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Carbonic Anhydrase Inhibitors: As A Anticancer Agent

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ABSTRACT

Cancer is a dreaded disease, caused by unrestrained and irregular cell division, leading to formation of an agglomeration of cells called tumour. The wild growth in the form of a tumour may affect and ultimately block the functioning of the organ concerned, if not treated. It might have dangerous consequences, posing direct threat to the life of the organism.

INTRODUCTION

At the turn of the twenty-first century, it was the case that there was some chance of survival for all the known types of childhood cancer. The drug Glivec, launched in 2001, is now cure for 75% of patients with chronic myeloid leukemia, a type of cancer of blood and bone marrow with excess immature white blood cells. The 5-Fluorouracil is a well-established chemotherapy drug to restrain the progress of cancer. But its combination with Avastin, which prevents tumours developing their own blood supply, is much more effective against certain colon cancers. Avastin when combined with Taxol, launched in 1992, increases Taxol's effectiveness against breast cancer. Avastin was launched in the year, 2004 and is quite promising. 5-Fluorouracil interferes with cell proliferation by modifying natural uracil to incorporate stubbornly unreactive fluorine. Taxol is a rare metabolite of the Pacific yellow tree and its synthesis in laboratory involves high costs. Avastin has very complex structure. It is an antibody against a protein involved in blood vessel growth. Research on the subject shows that malignant tumours are often surrounded by a dynamic microenvironment specified by low pH (acidic) and low levels of oxygen, glucose and other nutrients [1]. In order to overcome these severe conditions, cancer cells acquire various adaptive features which are thought to be responsible for the development of invasive and metastatic physical entities [2-4].

It is now known that cancer is not only a genetic disorder but also a disease of dysregulated metabolism. As a result of regional hypoxia (i.e. shortage of oxygen in tissues), cancer cells fulfil their need for high levels of ATP by switching their metabolism from aerobic respiration to fermentative glycolysis, a phenomenon known as Warburg Effect [5-6]. Metabolic reprogramming results in pre-malignant lesions and this is the cause of pH dysregulation which coupled with poor vascularisation determines the formation of cystostatic and/or lethal microenvironment [7]. In general, cancer cells try to compensate these changes in the internal pH by enhancing expression of a series of proteins and membrane transporters such as Carbonic Anhydrase IX and XII, amongst others [8-10]. This knowledge has led to targeting

these pH modulating proteins as an approach to treat recurrent, metastatic and drug resistant tumours [9-13]. Carbonic Anhydrase IX and XII are found profusely in the multiple and metastatic cancer cell-lines and represent well established targets both for tumour imaging, as diagnostic markers, as well as for treatment of tumours expressing them [14-19]. It has led in the past few years to the search for effective, potent and selective inhibitors of the fifteen reported isoforms of Carbonic Anhydrase [20-24] with particular emphasis on the cancer related CAIX and CA XII [25-26]. However, the differences between the active sites of different CA isoforms are minimal, subtle and this often results in the inhibition of both the target and off-target isoforms of CA [23,26,27].

Although a vide variety of Carbonic Anhydrase Inhibitors (CAIs) has been made available in the past [22,28,29], one of the most common approaches to design small molecules targeting this family of metalloenzymes comprises inserting zinc binding moieties into the structure of the inhibitor. The sulphonamide group is one of the most important and widely used moieties [22,30-33]. In all of the crystallographic /molecular modelling studies reported so far, the primary sulphonamide derivatives have been shown to bind to the catalytic zinc ion in the active site of CA in their deprotonated form [34,35] (Figure 1).

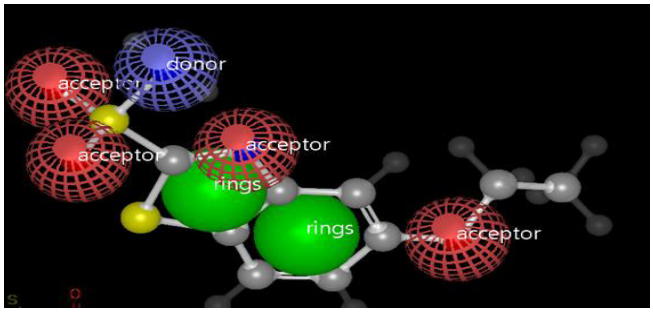

Figure: Ethoxzolamide EZA(A Carbonic Anhydrase Inhibitors).

CONCLUSION

The research group consisting of Melissa D'Ascenzio, Simone Carradori, Celeste De Monte, Daniela Secci of Sapienza University of Rome, Italy and co-workers have demonstrated that heterogeneous saccharine derivatives are excellent inhibitors of CAIX and CAXII in low, nanomolar/ micromolar quantity [36]. However, it has recently been demonstrated that even secondary/tertiary sulphonamides are able to selectively inhibit the cancer related isoforms, CA IX and XII, suggesting a different mechanism of action compared to the classical, primary sulphonamides.

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