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Investigation into Small Molecule Inhibitors of Calcium Binding Protein to Suppress Tumor Growth and Metastasis

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Overexpression of S100P calcium binding protein is associated with many forms of cancer. The interactions S100P has with many other proteins involved in proliferation, intracellular signaling, and migration make it an attractive target for medicinal chemists investigating novel methods of inhibiting an enzyme that is largely responsible for cancerous growths. Recent studies have found promising lead compounds – small molecule inhibitors of S100P, specifically in nasopharyngeal and pancreatic cancer cell lines. These not only inhibit the action of S100P, but are often times shown to downregulate many other protein complexes implicated in cancer. Promise has been shown in the construction of medicinal compounds that are able to effectively target and inhibit S100P, thus slowing growth and metastasis of tumors. These studies however were conducted *in vitro,* so current research must be aimed further characterizing the properties of these compounds within living systems, as well as ensuring that they are selectively toxic toward cancerous cells, leaving the host largely unharmed.

Introduction

Within a cellular network, a complex, multi-faceted symphony of signaling and internal regulation is constantly at work. The mineral calcium is an important intracellular second messenger, oftentimes playing an integral role in signal transduction cascades, the phosphorylation of many proteins, and the activation of many enzymes and cellular processes. Cancerous growths are the result of such signal transduction pathways falling out of balance. Amplified proliferation and differentiation signals are sent with little repression in tumorous growths. Because of its major role within these processes, calcium, as well as its related binding and uptake proteins, are an interesting investigation in the field of cancer therapeutics.

The protein S100P, a member of the S100 family of proteins, is one of many proteins that is found to often times be overexpressed in solid carcinoma growths (Jiang et al. 2011). Nine of the ten most common cancers in the world lay within this category (Cancer Facts and Figures 2023). Often times in the complex instance of cancer, one cannot implicate one single protein; rather, there are multiple protein complexes interacting with one another, each sending signals to another, resulting in various pathways for uncontrolled proliferation to occur through. This is the case with the S100P calcium binding protein, as its overexpression has ramifications extending far beyond the localized interaction

with ions. S100P has been shown to interact with Receptor for Advanced Glycation End Products (RAGE), Epidermal Growth Factor Receptor (EFGR), Mitogen-Activated Protein Kinase (MAPK), Metalloproteinases (MMP2 and MMP9), as well as transcription factors such as Erk and NF-κB (Jiang et al. 2011).

Recent Progress

With such a wide array of interactions, one can observe why overexpression of S100P can lead to uncontrolled cell proliferation rather quickly. Research groups have begun to postulate that early detection of elevated quantities of S100P via methods such as quantitative real time PCR (QRTPCR) could be an efficient method of screening utilized in the near future (Jiang et al. 2011). Other groups have looked to develop small molecule inhibitors of S100P in an attempt to halt cell proliferation in nasopharyngeal and pancreatic carcinomas.

Work Performed with Nasopharyngeal Carcinoma Cells

In 2019, Zhang et al. published a paper showing the possibility of down regulating calcium binding protein S100P with a family of aromatic dione-thiophene compounds (Zhang et al. 2019). The leading compound discovered, dubbed Compound 4a within the study decreased cancerous cell proliferation by 74%, while reducing invasion potential with concentrations as low as 2 micromoles per liter. Additionally, Compound 4a reduced the expression of RAGE, EGFR, CD44, MMP2, and MMP9 proteins that are also associated with cancerous developments. The reduction in the metalloproteases in particular is extremely encouraging, as these proteins are heavily involved in degrading the extracellular matrix that keep cells in mucosal linings from migrating to other tissues. Compound 4a was also successful in inducing apoptotic behavior in a time and concentration dependent manner, causing nearly 70% of cells to be apoptotic at a concentration of 10 micromolar per liter (Zhang et al. 2019).

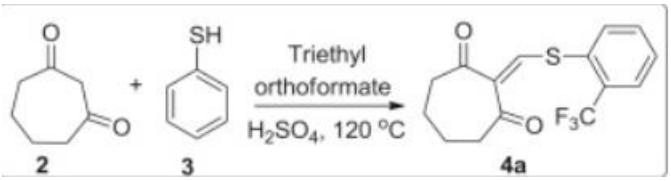

Figure 1: Synthesis of the Compound 4a that exhibited the most promise in the study examining dione-thiophene action against nasopharyngeal cancer lines. (Zhang et al. 2019)

Work Performed with Pancreatic Carcinoma Cells

Pancreatic cancer is one of the most lethal cancers in our present medical world, and similar to all other cancers discussed thus far it will often carry overexpressed S100P. In 2020, Camera et al. published a study providing a number of possible lead compounds for inhibition of cancerous growth that use S100P as their main target (Camera et al. 2020). The group performed much work characterizing the binding pocket of S100P, utilizing rational drug design in an attempt to build a molecule with inhibition properties. From a library of 650,000 possible compounds, a number of the compounds were discovered to fit into the pocket, while halting metastatic behavior of cancerous cells (Camera et al. 2020). However, these compounds lacked significant effect on the metabolism of the cell and were not greatly successful in inducing apoptotic behavior. IC50 concentrations were measured for each of the derivatives, characterizing their pharmacodynamic properties.

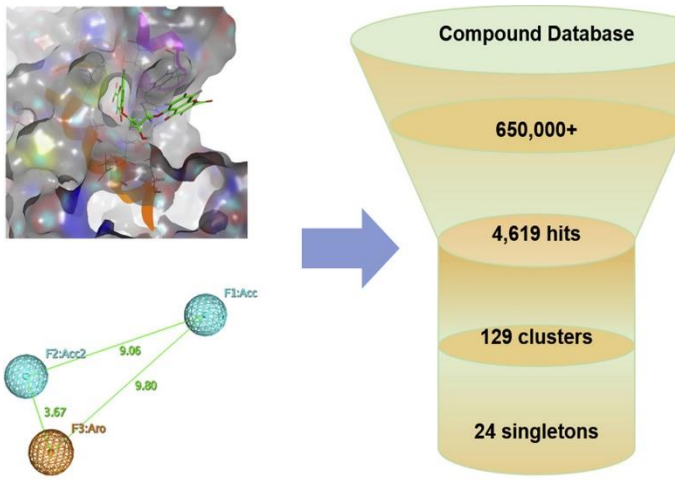

Figure 2: Schematic of the workflow performed by Camera et al. investigating small molecule inhibitors of S100P. The number of invaded cells is drastically reduced in the presence of "Compound 4" pictured above in BxPC-3 cells which express S100P. Little activity is shown in the S100P negative cell lines, Panc-1. (Camera et al. 2020).

Discussion

While the discovery of each of these families of compounds was extremely encouraging, the question that remains largely unanswered is whether they are specifically targeting cancerous growths, or if it would be intrinsically toxic to all cells within a culture. An additional limitation is that these studies were performed with specific types of cancer cells (nasopharyngeal or pancreatic). A future study detailing the activity of these compounds against a variety of other carcinoma tissues would provide a great impact, showing possibility for the development of a more general medicinal compound against carcinomas, broadly. For administration of the compound, further development would have to be done to optimize its pharmacokinetics, distribution, and safety. Nevertheless, initial data for these lead compounds is encouraging and evidences the interlinking of S100P with many other cancer-associated biomolecules. Through each of these studies, we can again confirm that S100P is implicated in metastatic behavior of cancerous cells, and that it is possible to inhibit this calcium binding protein to slow the progression of cancer.

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