The value of calprotectin S100A8/A9 complex as a biomarker in colorectal cancer: A systematic review

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Summary

Purpose: Associations between inflammation and carcinogenesis have been reported for many years, as originally postulated by Virchow in his studies, but the results from prospective cohort studies remain controversial. We evaluated the role of calprotectin as a biomarker for colorectal cancer (CRC).

Methods: The MEDLINE/PubMed database was thoroughly searched using the keywords: "inflammation", "colorectal cancer, "calprotectin", "carcinogenesis" and/or "biomarkers". We focused on human and animal (rodent) studies of CRC and the role of calprotectin as a new biomarker and its potential value to the diagnosis, follow-up and CRC prognosis.

Results: According to the literature, calprotectin seems to be a reliable sensitive marker in the diagnosis and postoperative evaluation of CRC patients at the cost of low specificity and no correlation with the progress and stage of disease.

Conclusions: Calprotectin stands for a novel but well-evaluated biomarker in CRC. The experimental studies focus on the CRC microenvironment and suggest that malignant cells and tissues overexpress S100A8 and S100A9 and the heterodimer S100A8/A9.

Key words: biomarkers, calprotectin, carcinogenesis, colorectal cancer, inflammation

Introduction

CRC is the third most common malignancy worldwide [1], with the survival of patients with CRC being closely related to the stage at diagnosis. Early detection of CRC is associated with improved outcomes [2] and lower cost of treatment. Current screening tests for CRC include the detection of blood in stool samples and the visualization of gross abnormalities by colonoscopy. Colonoscopy is still the gold standard method for CRC screening, diagnosis and treatment with the obstacle of being invasive and thus being associated with poor patient acceptability and relatively high cost. In contrast, stool tests are non-invasive, do not require bowel preparation, may represent the entire colon, and are suitable for mass screening, and the specimens are easy to transport [1].

Stool markers are currently classified as those that leak through, are secreted by, or are shed from neoplastic cells [3]. Hemoglobin is a leaked protein measured in the conventional fecal occult blood test (FOBT), which is commonly used in large-scale CRC screening programs [1,4]. Calprotectin is another leaked protein that may be a marker for CRC [4]. These markers, however, have relatively poor sensitivity and specificity. Indeed, there are still no non-invasive screening tools that show high sensitivity and high specificity for CRC.

In this article we aimed to provide a summary and critical evaluation of the studies presenting

the potential role of calprotectin as a biomarker in CRC.

General principles

Biomarkers have attracted much attention in the field of cancer research as measurable molecules that express a specific biological process in the organism at a given time [5]. In order for a biomarker to be useful it should be able either to detect the disease itself or express its progression. So a useful biomarker should detect the presence of a subclinical malignant disease or be a measure of disease progression. Furthermore, a biomarker could define the optimal surveillance intervals and possibly identify pathogenic pathways which could guide monitoring and treatment. We should not fail to mention that in order for a biomarker to be employed in modern healthcare system, its use should be cost-effective.

S100A8 (calgranulin A or migration inhibitory factor-related protein 8; MRP-8) and its binding partner S100A9 (calgranulin B, or MRP-14) are members of the S100 calcium-binding family of proteins, which exhibit increased levels in a number of inflammatory and autoimmune states [6]. S100A8 and S100A9 form a heterocomplex, termed S100A8/A9 or calprotectin, but the 2 proteins may also have distinct functions and are regulated in part by different mechanisms [7].

The role of S100A8 and S100A9 in biology and disease is complex [8-10]. S100A8 and S100A9 (S100A8/A9) are generally viewed as inflammatory, but further studies have revealed both anti-inflammatory and immune regulatory actions [9,10]. They belong to a multigenic family of S100 proteins that are differentially expressed in a wide variety of cell types [11].

The effects of S100A8/A9 appear to be mediated by altered Ca^{+2} flux following the receptor for advanced glycation end products (RAGE) activation, because both cardiac S100A8 and S100A9 are found to co-immunoprecipitate with RAGE following lipopolysaccharides (LPS) injection and RAGE blockade abolishes the decreased Ca^{+2} flux by S100A8 or S100A9 [12]. Released S100A8/A9 exert extracellular functions, some of which are mediated by Toll-like receptor 4 (TLR4) [13], RAGE [12], or other receptors [14]. S100A8/A9 are released from damaged and dying cells or activated cells through an atypical pathway that appears to require protein kinase C [15] and RAGE [16], and S100A8 and S100A9 are therefore included in the group of proteins termed damage-associated molecular pattern (DAMP) molecules [10].

Methods

The MEDLINE/PubMed database was searched for publications with the medical subject headings ''inflammation, colorectal cancer, calprotectin, carcinogenesis, biomarkers''. Three independent reviewers (DM, AA and ES) performed the literature search, the study selection and the data extraction. All the references from the identified articles were searched for relevant information. The end date of the review was August 2015.

We focused on human and animal (rodent) studies of CRC and the role of calprotectin as a new biomarker and its potential value to the diagnosis, follow-up and CRC prognosis. We excluded articles that were not written in English or articles which their full texts and abstracts were not accessible or comprehensive. Moreover, we excluded review articles and meta-analyses from our pool of data.

Results

From the 21 articles that were deemed appropriate for analysis, the vast majority were clinical studies (prospective, case-control, randomized controlled trials and cross-sectional studies) and the rest were experimental studies based on tissue/cell lines.

Clinical studies

Meucci et al. [17] showed that in unselected outpatients referred for colonoscopy the mean levels of calprotectin were significantly higher in patients with neoplastic and inflammatory disorders when compared with subjects with a normal colonoscopy or trivial endoscopic findings (p<0.05). Elevated calprotectin levels (>50 mg/dl) were detected in 85% of the patients with CRC, and 81% of those with inflammatory conditions but also in 37% of patients with normal or trivial endoscopic findings [17].

Parente et al. [18] in their study tested the hypothesis that a combination of fecal tests, such as tumor M2-PK, calprotectin and i-FOBT, performed on a single stool sample, may help identify patients with a higher risk of CRC in a selected population of patients requiring colonoscopy for alarming abdominal symptoms. In terms of tumor M2-PK, with a cut-off level at 4 U/ml, the overall sensitivity for CRC was 87% (95% CI: 75-94); this detection rate is superior to the sensitivity of both i-FOBT and fecal calprotectin, which were 62% (95% CI: 47-74) and 86% (95% CI: 62-93), respectively. With a cut-off level of 10 U/ml, M2-PK sensitivity for CRC reduced to 68% (95% CI: 54-

79), but specificity increased to 89% (95% CI: 84-92), which is similar to that of i-FOBT. In terms of sensitivity by tumor stage, no relevant difference could be found between stages I and IV, although sensitivity was maximal for stage IV. The specificity of tumor M2-PK in terms of detecting CRC in this study was estimated to be 63% (95% CI: 56-69) at the proposed cut-off level of 4 U/ml; this rate was superior to that of calprotectin, which was 40% (95% CI: 33-46), but inferior to FOBT, which was 89% (95% CI 84-92). Considering the still high false-positive rate of M2-PK and also of calprotectin, it is very important to enhance the accuracy of the tests, by combining them with other markers.

Luley et al. [19] investigated the expression levels and localization of calprotectin in normal and neoplastic tissue in patients with colorectal tumors, polyps, and in healthy controls. Mucosal calprotectin was expressed in significantly higher concentrations in carcinoma (94.2±31.2 ng/mg total protein) and adenoma (122.8±60.3 ng/mg total protein) in comparison with mucosal biopsies from healthy controls (20.4±5.4 ng/mg total protein), tumor-adjacent mucosa from patients with CRC (21.6±5.1 ng/mg total protein), and adenoma (45±14.6 ng/mg total protein, all p<0.05) [19]. Immunohistochemistry showed calprotectin reactivity mainly in granulocytes and macrophages with only singular reactive epithelial cells [19]. These data clearly demonstrated that in colorectal neoplasia, calprotectin expression is a tumor-specific and early event accompanied by active neutrophil recruitment.

Tibble et al. [4] compared the sensitivity and specificity of fecal calprotectin and FOBT in patients with CRC. Median fecal calprotectin concentration in patients with CRC (101 mg/l, 95% CI 57-133) differed significantly from normal (2.3 mg/l, 95% CI 1.6-5.0) with 90% of patients having elevated levels (normal <10 mg/l) whereas only 58% had positive FOBT (p<0.05). There was no significant difference in fecal calprotectin levels when considering location or Dukes' tumor stage. Fecal calprotectin appears to be a simple non-invasive surrogate marker of inflammation in patients with CRC/adenomatous polyps. It has a number of significant advantages over FOB testing in the detection of colorectal neoplasia, most notably a sensitivity of 79% compared with 43% when considering malignancy and polyps as a whole.

Kim et al. [20] investigated whether a combination of the FOBT and fecal calgranulin B (CALB) has increased sensitivity and specificity for a diagnosis of CRC. Mean CALB level was significantly higher in CRC patients than in controls (p<0.001) whereas it was not associated with tumor stage or cancer site [20].

Lehmann et al. [21] determined calprotectin release before and after CRC operation and compared it with and histopathological parameters. Out of 80 patients with CRC 26 had rectal carcinoma, 29 had left-sided tumors, 23 had right-sided tumors and 2 had bilateral carcinoma. In total, 71.2% of the patients had increased levels of calprotectin before the operation (median 205 µg/g, range 50-2405) and experienced a significant decrease three months after the operation (46 µg/g, range 10-384, p<0.0001) [21]. Patients with T3 and T4 tumors had significantly higher values than those with T1 and T2 cancers (p=0.022) [21]. For all other tumor parameters (nodes, metastases, grade) and location, no significant difference in calprotectin concentration was found [21].

Kristinsson et al. [22] evaluated the role of calprotectin in detecting colorectal neoplasia in first degree relatives of patients with CRC. Out of 253 first degree relatives of patients with CRC, 5 cases had asymptomatic cancers. The specificity of fecal calprotectin for adenomas at cut off levels ≤10, ≤15, and ≤20 mg/l were 47.4, 59.6 and 71.1%, respectively [22]. The sensitivity at the same cut off levels was 56.2, 45.2 and 31.5% and 4/5 of patients with carcinoma had calprotectin values >15 mg/l [22]. The sensitivity of FOBT for adenomas was 8%, and 4/5 of patients with carcinoma had negative FOBT. The specificity for adenomas was 95%.

The same team evaluated the calprotectin expression in CRC patients and investigated the potential correlation of calprotectin with localization or staging of the tumor and the effect of surgical treatment [23]. They found a median fecal calprotectin concentration of 50 (range 2-950) mg/l in CRC patients, which was significantly (p<0.0001) higher than in control patients (median 5.2 mg/l) [23]. After surgery the values of calprotectin fell greatly [23]. There were no significant differences in fecal calprotectin concentration among patients with different tumor stages [23].

Hoff et al. [24] in the Norwegian Colorectal Cancer Prevention (NORCCAP) trial evaluated the potential role of fecal calprotectin as a screening test compared with flexible endoscopy and FOBT. The calprotectin test was positive in 24-27% of screenees irrespective of the risk of progression of adenomas [24]. Additionally, only 63% of CRCs

cases had a positive calprotectin test. The specificity of calprotectin for any neoplasia and not only malignancies was 76% [24]. Due to low specificity, calprotectin was evaluated as inappropriate screening modality for CRC.

Karl et al. [25] initiated a proteomics-based search for novel biomarkers to improve the sensitivity of detection of CRC in stool samples including iFOBT, hemoglobin-haptoglobin, calprotectin, carcinoembryogenic antigen, and the novel fecal markers tissue inhibitor of metalloproteinase-1 (TIMP-1) and S100A12. Calprotectin was one of them and presented an area under the curve (AUC) of 0.9 [25]. The highest sensitivity (88%) for the detection of CRC at 95% specificity was obtained with the marker pair S100A12 and hemoglobin-haptoglobin [25].

Khoshbaten et al. [26] evaluated the diagnostic value of fecal calprotectin as a screening biomarker for gastrointestinal (GI) malignancies. The mean fecal calprotectin level was 241.1±205.2 (range 3.4-610.0, median 19.3) in CRC group with the difference between CRC and control group being statistical significant at the level of 0.001 [26]. The optimal cut-off point for fecal calprotectin was ≥75.8 mg/L for distinguishing CRC from normal cases (sensitivity and specificity of 80% and 84%, respectively) [26]. These results indicate that fecal calprotectin might be a useful and non-invasive biomarker for distinguishing CRC from non-malignant GI conditions.

Kronborg et al. [27] investigated the pretest values of fecal calprotectin for the detection of adenomas in high risk individuals undergoing colonoscopy. They found that calprotectin levels in cancer patients were significantly higher than those in all other subgroups (median 17.6 mg/l, range 11.5-31.0) [27]. With a cut off limit of 10 mg/l, the sensitivity for cancer was 74% and for adenoma 43% [27]. Specificity values were 64% for no cancer and 67% for no neoplasia (cancer+adenoma) [27]. Due to low specificity values, calprotectin is not an appropriate screening marker for CRC despite its usefulness in diagnosing CRC in high-risk patients.

Limburg et al. [28] prospectively evaluated the role of calprotectin as a screening biomarker in above-average risk CRC patients. Fecal calprotectin levels did not differ significantly between subjects vs subjects without colorectal neoplasms (p=0.33) [28]. Number of malignant lesions (p=0.85) or tumor size (p=0.86) did not significantly affect fecal calprotectin concentrations [28]. Thus the authors discouraged the application of calprotectin as a screening biomarker in CRC patients.

Johne et al. [29] found fecal calprotectin levels significantly elevated in symptomatic CRC and in asymptomatic CRC detected in high risk subjects. Calprotectin levels were significantly decreased 3 months after cancer removal [29]. A cut-off limit of 50 μg/g resulted in a sensitivity of 89% in CRC patients and 79% in high risk subjects [29].

Damms et al. [30] found increased calprotectin levels in CRC (164 μg/g) compared to the control group (median 25.8 μg/g). Calprotectin was effective in identifying CRC but lacked analytical sensitivity in separating CRC from adenoma as well as adenoma from the control group [30].

Table 1 summarizes the role of calprotectin in CRC based on the results of clinical studies.

Experimental studies

Ang et al. [31] studied S100A8/A9-expressing cells in colorectal tumors relating their presence to clinicopathological parameters and Smad4 status. Loss of Smad4 expression was observed in 14% colorectal tumors and was associated with reduced numbers of S100A8-positive (p=0.03) but not S100A9-positive stromal cells (p=0.26) [31]. High S100A9 cell counts were associated with large tumor sizes (p=0.0006), poor grade of differentiation (p=0.036) and poor survival in patients with Smad4-negative tumors (p=0.02) [31].

Duan et al. [32] analyzed the roles and molecular mechanisms of S100A8 and S100A9 in CRC and matching distal normal tissues in vitro. S100A8 and S100A9 were elevated in more than 50% of CRC tissues and their expression in tumor cells was associated with grade of differentiation, Dukes' stage and lymph node metastasis [32]. Moreover, CRC cell lines treatment with recombinant S100A8 and S100A9 proteins promoted the viability and migration of CRC cells [32].

Ichikawa et al. [33] evaluated S100A8/A9 as activators of key genes and pathways in colon tumor progression. They found that chemokines were upregulated in tumors and elevated in sera of tumor-bearing wild-type S100A9 mice [33]. Mice lacking S100A9 showed significantly reduced tumor incidence, growth and metastasis, reduced chemokine levels, and reduced infiltration of CD11b(+)Gr1(+) cells within tumors and pre-metastatic organs [33]. This was attributed to the fact that products of these genes promote leukocyte recruitment, angiogenesis, tumor cell migration, wound healing, and formation of pre-metastatic niches in distal metastatic organs.

Table 1. Summary of clinical studies evaluating the role of calprotectin in CRC

Authors	Year	Study design	Biomarkers	Conclusions	Statistical analysis
Parente et al [18]	2012	Prospective study	i-FOBT, M2-PK, calprotectin	For CRC detection: The best combination to predict the risk of CRC was i-FOBT+M2-PK Calprotectin presented a low specificity for the disease.	i-FOBT: specificity=0.89, PPV=0.53. M2-PK: sensitivity=0.87, NPV=0.96. Calprotectin: sensitivity=0.93, NPV= 0.93, specificity=0.39.
Meucci et al [17]	2010	Prospective study	Calprotectin	Fecal calprotectin cannot identify those with significant colorectal disease. Normal results can rule out organic disease among patients with bowel symptoms.	Organic disease: sensitivity=1 NPV=1 Functional disease: sensitivity=1 NPV=1. $p<0.05$.
Luley et al [19]	2011	Case-control study	Calprotectin	Calprotectin points out a possible biological link between inflammation and neoplastic transformation in CRC.	$p<0.04$.
Tibble et al [4]	2001	Case-control study	Calprotectin and FOBT	Fecal calprotectin is a sensitive non-invasive marker of CRC. It is more sensitive than FOBT at the cost of a somewhat lower specificity.	Calprotectin: sensitivity=0.79, specificity=0.72. FOBT: sensitivity=0.43, specificity=0.92 for CRC.
Kim et al [20]	2014	Case-control study	Calgranulin B (CALB) and FOBT	A combination of FOBT and CALB may have greater sensitivity and specificity for predicting CRC than using a single marker.	CALB: specificity=0.90, sensitivity=0.89.
Lehmann et al [21]	2014	Prospective study	Calprotectin	Fecal calprotectin decreases significantly after CRC operation. Its value depends exclusively on the individual T-stage.	Calprotectin before and after operation: $p<0.001$. Correlation of calprotectin and tumor parameters: $p=0.132$.
Kristinsson et al [22]	2001	Cross sectional study	Calprotectin and FOBT	In a high risk group like first degree relatives of patients with CRC, fecal calprotectin could be considered as first test in selecting patients for endoscopy.	Calprotectin levels<20 mg/l: specificity= 0.71, sensitivity=0.31.
Hoff et al [24]	2005	Randomized control trial (RCT)	Calprotectin and FOBT	Fecal calprotectin cannot be recommended for population screening purposes.	Calprotectin: PPV=0.25, sensitivity=0.27, specificity=0.76. FOBT: PPV=0.12, sensitivity= 0.35, specificity=0.90.
Karl et al [25]	2008	Case-control study	Six biomarkers. One of them was calprotectin	Depending on the specificity selected, calprotectin was not evaluated as a reliable marker.	S100A12 AUC=0.95, TIMP-1 AUC=0.92, hemoglobin-haptoglobin AUC=0.92, hemoglobin AUC=0.91, calprotectin AUC=0.90, carcinoembryogenic antigen AUC=0.66.
Khoshbaten et al [26]	2014	Case-control study	Calprotectin and FOBT	Fecal calprotectin is a useful marker for distinguishing CRC from non-malignant GI conditions. That is not the case for gastric cancer.	Calprotectin: sensitivity=0.8 and specificity=0.84.
Kronborg et al [27]	2000	RCT	Calprotectin and FOBT	Fecal calprotectin is a useful marker for CRC diagnosis in high risk groups, but specificity is too low for screening of average risk persons.	Calprotectin: sensitivity=0.74, specificity=0.64.
Limburg et al [28]	2003	Prospective study	Calprotectin and FOBT	In above average risk CRC patients, fecal calprotectin was a poor screening biomarker for colorectal neoplasia.	Calprotectin: sensitivity=0.37, specificity=0.63, PPV=0.23, NPV=0.76.
Johne et al [29]	2001	Case-control study	Calprotectin	Calprotectin could be used as a screening marker in high risk groups for CRC.	Calprotectin: sensitivity=0.89, specificity=0.68, NPV=0.99.
Damms et al [30]	2008	Case-control study	Calprotectin	Fecal calprotectin is effective in identifying active IBD and CRC but lacks analytical sensitivity in separating CRC from adenoma as well as adenoma from the control group.	Calprotectin: sensitivity=1, specificity=0.79, AUC=0.922.

CRC: colorectal cancer, PPV: positive predictive value, NPV: negative predicted value, GI: gastrointestinal. For other abbreviations see text.

Table 2. Summary of experimental studies evaluating the mechanisms of the involvement of calprotectin in CRC

Authors	Year	Study design	Biomarkers	Mechanism	Conclusions
Ang et al [31]	2010	Experimental-cell lines	S100A8/A9	S100A8 and S100A9 activated Smad4 signaling as evidenced by phosphorylation of Smad2/3; blockade of the receptor for the advanced glycation end products inhibited this response.	S100A8 and S100A9 enhanced migration and proliferation in Smad4-positive and Smad4-negative cancer cells. Transient depletion of Smad4 resulted in loss of responsiveness to exogenous S100A8, but not S100A9.
Duan et al [32]	2013	Experimental-cell lines	S100A8/A9	β-catenin over-expression in CRC cells by Adβ-catenin increased cell viability and migration. β-catenin knock-down by Ad-siβ-catenin reduced cell viability and migration.	S100A8 and S100A9 are linked to the CRC progression
Ghavami et al [39]	2004	Experimental-cell lines	S100A8/A9	Annexin V/phosphatidylinositol staining revealed that cell death was mainly of the apoptotic type. The apoptotic effect of human S100A8/A9 and DTPA was inhibited significantly (p<0.05) by Zn^{+2} and Cu^{+2}.	S100A8/A9 exerts its apoptotic effect on two colon carcinoma cell lines through a dual mechanism.
Ichikawa et al [33]	2011	Experimental-cell lines	S100A8/A9	S100A8/A9 interacts with RAGE and carboxylated glycans on colon tumor cells and promotes activation of MAPK and NF-κB signaling pathways.	S100A8/A9 activates specific downstream genes associated with tumorigenesis and in promoting tumor growth and metastasis.
Kim et al [34]	2012	Experimental-cell lines	S100A8/A9	IL-6 induced STAT3-dependent upregulation of S100A8/A9 and IL-8 was associated with positive feedback activation of S100A8/A9.	IL-6 and IL-8 released from myofibroblasts upregulate S100A8/A9 in CRC microenviroment.
Stulik et al [35]	1999	Experimental-cell lines	S100A8 and S100A9	Possible apoptotic mechanisms.	A possible participation of S100A8 and S100A9 in CRC regression.

For abbreviations see text

Kim et al. [34] investigated the role of myofibroblasts in the upregulation of S100A8/A9 as well as in the differentiation of myeloid cells in the CRC microenvironment. They found an increased expression of S100A8/A9 in inflammatory cells of the peri- and intra-tumoral areas, along with myofibroblasts in colon cancer tissue [34].

Stulik et al. [35] evaluated the expression of S100A8 and S100A9 in tissues of macroscopically normal colon mucosa and CRC. The level of S100A9 protein, in comparison with matched normal colon mucosa, was significantly increased in malignant tissues in 70% of the cases [35]. Furthermore, S100A8 exhibited an increased expression in the same specimens of malignant tissues as the S100A9 protein [35]. There was no correlation between the severity of disease and the over-expression of S100A9 [35].

Table 2 summarizes the mechanisms of expression and action of S100A8 and S100A9 as proteins and heterocomplex in normal and malignant colon cells.

Discussion

The fecal calprotectin method seems to be a useful adjuvant tool to the investigation of patients at high risk for colorectal neoplasia, but its value in a truly asymptomatic population such as those who would be considered for entry into a national screening program for CRC needs to be further determined. A meta-analysis suggested that patients with colorectal neoplasia had non-significantly higher calprotectin levels (132.2 μg/g) compared with non-cancer controls (p=0.18) [36]. Sensitivity and specificity of calprotectin for the diagnosis of CRC were 0.36 and 0.71, respectively, with an AUC of 0.66 [36]. Thus, calprotectin cannot be recommended as a screening test for CRC in the general population [36].

The increase of calprotectin in CRC patients is, however, highly variable with levels ranging from insignificant to 100% sensitivity [17-28,30,36]. CRC is associated with a local acute inflammatory reaction of variable intensity. The recruitment of

neutrophils to the tumor site is hypothesized to be due to the local release of chemotactic factors [4,22]. Calprotectin enters the bowel lumen by migration rather than by bleeding or shedding of tumor cells. The neutrophilic infiltrate is variable and might be related to the tumor size, suggesting calprotectin would be a less sensitive marker in smaller tumors [37].

Being mainly an inflammation-related malignancy, CRC consists of an acute inflammation phase, a chronic inflammation phase and a tumorigenesis phase. Both glycans and RAGE are important in the chronic inflammation and tumorigenesis phases. The signals and stage of disease that trigger the expression of carboxylated glycans and RAGE on colon tumor cells and of the stimuli that promote infiltration of S100A8/A9-positive myeloid progenitors within the tumors are not known. Mediators such as vascular endothelial growth factor, TNFα and transforming growth factor-β secreted in response to inflammation or tumor hypoxia mobilize S100A8/A9-positive cells that promote pre-metastatic niches in the lung, facilitating thus homing of tumor cells to metastatic sites [38].

Conclusions

Calprotectin stands for a novel but well-evaluated biomarker in CRC. It seems to be a reliable sensitive marker in diagnosis and postoperative evaluation of CRC patients at the cost of low specificity and no correlation with the progress and stage of disease. The experimental studies on the subject are mainly focused on the CRC microenvironment and mainly suggest that malignant cells and tissues overexpress S100A8 and S100A9 and the heterodimer S100A8/A9. The main pathway of action seems to be that of programmed cell death (apoptosis).

Authors' contributions

DM: study concept and design; DM,AA,ES: acquisition of data; DM,AA,ES: analysis and interpretation of data; DM,DD,NN: drafting of the manuscript; GAM,AP,NN,EF: critical revision of the manuscript for important intellectual content; NN, EF: study supervision.

Conflict of interests

The authors declare no confict of interests.

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