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Autophagy in the Treatment of Cancer Cells

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Autophagy is a process that involves the lysosomal degradation of cellular components by the cell itself. It degrades these cellular components to use their nutrients for survival by reducing their proliferation. Autophagy can be activated by the cell's environment. If the outside stressors of the environment are high, autophagy can be used to such a great extent that it activates a programmed cell death (Gagliostro 4). Ceramides, certain types of transmembrane components also called sphingolipids (SPLs), are very important in the cell's growth, proliferation, differentiation, and even cellular death. These ceramides have been shown to negatively affect cellular outcome in cancer cells and to activate an autophagic response in cells which leads to cellular death (Gagliostro 4). By inducing the autophagic response in a cancer cell it can essentially self-abort and lyse by self- degrading its components. Current research suggests this as a possible new treatment for cancer.

Introduction

Is there a way that cancer cells can be programmed to self-abort during their cell growth cycle? Is it possible to inhibit their full development before they replicate into daughter cells? Autophagy, otherwise called autophagocytosis, is a catabolic cellular process that physiologically controls cell survival. Autophagy is activated in times when the cell is under great stress. It is a pathway which degrades cellular components to maintain metabolic homeostasis and is also involved in the degradation of damaged proteins. Autophagy normally does not cause cancer cells to die but when unrestrained, the autophagic response can activate programmed cell death by the consumption of too many cellular components (Matthew 961). Cellular arrest in development and growth at the G0/S phase has been shown to halt tumor growth in cancer cells by the use of stress inducers but has also triggered these cells to become more resistant to certain chemotherapies (Gagliostro 3). This shows the difference between autophagy and unrestrained autophagy as it relates to cancer cells.

Recent Progress

What has been shown in recent studies is that dhCer desaturase, an enzyme that desaturates ceramides, inhibition can reduce cell propagation. The use of Des1 inhibitor, a protein, to treat gastric cancer cells induced an autophagic effect and slowed proliferation of the cell but in turn did not affect the viability of the cells; they continue to replicate but at a much slower rate. This induces a more unrestrained autophagic response which increases the rate of cellular self-degradation. Many of the cells were frozen at the G0 phase (Gangliostro 7). In the cells exhibiting a halt in cellular growth dhCer levels were taken and shown to linearly increase during the first 24 hours of cellular growth in cells treated with the Des1 inhibitor and decreased thereafter (Gagliostro 7). Ceramide and dhCer have been shown to induce autophagy and ER stress. This induction of the autophagic response is crucial in provoking cellular death. Increased levels of LC3 II, an autophagosomal protein, were seen in treated cells that were halted at the G0 phase. Thus supporting the hypothesis that dhCer was associated with the induction of autophagy in cells (Gagliostro 7).

Even though autophagy can indeed result in the activation of a programmable cellular death, it can also aid in the survival and viability of the cell. Only in cases where the environmental stressed is so severe does it become

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detrimental to the cell. The rate at which it lyses cellular components for nutrient uptake and survival cannot withstand the rate at which the outside stressors are accumulating. A cell lyses during programmed cellular death because it breaks down the membranous cellular components during autophagy and the cell cannot withstand the external pressure and lyses. It has been shown in this study that dhCer-induced autophagy does indeed aid in cellular survival. To show this Gagliostro and associates blocked the formation of autophagosomes with a kinase inhibitor (3MA). This inability to induce the atuphagic response inhibited cells treated with the des1 inhibitor to survive at all (Gagliostro 9).

There is still much to learn about how dhCer and autophagy affect cellular growth resprodution, and viability. There are many factors to consider before dhCer can be used as a target for therapy. This study has indeed shown the important relationship between dhCer levels and cellular death by an autophagic response. Cell type, kinds of stress, and levels of Cer all play a role in determining whether the cellular processes cross the "tiping point" between increasing survivability of the cell and detrimentally affecting cellular growth (Galgiostro 10).

How does the cell balance the use of Cer in determining at what point its accumulation within the cell leads to cellular death and at what point before cellular death that it aids the cell in survival? Brocklyn and his associates describe a balancing effect between the cellular lipid Ceramide and another lipid called shingosine-1-phosphate (S1P). These two lipids are signaling molecules in a process called the sphingolipid rheostat. Sphingosene kinase is an enzyme that regulates these two interconvertible lipids that creates the balance between life and death (Brocklyn 1).

Ceramide prefers anti-proliferation pathways which ultimately leads to cellular death; such as autophagy and apoptis. Shingosine-1-phosphate induces proliferation and cellular survival pathways (Brocklyn 1). Finding a homeostasis in the accumulation of these two lipids is what allows the cell to remain viable. Sphingosene Kinase has even been investigated in the process of aging. Perhaps it is through the inhibition of this enzyme that the previous studies results were obtainable.

In retrospect, by eliminating either the formation or the function of this specific enzyme, the balance between dhCer and S1P would not be maintained intracellularly and thus could leave the cell open to a number of responses induced by outside stressors to the cell. If the outside stressors were increasingly high this would favor the production of dhCer and thus would induce autophagy and cellular death. In what appeared to be the use of Cer in lower doses as a singal for cellular survival pathways could have actually been the accumulation of S1P within the cell, which would explain the cell's "use of autophagy" as a survival response and increased proliferation.

Discussion

Is it possible that the use of ceramides in the treatment of cancer cells would be a beneficial way to induce cellular death and self-absorption? True, it certainly seems probable; but because both cancer cells and human cells use sphingolipid membrane components, how would the induction of outside stressors on the cell to activate these ceramide components differentiate between cancer cells and regular cells? The use of antibodies against proteins specific to these cancer cells has proven to be an effective way of targeting cancer cells in the induction of environmental responses to trigger ceramide induced autophagy (Gagliostro 4). The problem associated with this type of experimental use in cancer treatment is the vast diversity of cancer cells. Gastrointestinal cancer cells, for example, may differ widely in their function, cellular growth, and proliferation from all other forms of cancer. Because they differ so widely even among this form of cancer what may work in treating one form may not even work treating the same category of cancer cells.

In conclusion, the balance between life and death of a cell in the form of this enzyme might prove to be a much more attractive target in the treatment of cancer cells. Many issues still surround this form of treatment because of the similar pathways used in healthy cells. Differentiating between the two would aid in targeting only cancer cells while leaving the host cells unharmed. Because of the cast array and cancer cells and their differing physiological and chemical properties what may work in treating one cell may not work in the other; thus making each study specific to a certain type of cell and increasing the difficulty with which the application of these studies can be performed.

References

Gagliostro, Vincenzo et al. "Dihydroceramide Delays Cell Cycle G1/S Transition via Activation of ER Stress and Induction of Autophagy." *The International Journal of Biochemistry and Cell Biology.* (2010), doi:10.1016/j.biocel.2012.08.025.

Matthew, Robin et al. "Role of Autophagy in Cancer." *Nature Review.*7.12 (2007): 961-967. Web.

Van Brocklyn, JR and Williams, JB. "The Control of the Balance Between Ceramide and Sphingosine-1-Phosphate by Sphingosine Kinase: Oxidative Stress and the Seesaw of Cell Survival and Death." *Comparative Biochemistry and Physiology Part B, Biochemistry and Molecular Biology.* 163.1 (2012): 26-36. Web.

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