Targeting Lysosomes in Colorectal Cancer: Exploring the Anticancer Activity of a New Benzo[a]phenoxazine Derivative

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Abstract: Colorectal cancer (CRC) has been ranked as one of the cancer types with a higher incidence and one of the most mortal. There are limited therapies available for CRC, which urges the finding of intracellular targets and the discovery of new drugs for innovative therapeutic approaches. In addition to the limited number of effective anticancer agents approved for use in humans, CRC resistance and secondary effects stemming from classical chemotherapy remain a major clinical problem, reinforcing the need for the development of novel drugs. In the recent years, the phenoxazines derivatives, Nile Blue analogues, have been shown to possess anticancer activity, which has created interest in exploring the potential of these compounds as anticancer drugs. In this context, we have synthesized and evaluated the anticancer activity of different benzo[a]phenoxazine derivatives for CRC therapy. Our results revealed that one particular compound, BaP1, displayed promising anticancer activity against CRC cells. We found that BaP1 is selective for CRC cells and reduces cell proliferation, cell survival, and cell migration. We observed that the compound is associated with reactive oxygen species (ROS) generation, accumulates in the lysosomes, and leads to lysosomal membrane permeabilization, cytosolic acidification, and apoptotic cell death. In vivo results using a chicken embryo choriollantoic membrane (CAM) assay showed that BaP1 inhibits tumor growth, angiogenesis, and tumor proliferation. These observations highlight that BaP1 as a very interesting agent to disturb and counteract the important roles of lysosomes in cancer and suggests BaP1 as a promising candidate to be exploited as new anticancer lysosomal-targeted agent, which uses lysosome membrane permeabilization (LMP) as a therapeutic approach in CRC.

Keywords: Nile Blue analogue; benzo[a]phenoxazine; anticancer drug; colorectal cancer; lysosome membrane permeabilization

1. Introduction

Colorectal cancer (CRC) is reported as the third most diagnosed cancer and the second deadliest worldwide. Despite primary prevention being the key strategy to reduce the impact of CRC, with the growth of the world population associated with poor lifestyle choices, it is expected that the global burden of CRC will increase [1]. Overall, the number
of effective CRC chemotherapeutic agents approved for use in humans is still very limited [2]. Moreover, tumor resistance and secondary effects stemming from the classical chemotherapy remain a major clinical problem, reinforcing the need for the identification of new intracellular targets and the discovery of drugs with an effective action [3,4]. In this field, lysosomes have been emerging as attractive targets for the development of new drugs [5,6]. The lysosomes are single membrane-enclosed cytoplasmic organelles and are the main digestive structure in eukaryotic cells, playing critical roles in several cellular processes such as autophagy, apoptosis, protein maturation, membrane repair, cell signaling, and energy metabolism [7–10]. Lysosome function and dysfunction have been found to play important roles in human disease, including cancer. Cancer cells have numerous, relatively large and acidic lysosomes, and these are thought to be more fragile than normal-sized lysosomes [11,12]. Overexpression of lysosomal proteases is commonly observed in cancer cells, which often correlates with poor prognosis and increased recurrence of many cancers [6,13]. In addition, it has been reported that cancer cell lysosomes are associated with drug resistance through drug sequestration, whereby substances become trapped in the acidic lumen of lysosomes [14,15]. Thus, it is clear that the lysosome arises as a promising therapeutical target as it shows vulnerability that can be exploited through the use of lysosome-targeting agents.