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Human colorectal cancer cells become more responsive to Vemurafenib after sensitization with 3-Bromopyruvate

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Abstract

Colorectal cancer (CRC) is the second most common malignant neoplasm in women and the third most prevalent in men worldwide. In Brazil, about 36,000 new cases of CRC are estimated among men and women for 2018-2019. With advances in treatment, early CRC is being "reclassified" from a deadly disease to an illness that has great chance of cure. However, so far, the survivors who have completed treatment and are cancer-free, frequently suffer from late/long-term side effects, and some patients with metastasis have poor response to the therapies. In this context, the discovery of new therapeutic strategies is urgently needed. In this project we aimed to validate the hypothesis that 3-Bromopyruvate (3-BP), an alkylating agent, would be able to sensitize the human CRC cell lines to treatment with Vemurafenib, a BRAF inhibitor. Therefore, human CRC cell lines (HT-29 and HCT-116) were challenged with 3-BP followed by the treatment with Vemurafenib. Both cell lines were more responsive to Vemurafenib after sensitization with 3-BP (IC50 values were 7- and 1.4-fold lower than with Vemurafenib alone, for HT-29 and HCT-116 cells, respectively). The findings presented here, highlight the potential of 3-BP in increasing the response of metastatic cancer cells to Vemurafenib.

Key words:
Colorectal cancer, 3-Bromopyruvate, Vemurafenib.

Introduction

Colorectal cancer (CRC) is the second most common malignant neoplasm in women (614,000 cases) and the third most prevalent in men (746,000 cases) worldwide [1]. In Brazil, about 36,000 new cases of CRC are estimated for 2018/2019 [2]. The chemotherapy used for the treatment of CRC consists of a combination of fluorouracil and oxaliplatin, but this combination may be ineffective in patients with resistant tumor cells and with metastasis [3,4]. In this context, new therapeutic opportunities become necessary. One of the aims of the present project is to validate the hypothesis that 3-Bromopyruvate (3BP) is able to sensitize cancer cell lines to chemotherapy with Vemurafenib. Indeed, our findings show that KRAS and BRAF mutated cells become more responsive to Vemurafenib after pre-treatment with 3-BP.

Results and Discussion

Cell lines from human colorectal adenocarcinoma, HT-29 and HCT-116 were used. HCT-116 cells carried KRAS mutation (G13D), while HT-29 in BRAF mutation (V600E) [5]. Cell viability was assessed by MTT reduction after 24h treatment with Vemurafenib alone (0.25-100 µM) or in combination with 3-BP (25 µM for HCT-116 and 50 µM for HT-29) for 24 hours. Cells were challenged with 3-BP for 2 hours prior to treatment with Vemurafenib. As it can be seen at Figure 1, Vemurafenib was more effective in dropping the viability of both cell lines after pre-treatment with 3-BP.

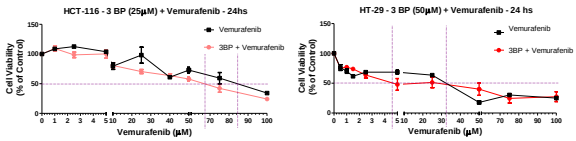

Figure 1. Influence of the combination of Vemurafenib and 3-BP in human CRC cells viability. Cells were treated with Vemurafenib alone or in combination with 3-BP (25 µM, for HCT116 and 50 µM for HT-29) for 24h. Cells were pre-incubated with 3-BP for 2h, followed by treatment with different concentration of Vemurafenib.

Importantly, in the presence of 3-BP, the IC_{50} values were 7- and 1.4-fold lower than with Vemurafenib alone, for HT-29 and HCT-116 cells, respectively (Figure 2).

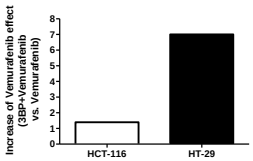

Figure 2. Antitumoral action of Vemurafenib is more effective in the presence of 3-BP.

Conclusions

The findings presented here indicate the potential of 3-BP to increase the response of metastatic tumor cells (mainly mutated BRAF cells) to low dose of Vemurafenib, which would lead to a decrease in the side effects of this drug. The next step of the study is to scrutinize the molecular mechanism by which it occurs.

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