Introduction

The National Cancer Institute now suggests that one in seven individuals in the United States will develop breast cancer at some point throughout their life. In 2010 alone, it is estimated there will be an additional 1.5 million new breast cancer cases worldwide [1]. Due to the fact that these rates of cancer are increasing each year, as well as more fatalities each year, researchers need to find new and alternative methods to treat, or even to prevent cancer. Cancer forms when cells accrue multiple mutations and are allowed to divide indefinitely without having these mutations repaired. Our best lines of defense, chemotherapy and radiation treatments, are even flawed because of the untoward side effects on healthy cells.

We propose that triptolide, an extract from the herb *Tripterygium wilfordii* Hook F, which has been shown to have anti-cancer properties will also work to stimulate lysosomal involvement in inducing apoptosis in human breast cancer.

Triptolide has been used for over 200 years in Chinese medicine and it was not until recently that the health benefits of the extract have been fully understood. Triptolide is known to induce apoptosis in various cancer cells through the activation of p53 [2–4]. We believe that there are other mechanisms at work within the cells when treated that also cause apoptosis to occur. Because of the role of lysosomes in the degradation of cellular debris as well as during apoptosis we believe that triptolide is responsible for activating lysosomal-mediated cell death. In our lab we have tested the effects of triptolide on MCF-7 cells and have seen a decrease in cell viability and an increase in cell death suggesting that triptolide is capable of causing cell death in this cell line.

Rationale

Apoptosis can be triggered in a variety of ways, activation of p53, change in membrane-permeability of mitochondria, through lysosomal involvement, as well as a host of other mechanisms [9].

Does triptolide induce lysosomal-mediated apoptosis in human breast cancer cells?

M.E. Messina Jr., R. Halaby*

Montclair State University, Department of Biology and Molecular Biology, 1 Normal Avenue, Montclair, NJ 07043, United States

A R T I C L E   I N F O

Article history:
Received 11 September 2010
Accepted 17 March 2011

A B S T R A C T

With breast cancer plaguing the United States as the second leading cause of cancer related deaths amongst women, as well as the adverse effects of current treatment options there is a need to develop safer and noninvasive treatments. Triptolide is an extract from the herb *Tripterygium wilfordii* Hook F, and has been used in Chinese medicine for over two centuries and is now used to treat certain autoimmune diseases, such as rheumatoid arthritis. Based on the anti-proliferative, anti-inflammatory, and anti-cancer properties of triptolide we believe that it will stimulate apoptosis in human breast cancer cells. Triptolide is known to induce apoptosis in many cancer cells lines, but the exact mechanisms that regulate this are largely unknown. It has been suggested that triptolide activates the p53 pathway to trigger apoptosis in these cells. However, we believe that there are other mechanisms at work including the activation of lysosomal-mediated apoptosis.

© 2011 Elsevier Ltd. All rights reserved.
Lysosomes act as “cell dumping site” where they digest damaged cellular components, remove waste products from the cell, and are known to be a part of the apoptotic process. This organelle contains an array of enzymes that are capable of breaking down proteins, carbohydrates, and lipids [10]. Lysosomal-mediated apoptosis is still largely under investigation and not fully understood, however what is known for certain is the membrane of the lysosome becomes more permeable. Originally, this was thought to only be a part of necrosis [11] with the acidic hydrolases leaking into the cytosol, however, research now suggests specific lysosomal enzymes play an active role in triggering apoptosis [11,12].

While the data on lysosomal-mediated apoptosis is still accumulating, of the roughly 50 hydrolases present in lysosomes, cathepsins are best understood in terms of their role in triggering apoptosis [11,12]. Known to degrade proteins that are necessary for proper cellular functioning, cathepsins are an essential part of apoptosis. How a cell dies is dependent upon how permeable the membrane of the lysosomes becomes, the cell dies via necrosis or apoptosis. If there are large amounts of hydrolases released (as is the case in cell trauma) necrosis will occur, however if there are lower levels present this can trigger apoptotic signaling. Triptolide treatments create an oxidative stress [12,13] within the cancer cells; this can be the triggering mechanism that causes lysosomal membrane permeabilization. To demonstrate that lysosomal pathways are also involved in triptolide-induced apoptosis, we plan to examine MCF-7 human breast carcinoma cells treated in the presence or absence of triptolide by fluorescent staining using LysoTracker™ to visualize lysosomes and acridine orange staining to assess lysosomal membrane integrity.

Triptolide has been thought to induce apoptosis exclusively via the p53 pathway [14]. However we hope to provide evidence that will show there are other mechanisms, namely using lysosomes, by which triptolide induces cell death. Through the oxidative stress created by triptolide treatments we hope to show that this induces lysosomal membrane permeabilization, leading to release of the hydrolases into the cytosol where they can digest the cell. Furthermore, by the activation of cathepsins by the release of the hydrolases we hope to elucidate alternative mechanisms which may also play a role. Lastly, while caspase activation is commonly thought to be a result of a change in mitochondrial membrane permeability, it has been demonstrated that an increase in lysosomal pH can trigger the activation of pro-caspase 3 [15]. Due to the fact that triptolide is known to create oxidative stress within cancer cells, it is possible for a caspase cascade to be triggered via the lysosomes. Fig. 2 is our proposed model for triptolide-induced apoptosis through a lysosomal mediated pathway.

Conclusion

Because of the adverse affects of current cancer treatments, new alternatives are warranted. Our hypothesis is that triptolide induces lysosomal-mediated apoptosis in human breast cancer cells. Because of the known anti-cancer properties of this herb and the role that lysosomes play in cellular digestion, autophagy, and phagocytosis, fully understanding how triptolide regulates this organelle would be extremely beneficial in trying to develop novel and alternative treatment methods.

Conflicts of interest statement

None declared.

Acknowledgment

The project described was supported by a grant from The Margaret and Herman Sokol Institute for Pharmaceutical Life Sciences at Montclair State University.

References


