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Background:

Stem cells is a growing field of research with great potential for many medical applications. Two most common types of stem cells are adult and embryonic stem cells.

Human embryonic stem cells (hESC) come from the inner cell mass of a blastocyst. [2] There has been considerable excitement about these stem cells because they exhibit both self-renewability and pluripotency when exposed to the right conditions in vitro. [1] Pluripotency is a characteristic of hESC that enables them to differentiate into virtually any cell type. With hESC being pluripotent it is hoped that in the future, stem cells can be used to treat various injuries and diseases. [2] Before this hope can become reality, several areas of research need to be explored.

One area of research being conducted focuses on maintaining genetic integrity of stem cells in culture. During long term culture, stem cells have been noted to develop an abnormal karyotype. [1]. [3] It is important to understand why this may be happening so that stem cells can be cultured without the loss of their genetic integrity.

It is possible that in the cell cycle of a cell, the mechanism of chromatin structure and assembly actually breaks causing the process of cancer. Since stem cells and cancer cells are so much alike, this might play a role in what's causing stem cells to form an abnormal karyotype.

Hypothesis:

We believe the same mechanism of histone structure that fails in cancer cells is also what fails in abnormal hESC.

Methods:

Genes that are associated with histone structure will be identified by searching through Gene Ontology's ™ database (GO) [4]. This will produce a list of approximately 200 genes to begin our analysis. To accompany this list a database will be created for mRNA expression data from both normal and disease stem cells. The database and schema will be housed on GUS in the BCCL. Due too the unique nature of the probe-ID's included in the mRNA data, probe ID's will be identified for each gene from GO. This will be done in conjunction with the validation of gene sequences for our current list of genes. Normalized mRNA expression will be used to calculate the base correlation coefficients between abnormal and normal stem cells using Network Builder ™. In mathmatica™ we will validate the networks of genes we have created using Pathway Studio™. Each validated network will be modeled and simulated using cellular automata a discrete simulation method (expected to begin next summer).

Expected Results:

From calculating base correlation coefficients, we expect to establish a range of correlation values to compare when creating smaller networks. Clustering gene against gene, we expect to distinguish if genes have common interactions based on similar scores. Scores are calculated normalizing the number of clustering based predicted interactions by the number of probe ids associated with each gene,. The second round of non-linear correlation coefficients will be compared against the original to identify any reduction in range or increased significance (distance from 0.5 or –0.5) For example, a increase of range would indicate that the genes do not represent an complete network, a narrow range of scores indicates a common interaction between the genes and most genes involved in the network have been included.

Tools:

-Netaffx is being used to lookup gene sequences,
-NCBI for blasting,
-Mathematica is a programming language and will be used to identify relationships between expression values.
- Network Builder ™
- Gene Ontology ™
- Pathway Studio ™

References:

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[2] - Skottman H., Hovatta O. (2006) "Culture conditions for human embryonic stem cells" Reproduction. 132: 691-698

[3] – Baker E. C. D., Harrison J. N., Maltby E., et al. (2007) "Adaptation to culture of human embryonic stem cells and oncogenesis in vivo" Nature Biotechnology. 25: 207-15

[4] - The Gene Ontology Consortium. Gene Ontology: tool for the unification of biology. Nature Genet. (2000) 25: 25-29

[5] - Chambers I., Smith A. (2004) "Self-renewal of teratocarcinoma and embryonic stem cells" Oncogene. 23: 7150-60

[6] - Rao R. R., Stice S. L. (2004) "Gene expression profiling of embryonic stem cells leads to greater understanding of pluripotency and early developmental events." Biol Reprod. 76: 1772-8