showing controversial results regarding the usefulness of ALCAM for prognosis in colorectal cancer, the only meta-analysis published to date indicates that high CD166 expression is associated with a worse prognosis, being a predictive factor of survival in this disease. It is worth mentioning 2 points in this study; the first, that multivariate analysis was used in the study by Lugli et al.[20] instead of univariate (it is being significantly negative, with the other not having significance) as well as the correction factor for the weight of the studies analyzed, which equalized, with a difference of 0.5 percentage points, a sample of 1,274 against 110 patients.[20-22]

One of the biases cited by Zhang et al.[22] in relation to previous studies is the heterogeneity of the methods for searching for CD166 expression. As already mentioned, there may be differences in relation to the role of these distinct forms in tumor genesis. In meta-analysis, different results were observed where membranous expression was associated with worse prognosis and, in others, the meanings were not significant. Studies that analyzed both membranous and cytoplasmic expression reflected in a worse prognosis.[2,21,23]

Therefore, the association between ALCAM and prognosis in colorectal cancer is not yet fully accepted, and with contradictory studies. Although the only meta-analysis on the topic showed a significant association, it is important to highlight that there were limitations and the value found was closer to a weak association than a strong one.[22]

It is important that new studies can clarify the role of CD166 in colorectal cancer, in order to open up new diagnostic and therapeutic paths. The study of the detection of ALCAM by means of imaging studies has been studied for approximately one decade, when Schliemann et al. showed that the detection of ALCAM is an accessible target to be used in immunoPET-scan examinations. Other studies have also shown that it is possible to identify the expression of ALCAM by imaging, especially by isolating new specific sites of conjugation.[24,25]

ALDH

ALDH, an acronym for aldehyde dehydrogenase, represents a group of enzymes dependent on nicotinamide-adenine dinucleotide phosphate (NAD[P]+) responsible for catalyzing oxidation reactions of aldehydes in general, a substance that is very present in the environment and also produced by some endogenous metabolic processes.[4] Endogenous aldehydes are those generated by the metabolism of amino acids, alcohol, lipids and vitamins. Exogenous drugs are present in several products. Some are responsible for the tastes and odors in food, and other combustion products, present in cigarette smoke and automotive combustion residue. Apart from these sites, 1 of the most important sources is through the metabolism of cytotoxic drugs and xenobiotic agents.

Throughout the gene universe, more than 160 complementary DNAs were isolated and sequenced, being represented in the 3 taxonomic domains, which suggests a vital role in the course of evolutionary history. In the human genome, studies have demonstrated the existence of 19 supposedly functional genes and many pseudogenes.[26] These isoenzymes, resulting from the expression of these functional genes, are classified according to substrate, intracellular distribution, their distribution in organs and tissues, and also their chromosomal location. As a result, the nomenclature of each isoenzyme depends on the combination of all these factors.[4]

In addition to its cytoprotective function through the elimination of circulating aldehydes, the metabolism of aldehydes brings another vital biological function: the synthesis of biomolecules derived from aldehydes, such as RA and folate for example.[27] There is solid evidence showing an important role of ALDH in modulating cell proliferation, differentiation, and longevity, especially linked to its AR function. Some isoenzymes still have functions that are apparently independent of their enzymatic action, such as absorption of ultraviolet irradiation in the cornea and, also, as a binding protein for hormones and other smaller molecules.[28]

Its action in the different tissues was further strengthened with the sequencing of the human genome and the identification of mutations in the ALDH genes that lead to the loss of its enzymatic activity. These mutations have been linked to various diseases, such as cataracts (ALDH1A1), epilepsy (ALDH7A1), heart disease (ALDH2), alcohol hypersensitivity (ALDH1A1), and other metabolic abnormalities.[28]

ALDH1, a subgroup found primarily in the cellular cytoplasm of various tissues, is formed mainly by the isoenzymes ALDH1A1, ALDH1A2, ALDH1A3, which have the retinal as the main substrate and the ALDH1B1, which, unlike the others, is more distributed in the mitochondria and has acetaldehyde as its most prevalent substrate.[4] According to the original nomenclature, the ALDH family was divided into 3 classes: class 1, forms found in the cytoplasm; class 2, mitochondrial forms; and class 3, the tumor form.[29] However, with the advancement of genetic technology and the consequent discovery of more isoforms, in 1999 a classification into families and subfamilies based on the similarity of amino acid sequencing was adopted, updated every 2 years.[30] This classification uses the Dayhoff cutoff points, which proteins sharing ≥40% of their sequencing are united into a specific family, identified by an Arabic numeral, while those that share ≥60%, classified in the same subfamily, identified by 1 letter.[31]

The ALDH1 family has its function related to the synthesis of RA and its most prevalent subfamily is ALDH1A (especially ALDH1A1), being found in practically all species, while ALDH1B is present in mammals, but is not found in birds and fish.[26] Although more recently there has been a trend towards an individualized study of each subfamily, the association of ALDH with cancers encompasses the entire ALDH family1.[4,32]

The relationship of ALDH to carcinogenesis has been studied since the early 1990s; however, the specific mechanisms of the effects on cancer and normal stem cells have not yet been fully elucidated. However, there is a high probability that this link is related to retinal metabolism, which actively acts in the regulation of normal and, also, cancerous stem cells.[4]

This mechanism of action goes through the concept of cancer stem cells, where cells with pluripotent potential undergo some process in their self-regulation and start proliferation.[33] The action of the retinoid signaling pathway in this regulatory system is explained by retinal metabolism, which is oxidized in RA (in a reaction catalyzed by ALDH) and, when binding to intracellular receptors, stimulates a cascade effect that can act on 2 transcription pathways, depending on whether the cell is normal or cancerous. If normal, it transcriptions the RA beta receptor gene, leading to cell differentiation, growth inhibition, and apoptosis. In cancer stem cells, RA acts in the transcription of the c-MYC and cyclinD1 genes, stimulating anti-apoptosis, cell proliferation and tumor growth. In addition, by feedback mechanism,

increased ALDH1 levels may result in increased endogenous AR synthesis.[4]

The relationship between ALDH and CRC has been studied since the end of the first decade of the millennium, with the main focus being on evidence that suggested that the concept of cancer stem cells could be applied to colorectal cancer.[34] After this concept was established, research with the CD133 and CD44 markers was initiated, but the results were not controversial regarding the specificity for colon stem cells. For example, there are studies that show results where CD133+ stem cells developed tumor in guinea pigs; however, 1 year later, another study presented results where both CD133+ and CD133- cell subpopulations also developed this tumor.[35,36] ALDH had already shown signs of being an important marker for the identification and quantification of stem cells in hematopoietic tissues and also in breast cancer, resulting in the need to seek a more specific marker for colorectal tumors.[37,38]

In the first publication on the correlation between ALDH1 and colon cancer, published by Huang et al.[39] In 2009, a direct comparison of ALDH1A1 expression with the hitherto main markers, CD133 and CD44, in normal colon cells was performed. Samples of supposedly normal tissue, apparently normal tissue in patients with familial adenomatous polyposis (FAP), tissues diagnosed with adenoma and, also, adenocarcinomas were compared. In addition, the study implanted tumor tissue in guinea pigs to evaluate oncogenic characteristics. It was noted that the ALDH1A1 identified cells with characteristics of stem cells, indicating that it is a more selective marker for differentiated cells and also more specific than CD44 or CD133. It was also identified that in cases where there was positivity for ALDH together with CD44 or CD133 positive, there was a tendency to faster generation of tumors in guinea pigs. Another important finding was that the quantification of ALDH1 positivity in immunohistochemistry may indicate the presence of stem cells, which in turn are associated with tumor genesis.[39,40] In the same year, the same team published another study associating the presence of ALDH with malignant progression from colitis to carcinoma.[41]

Although most studies treat the ALDH1 family in a generalized way or using ALDH1A1 as a representative, there are also lines of research with specific subfamilies, of which ALDH1B1 has shown specificity for colon cancer.[32,42] In colon adenocarcinomas, there was a positive immunohistochemistry result for ALDH1B1 in 97.5% of the cases, well above the 36.6% found for ALDH1A1 in the same sample. In addition, the intensity of staining was significantly higher in the analysis of the samples tested for ALDH1B1. Regarding the expression of ALDH1B1 in normal colon tissue, its presence was identified only in small undifferentiated areas, close to the crypts, that is, a restricted area, very different from the result found in neoplastic tissues, where it is present in the entire area.[32]

After the establishment of ALDH as an important and potential marker for CRC, immunohistochemical studies were carried out in several regions of the world.[43,44] One of the most recent was carried out in Egypt in 2017, which showed no statistical significance between ALDH1 expression (classified as high if above 20% positivity for ALDH1 and low, if lower) with adenoma samples; however, when analyzing ALDH1 expression in carcinoma samples, a positivity of 76% was observed. of which approximately 70% had high expression. In addition, it was observed that only 6% were expressed in the stroma, which shows evidence of the presence of the B1 subfamily.[45] The same result was observed by Hou et al.,[44] who found positive expression of ALDH1 of 76.5% in cancerous tissues and 13.3% in normal colon, showing a statistical difference between the 2 groups. In addition, ALDH1 expression was significantly correlated with histological grade, TNM, and lymph node metastasis.[44] Similar results were found in relation to lymph node metastasis,32,45 while in others they were not.[46,47]

One of the most controversial factors is the relationship between ALDH expression and prognosis. In 2015, it was published by Chen et al.[48] systematic review and meta-analysis that, after excluding 116 publications for various reasons, analyzed 9 studies, all with immunohistochemical analysis. The prognostic indicators analyzed were overall survival, disease-free survival, T-stage, N-stage, and tumor differentiation. The results showed that ALDH1 is an important predictor of worse outcome in relation to overall survival and disease-free time, as well as being correlated with the T and N stages (tumor size and lymph node invasion) and, also, the degree of differentiation. In addition, a difference between Western and Eastern populations has been described, relating high expression of ALDH1 with worse overall survival in Eastern regions and worse disease-free survival in Western countries.[48] However, in addition to the biases inherent to the short follow-up time of the disease, since ALDH1 was a relatively recent marker at the time, and also to the small number of studies analyzed, it was possible to observe indications of errors in the meta-analysis, such as the attribution of 1 study carried out in Finland to Brazil.

Studies published later revealed that the association of ALDH expression with prognosis should take into account the specific characteristics of this expression, since generalized analysis can lead to misunderstandings and controversies.[43,45] In the study published by Holah et al.[45,] it is observed that epithelial expression is associated with a worse prognosis, while stromal expression, on the contrary, is associated with both a good prognosis and a smaller tumor size. This dissociation, in turn, can be explained based on the difference in expression between the subfamilies of ALDH1, as seen above, on the differences between ALDH1A1 and B1.[32,45]

In addition to the stimulating effects on tumor genesis, several studies have also shown a mechanism

of resistance to chemotherapy drugs, mediated by ALDH.[4,49] This mechanism has its main hypothesis based on the metabolic function of ALDH, involving the metabolism of alcohol and also of conventional chemotherapy drugs, such as oxazaphosphorin, cyclophosphamide, and procarbazine. Currently, approximately 14 different ALDH inhibitors are available, but they can cover only 3 of the 19 ALDH isoenzymes.[50] Even so, positive results are observed. In a study carried out with in vitro inhibition of ALDH in cell lines of colorectal carcinomas using diethylaminobenzaldehyde (DEAB) and also with molecular inhibition with siRNA (short interference RNA), the results showed that the inhibition by DEAB partially sensitized common chemotherapy drugs and the inhibition by siRNA led to the sensitization of some cell lines both capecitabine and 5-FU.[49]

Currently, the lines of research in relation to ALDH and CRC are directed to the study of the mechanisms related to AR for a better understanding of the relationship between tumor genesis and ALDH, the relationship between ALDH and prognosis, for a better use of this important marker, and also the development of specific drugs for the inhibition of ALDH activity.[51,52]

Future perspectives

Although the initial studies have pointed to ALCAM and ALDH1 as potential prognostic markers in CRC, there are still several points of conflict between the studies. These points are: 1) when studying the disease progression event in isolation, cases of lung metastasis and those that were not treated surgically had worse outcomes; 2) with regard to the event of death, also evaluated in isolation, outcomes were noted in patients with primary tumors of the rectum, advanced clinical stage (characterized by lymph node and metastatic disease), compromised surgical margins, presence of liver metastasis, and tumors with poorly differentiated histological grade, all factors that contribute to worse outcomes regardless of the positivity of the markers analyzed; 3) in the multivariate analysis between the factors lung metastasis, clinical stage, and ALCM marker, statistical significance was observed in the presence of lung metastasis, which did not occur with ALDH1, and a future study may clarify this finding. To minimize these points, it is necessary to make the maximum refinement in the research of these substances, quantitatively and qualitatively, so that the results can be conclusive.[53,54]

CONCLUSION

The immunohistochemical expression of the markers ALCAM and ALDH1 was not associated with the epidemiological and clinicopathologic characteristics evaluated. Regarding disease progression and death, it was also not possible to observe a relationship of correspondence with the markers evaluated.

Authors' contributions

Conceptualization: Cecilia Neves de Vasconcelos
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Methodology: Rodrigo K. Krebs
Writing (original draft): All authors
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