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# Monocarboxylate transporters 1 and 4 are associated with CD147 in cervical carcinoma

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**Abstract**. Due to the highly glycolytic metabolism of solid tumours, there is an increased acid production, however, cells are able to maintain physiological pH through plasma membrane efflux of the accumulating protons. Acid efflux through MCTs (monocarboxylate transporters) constitutes one of the most important mechanisms involved in tumour intracellular pH maintenance. Still, the molecular mechanisms underlying the regulation of these proteins are not fully understood. We aimed to evaluate the association between CD147 (MCT1 and MCT4 chaperone) and MCT expression in cervical cancer lesions and the clinico-pathological significance of CD147 expression, alone and in combination with MCTs. The series included 83 biopsy samples of precursor lesions and surgical specimens of 126 invasive carcinomas. Analysis of CD147 expression was performed by immunohistochemistry. CD147 expression was higher in squamous and adenocarcinoma tissues than in the non-neoplastic counterparts and, importantly, both MCT1 and MCT4 were more frequently expressed in CD147 positive cases. Additionally, co-expression of CD147 with MCT1 was associated with lymph-node and/or distant metastases in adenocarcinomas. Our results show a close association between CD147 and MCT1 and MCT4 expressions in human cervical cancer and provided evidence for a prognostic value of CD147 and MCT1 co-expression.

Keywords: CD147, monocarboxylate transporters, cervical carcinoma

## 1. Introduction

In order to maintain high growth rates in hypoxic environment, cancer cells switch to anaerobic glycolysis to obtain energy. Actually, this metabolic change is maintained even in the presence of oxygen, as described by Warburg [1]. One consequence of cytosolic glucose metabolism is the increase in intracellular lactic acid concentration, which has to be tightly regulated to allow tumour cell survival and proliferation. Acid efflux through Monocarboxylate Transporters (MCTs) constitutes one of the most important mechanisms involved in the maintenance of tumour intracellular pH [2]. Indeed, MCT upregulation has been recently reported in some tumours, including brain [3–5], colorectal [6,7], lung [8] and, more recently, we described upregulation of MCT1 and 4 in cervical cancer [9].

MCT expression appears to be influenced by altered physiologic conditions, however, the underlying molecular events involved in MCT regulation are poorly understood. Recently, it was demonstrated that prop-

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er expression and activity of MCT1 and MCT4 requires an ancillary protein known as CD147 or EMMPRIN [10–12]. On the other hand, silencing studies showed that maturation and cell surface expression of CD147 depends on MCT1 and MCT4 expressions [13, 14]. CD147 has already been described as a key element in tumour growth and metastasis by stimulating the synthesis of several matrix metalloproteinases, leading to enhanced tumour cell invasion [15,16], and also by stimulating angiogenesis [17]. This protein is described to be up-regulated in several human cancers [16,18,19], including cervical squamous cell carcinoma [20], where it was found to correlate with pelvic lymph-node metastasis and resistance to radiotherapy [21].

Given that CD147 is described as an MCT regulator, we aimed to assess the association between CD147 and MCT1, MCT2 and MCT4 expressions, in a large and complete series of cervical lesions. Also, and since CD147 is poorly explored in cervical carcinoma, we intended to unveil the prognostic value of CD147 expression, alone and in combination with MCTs.

## 2. Materials and methods

### *2.1. Case selection*

The material studied comprised 83 formalin-fixed paraffin embedded samples selected from the files of Pathology Division of Adolfo Lutz Institute, São Paulo, Brazil, which included biopsies of 28 chronic cervicitis (herein designated as "negative" for HPV-induced lesion), 26 Cervical Intraepithelial Neoplasia grade I (CIN 1, herein designated as low-grade squamous intraepithelial lesion – LSIL) and 29 Cervical Intraepithelial Neoplasia grades II and III (CIN2/3, herein designated as high-grade squamous intraepithelial lesions - HSIL). We also analyzed a series of formalin-fixed, paraffin-embedded tissue samples from 126 patients with squamous cells carcinoma (SCC, $n = 49$), adenocarcinoma (AC, $n = 50$) and adenosquamous carcinoma (ASC, $n = 27$) of the uterine cervix, examined and treated at two Institutions: Araújo Jorge Hospital and the Pathology Department of the School of Medicine of the Federal University of Goiás, Goiania, in Goiás State, Brazil. All histopathological diagnoses were revised and categorized according to the WHO classification [22]. Clinico-pathological data of the patients included age at diagnosis, HPV status, lymph-node and/or distant metastasis, recurrence and overall survival.

### *2.2. MCT immunohistochemistry*

Data on MCT1, MCT2 and MCT4 expressions was available for all the 209 samples [9]. MCT immunohistochemistry was performed according to avidin-biotin-peroxidase complex principle (R.T.U. VECTASTAIN Elite ABC Kit (Universal), Vector Laboratories, Burlingame, CA, USA), with the primary antibodies for MCT1 (AB3538P, Chemicon International, Temecula, CA, USA), MCT2 (sc-14926, Santa Cruz Biotechnology, Santa Cruz, CA, USA) and MCT4 (AB3316P, Chemicon International, Temecula, CA, USA), diluted 1:200, as previously described [7].

### *2.3. CD147 immunohistochemistry*

CD147 immunohistochemistry was performed based on the streptavidin–biotin–peroxidase complex principle (Ultravision Detection System Anti-polyvalent, HRP, Lab Vision Corporation, Fremont, CA), using a primary antibody raised against CD147 (18-7344, ZYMED Laboratories Inc., South San Francisco, CA, diluted 1:750). Briefly, deparaffinized and rehydrated sections were immersed in EDTA (pH 8.0), heated up to 98°C in a water bath for 15 minutes and washed in PBS. Endogenous peroxidases were inactivated with 3% hydrogen peroxide in methanol for 10 minutes, followed by washing in PBS. Tissue sections were incubated with blocking solution for 10 minutes and incubated at room temperature with the primary antibody for 2 hours. Sections were then sequentially washed in PBS and incubated with biotinylated goat anti-polyvalent antibody for 10 minutes, streptavidin peroxidase for 10 minutes, and developed with 3,3'-diamino-benzidine (DAB+ Substrate System, Dako, Carpinteria, CA) for 10 minutes. Negative controls were performed by using the adequate serum control (N1698, Dako, Carpinteria, CA) and cervical squamous carcinoma was used as positive control. Tissue sections were counterstained with haematoxylin and permanently mounted.

### *2.4. Immunohistochemical evaluation*

Sections were evaluated for immunoreaction, which included cytoplasmic and/or membrane positive staining. Immunoreaction extent was scored semi-quantitatively as follows: 0: 0% of immunoreactive cells; 1: $< 5\%$ of immunoreactive cells; 2: 5–50% of immunoreactive cells; and 3: $> 50\%$ of immunoreactive cells. Also, intensity of staining was scored semi-

qualitatively as 0: negative; 1: weak; 2: intermediate; and 3: strong. Immunoreaction final score was defined as the sum of both parameters (extent and intensity), and grouped as negative (score 0 and 2) and positive (3–6), as previously described [7]. Finally, since plasma membrane location of CD147 is essential for MCT1 and MCT4 membrane localization and activity [10–12], we also grouped the plasma membrane positive cases, including all the positive cases, with or without cytoplasmic expression. Immunohistochemical evaluation was performed blindly by two independent observers and discordant results were discussed in a double-head microscope and a final score was agreed.

### *2.5. Statistical analysis*

Data were stored and analyzed using the SPSS statistical software (version 14.0, SPSS Inc., Chicago, IL, USA). The comparison of CD147 expression between tumor and normal cells as well as the relationship between CD147 expression and the clinico-pathological parameters were examined for statistical significance using Pearson's chi-square ($\chi^2$) test and Fisher's exact test (when $n < 5$), being threshold for significance $p$ values $< 0.05$. The same analysis was performed in order to compare CD147 expression with MCTs. Survival curves were plotted using the method of Kaplan and Meier and data compared using the log-rank test, using a cut-off of 24 months. Due to lack of information, 18 cases of SCC and 1 case of ASC were not evaluated for clinico-pathological significance.

## 3. Results

We analyzed the expression of CD147 in a series of cervical samples which included 83 biopsies of cervix intraepithelial lesions and 126 surgical specimens of invasive cervical carcinomas. CD147 expression was mainly found in the plasma membrane (Fig. 1), with cases presenting both membrane and cytoplasmic staining and some only cytoplasmic expression. Figure 2 compares the frequency of CD147 expression in all the squamous epithelial lesions studied, as well as non-neoplastic and neoplastic glandular tissues. CD147 expression was significantly different in the various squamous epithelial lesions ($p < 0.001$, Fig. 2), showing a more frequent expression in squamous neoplasias than in their non-neoplastic counterparts. Concerning the glandular epithelium, since our series does not include adenocarcinoma precursor lesions, it was only possible

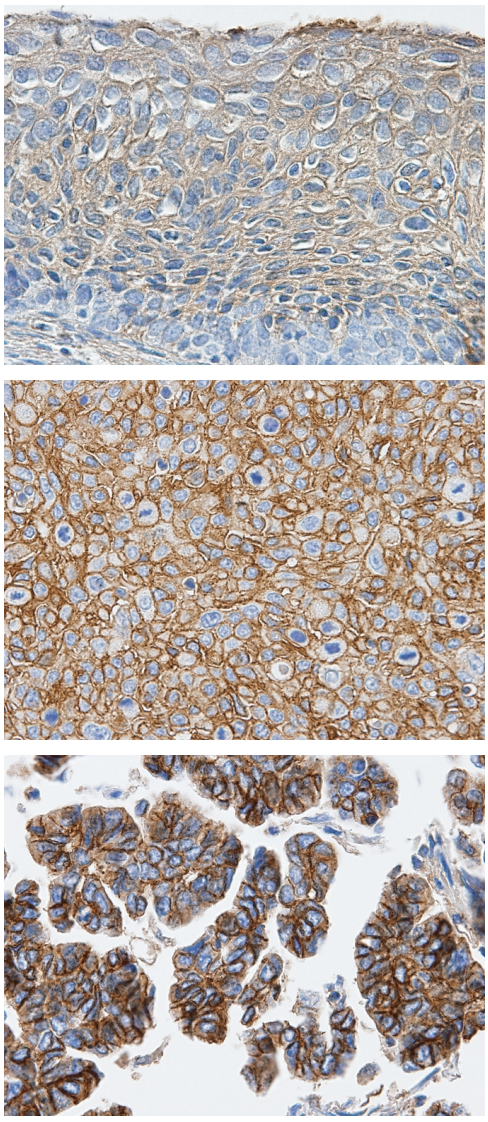


Fig. 1. Immunohistochemical expression of CD147 in cervical lesions. Representative cases of CD147 expression in: high-grade squamous intraepithelial lesion (**A**); squamous cell carcinoma (**B**); adenocarcinoma (**C**). All pictures are at 400X magnification.

to compare neoplastic lesions (AC) with non-neplastic glandular tissue from the biopsy material. Here, an evident gain in CD147 expression was observed in adenocarcinoma tumour cells (Fig. 1C), when compared to normal glandular tissue ($p < 0.001$, Fig. 2).

HPV status of the biopsy material was known and samples included 50/88 high risk HPV positive cases (6/28 cervicitis, 16/26 LSIL and 28/29 HSIL); however, no association was found between HPV infection and CD147 expression (data not shown). The clinico-pathological significance of CD147 expression, as well

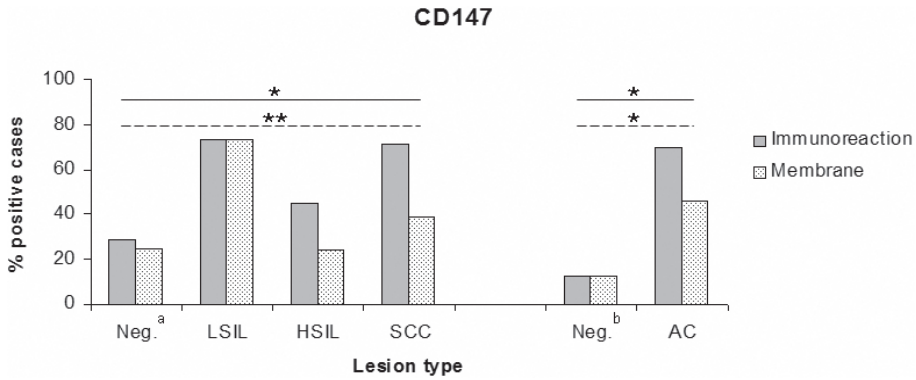


Fig. 2. Frequency of CD147 staining in all squamous lesions studied, including non-neoplastic and neoplastic glandular tissues. "Immunoreaction" refers to both cytoplasmic and membrane positive staining; "membrane" refers to plasma membrane positive cases, with or without cytoplasmic expression; [a]negative for HPV-induced cervical lesions; [b]non-neoplastic glandular epithelium; continuous line: statistical significance for immunoreaction results; interrupted line: statistical significance for membrane staining results; *$p < 0.001$; **$p = 0.001$. LSIL – low-grade squamous intraepithelial lesion; HSIL – high-grade squamous intraepithelial lesion; SCC – squamous cell carcinoma; AC – adenocarcinoma.

as co-expression of CD147 and both MCT1 and MCT4 was assessed for 99 carcinomas (Table 1). Considering all primary tumours, no association was found with the clinico-pathological data; however, since the 3 histological types behave differently and probably present different metabolic activity, associations were assessed by histological type. Regarding individual expression of CD147, no significant associations were observed, but co-expression of CD147 with MCT1 was significantly associated with lymph-node and/or distant metastases in adenocarcinomas ($p = 0.033$). No statistically significant associations were found with survival data (data not shown).

Consistent with the assumption that CD147 functions as a regulator of MCT1 and MCT4 expressions, we observed that both MCT1 and MCT4 correlated with CD147 immunoreaction ($p = 0.001$ for MCT1 immunoreaction and MCT4 plasma membrane expression; $p = 0.002$ for MCT1 plasma membrane expression and MCT4 immunoreaction, Table 2), while only MCT4 immunoreaction was associated with plasma membrane expression of CD147 ($p = 0.014$, Table 2). As anticipated, no association was found between CD147 and MCT2 expressions.

## 4. Discussion

MCTs were recently described as crucial proteins in cancer cell pH homeostasis [2]. Although regulation of MCT expression is still far from being well understood, one of the best characterized MCT regulation mechanisms is through the co-expression with CD147 at the plasma membrane [10–13].

The important contribution of CD147 in promoting tumour growth, invasion and metastasis has been widely explored in past years [16,19], however, in what concerns cervical cancer, this issue is far from being clarified. Here, we describe the expression of CD147 in a complete series of cervical carcinoma but also look at an important feature of this protein, little explored in cancer: the association with MCTs. In the present study, we observed an increase in CD147 expression in both squamous and glandular tumours, when compared to non-neoplastic corresponding tissues. Nonetheless, in opposition to previous results from Sier and collaborators [20], who described no staining in normal epithelial cells, we observed a considerable expression of CD147 in the non-neoplastic epithelium. However, the non-neoplastic epithelium herein described was in fact biopsy material from cervicitis, which may explain the presence of CD147, knowing that this protein has a role in inflammation [23]. The frequency of CD147 expression in our tumour series was around 70%, which is in accordance with previous results in cervical squamous cell carcinomas [21]. In opposition to what we previously observed for MCT2 and MCT4 [9], CD147, like MCT1, was not differently expressed among the three histological types studied and no association was observed with the clinico-pathological data, namely with lymph-node metastases, contrasting with what has been recently described [21].

Taking into consideration the close association between CD147 and MCTs [10–14], we sought for correlations between these proteins in a series of cervical lesions. We observed that both MCT1 and MCT4 overexpressions correlated with CD147, while only MCT4 was associated with CD147 plasma membrane stain-

Table 1
Correlation of CD147 and combined CD147 and MCT expressions with the clinico-pathological data of carcinoma cases

| | Expression | | CD147 immunoreaction | | CD147 membrane | | CD147+MCT1 | | CD147+MCT4 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Clinical data | | n | Positive (%) | $p$ | Positive (%) | $p$ | Positive (%) | $p$ | Positive (%) | $p$ |
| All carcinomas | | | | | | | | | | |
| Age[a] | | | | 0.204 | | 0.941 | | 0.598 | | 0.200 |
| | $>49$ | **48** | 64.6 | | 45.8 | | 16.7 | | 19.1 | |
| | $\leqslant 49$ | **58** | 75.9 | | 46.6 | | 20.7 | | 10.3 | |
| Histological type | | | | 0.734 | | 0.755 | | 0.819 | | 0.683 |
| | SCC | **49** | 71.4 | | 38.8 | | 16.3 | | 10.2 | |
| | AC | **50** | 70.0 | | 46.0 | | 20.0 | | 16.0 | |
| | ASC | **27** | 63.0 | | 44.4 | | 14.8 | | 14.8 | |
| Lymph node/metastases[b] | | | | 0.539 | | 0.254 | | 0.149 | | 0.376 |
| | Absent | **79** | 69.6 | | 43.0 | | 15.2 | | 12.8 | |
| | Present | **25** | 76.0 | | 56.0 | | 28.0 | | 20.0 | |
| Recurrence | | | | 1.000 | | 0.729 | | 0.667 | | 0.495 |
| | Negative | **95** | 70.5 | | 45.3 | | 17.9 | | 13.8 | |
| | Positive | **9** | 77.8 | | 55.6 | | 22.2 | | 22.2 | |
| SCC | | | | | | | | | | |
| Age[a] | | | | 1.000 | | 0.576 | | 0.664 | | 0.607 |
| | $>49$ | **14** | 78.6 | | 42.9 | | 14.3 | | 7.1 | |
| | $\leqslant 49$ | **17** | 82.4 | | 52.9 | | 23.5 | | 17.6 | |
| Lymph node/metastases[b] | | | | 0.553 | | 0.172 | | 1.000 | | 0.112 |
| | Absent | **26** | 76.9 | | 42.3 | | 19.2 | | 7.7 | |
| | Present | **5** | 100.0 | | 80.0 | | 20.0 | | 40.0 | |
| Recurrence | | | | | | | | | | |
| | Negative | **31** | 80.6 | | 48.4 | | 19.4 | | 12.9 | |
| | Positive | **0** | | | | | | | | |
| AC | | | | | | | | | | |
| Age[a] | | | | 0.305 | | 0.674 | | 0.942 | | 0.130 |
| | $>49$ | **24** | 62.5 | | 50.0 | | 20.8 | | 26.1 | |
| | $\leqslant 49$ | **25** | 76.0 | | 44.0 | | 20.0 | | 8.0 | |
| Lymph node/metastases[b] | | | | 0.405 | | 0.446 | | **0.033** | | 0.613 |
| | Absent | **39** | 66.7 | | 43.6 | | 12.8 | | 15.8 | |
| | Present | **8** | 87.5 | | 62.5 | | 50.0 | | 25.0 | |
| Recurrence | | | | 0.657 | | 0.690 | | 1.000 | | 0.587 |
| | Negative | **40** | 67.5 | | 45.0 | | 20.0 | | 15.4 | |
| | Positive | **7** | 85.7 | | 57.1 | | 14.3 | | 28.6 | |
| ASC | | | | | | | | | | |
| Age[a] | | | | 0.339 | | 1.000 | | 1.000 | | 0.538 |
| | $>49$ | **10** | 50.0 | | 40.0 | | 10.0 | | 20.0 | |
| | $\leqslant 49$ | **16** | 68.8 | | 43.8 | | 18.8 | | 6.3 | |
| Lymph node/metastasis[b] | | | | 0.756 | | 0.951 | | 1.000 | | 1.000 |
| | Absent | **14** | 64.3 | | 42.9 | | 14.3 | | 14.3 | |
| | Present | **12** | 58.3 | | 41.7 | | 16.7 | | 8.3 | |
| Recurrence | | | | 1.000 | | 1.000 | | 0.289 | | 1.000 |
| | Negative | **24** | 62.5 | | 41.7 | | 12.5 | | 12.5 | |
| | Positive | **2** | 50.0 | | 50.0 | | 50.0 | | 0.0 | |

[a]The age cut off was considered as the mean age of the patients at time of diagnosis; [b]Lymph node/metastasis includes both lymph-node and distant metastases. "CD147+MCT isoform" refers to co-expression of CD147 and MCT in the plasma membrane. SCC – squamous cell carcinoma; AC – adenocarcinoma; ASC – adenosquamous carcinoma.
"Immunoreaction" refers to both cytoplasmic and membrane positive staining; "membrane" refers to plasma membrane positive cases, with or without cytoplasmic expression.

ing. Although it was expectable to found correlations between membrane expressions, since part of the regulation involves membrane co-localization of the proteins [10,11], absence of CD147 is also responsible for lower levels of MCT1 and MCT4 whole protein expression [12] and for endolysosomal degradation of MCT4 [13], explaining the association between overall expressions. As anticipated, since the MCT2 chaperone is not CD147 but gp70 [11] and lack of CD147 does not affect MCT2 protein levels [12], we found no association between CD147 and MCT2 expression. Knowing that MCTs need to interact with CD147 to be

Table 2
Correlation between MCT and CD147 expressions in all cervical lesions

| MCT isoform | | | CD147 Immunoreaction | | CD147 Plasma membrane | |
|---|---|---|---|---|---|---|
| | | n | Positive (%) | *p* | Positive (%) | *p* |
| MCT1 | immunoreaction | | | **0.001** | | 0.110 |
| | Negative | **142** | 43.7 | | 32.4 | |
| | Positive | **109** | 64.2 | | 42.2 | |
| | plasma membrane | | | **0.002** | | 0.182 |
| | Negative | **179** | 46.4 | | 34.1 | |
| | Positive | **72** | 68.1 | | 43.1 | |
| MCT2 | immunoreaction | | | 0.322 | | 0.389 |
| | Negative | **106** | 50.0 | | 40.6 | |
| | Positive | **142** | 56.3 | | 35.2 | |
| MCT4 | immunoreaction | | | **0.002** | | **0.014** |
| | Negative | **126** | 44.4 | | 30.2 | |
| | Positive | **119** | 63.9 | | 45.4 | |
| | plasma membrane | | | **0.001** | | 0.146 |
| | Negative | **210** | 49.5 | | 35.7 | |
| | Positive | **35** | 80.0 | | 48.6 | |

"Immunoreaction" refers to both cytoplasmic and membrane positive staining; "membrane" refers to plasma membrane positive cases, with or without cytoplasmic expression.

functionally active [10,11], we hypothesized that co-expression of the transporters with the chaperone could favor the malignant potential of cancer cells. In fact, we observed that co-expression of CD147 and MCT1 in adenocarcinomas was more frequent in patients with lymph-node and/or distant metastases, being in accordance with the synergistic activity between MCTs and CD147, leading to an enhanced metastatic potential of cancer cells, through acidification of the tumor microenvironment [13]. Some other possibly relevant associations did not achieve significance, due to the number of cases representing each histological type; thus, larger studies are needed to confirm or decline these associations.

In sum, we evaluated the clinico-pathological significance of CD147 in cervical cancer, alone and in combination with MCTs, and provided evidence for the association between CD147 and both MCT1 and 4 expressions in human samples. We also showed that CD147 and MCT1 co-expression could have a prognostic value. Nevertheless, further studies are needed to explore the possible synergistic effect of these molecules in the metastatic potential of cervical carcinoma cells.

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