

A Meta-Analysis Aanzan Sachdeva, Sean Belenky Urban Barcoding Research Program

ABSTRACT

The role of the CLU (clusterin/Apo-J) gene in cancer genetics has been uncertain for over 20 years of research. While some studies suggest that CLU is an oncogene, others suggest that it inhibits tumorigenesis. Recent efforts in uncovering the function of CLU have reported its role in processes such as proliferation, apoptosis, and aggregation. It is believed that the elevated expression of CLU in humans may interfere with certain apoptotic pathways with isoforms of clusterin having differential effects. This meta-analysis assesses the effects of upregulating the intracellular form of CLU via expression vectors on cell proliferation as well as looking into intracellular clusterin's involvement with tumorigenesis. Data compiled from recent studies suggests that intracellular clusterin activates survival in target cells by affecting cell cycle progression and activating a caspase-3 independent apoptotic mechanism which would allow cells to undergo cell death earlier than others resulting in decreased rate of cell proliferation and tumorigenesis.

INTRODUCTION

What is Clusterin?

- Plays numerous roles in cell function.
- Is a protein encoded on chromosome 8 in humans
- Heavily expressed in the liver, brain, ovaries, and testes

Clusterin in Alzheimer's Disease and Cancers

- Clusterin is known to play a role in Alzheimer's Disease
- Linked with Cancer progression

The Isoforms of Clusterin

- Intracellular clusterin is one of clusterin's many isoforms
- Role in cancer genetics has been uncertain for over 20 years

HYPOTHESIS

Null Hypothesis: Upregulating CLU via expression vectors has no significant effect on cell proliferation and tumorigenesis

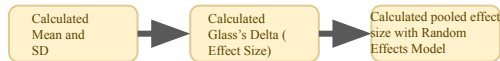
Alternative Hypothesis: The upregulation of the intracellular CLU (Clusterin/Apo-J) by expression vectors decreases cell proliferation and tumorigenesis by inducing pro-apoptotic activities.

METHODOLOGY

Meta Analysis

- 5 studies, 6 data sets
- Inclusion/Exclusion Criteria
- Expression Vectors

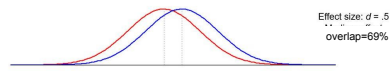
Variables to be observed (DV)	Assays and kits used to measure variables
Intracellular CLU mRNA production	Northern Blot
Cell count	Flow Cytometry analysis
Presence of intracellular Clusterin	Western Blot/ Immunocytochemistry



RESULTS

Study	Effect Size	% of Experimental group below the mean of control group
(Betuzzi, et al 2002)	0.57	73%
(Kim, et al, 2009)	--	--
(Scaltrini, et al, 2004) PNT1a	0.35	62%
(Scaltrini, et al, 2004) PC-3 cells	0.71	76%
(Lau, et al, 2005)	0.07	50-54%
(Santamaria, et al, 2004)	0.85	79%
Overall	0.51	69%

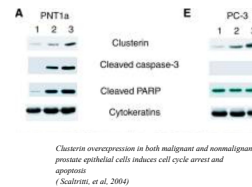
Overall effect size was 0.51
69% of the experimental group was below the mean of the control



- Large effect size= Strong relationship between variables
- 69% overlap between variables

Discussion

We know Intracellular clusterin somehow inhibited or slowed cell proliferation
→ Intracellular clusterin may have proapoptotic properties
→ Apoptotic cascades assessed to pinpoint the cause of decreased cell number.



Found that affects may vary depending on cell type
→ Since increased clusterin expression may inhibit caspase dependent apoptosis
→ May activate a different cascade, or other intrinsic pathway that
→ Tumor resistance via apoptotic induction.

Clusterin overexpression in both malignant and normal human prostate epithelial cells induces cell cycle arrest and apoptosis (Scaltrini, et al, 2004)

CONCLUSION

- *Alternate Hypothesis was supported
- * Suggests that the cell proliferation in cells that overexpress intracellular clusterin is significantly lower than in the control group cells

FURTHER STUDIES

Potential Sources of error

- Mean and Standard Deviation not directly provided by study, calculated manually

Limitations

- The data collection period
- Access to full peer reviewed articles

Further Development of Study

- Replicate results in larger meta analysis
- Test effects of clusterin in different target cell/ cell lines
- Inclusion and exclusion criteria should be modified to include studies that provide all statistical values.

Gene Therapy

- The use of intracellular clusterin to counteract the proliferative effect of clusterin
- Counteract cancer development

REFERENCES

Calero, M., Rostagno, A., Matsubara, E., (2000, July 27). Apolipoprotein J (clusterin) and Alzheimer's disease. Retrieved September 26, 2020, from [https://onlinelibrary.wiley.com/doi/abs/10.1002/1097-0029\(200008\)15:05:43.0.CO;2-J](https://onlinelibrary.wiley.com/doi/abs/10.1002/1097-0029(200008)15:05:43.0.CO;2-J)

Calero, M., Tokuda, T., Rostagno, A., (1999, December 1). Functional and structural properties of lipid-associated apolipoprotein J (clusterin). Retrieved September 26, 2020, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1220653/>