The links provided in the Cancer Issues tab on the MCFIP website establish the fact that the lack of a universal algorithmic model for application to chronic diseases has thwarted the integration of research. In addition to other links provided in the aforementioned tab that addresses common factors for leukemias, CTCF also correlates with leukemias other than just ALL as a causal path, e.g. AML, CML, CLL and MLL. Using bioinformatic search, anyone can perform DIY activity to verify this assertion.

The documents affixed to this article are provided for discussion purposes with qualified bioinformatic professionals relative to CTCF.

https://medicalxpress.com/news/2019-04-major-proteins-patients-acute-lymphoblastic.html

APRIL 26, 2019

First major study of proteins in patients with acute lymphoblastic leukaemia

by Lund University

The most common form of childhood cancer is acute lymphoblastic leukaemia (ALL). Researchers at Lund University in Sweden, in cooperation with Karolinska Institutet, SciLifeLab and the University of Cambridge, have now carried out the most extensive analysis to date of ALL at the protein level, by studying the activity in over 8,000 genes and proteins. The results show aberrant folding in the DNA string, which in turn affects the genes' activity. The study was recently published in *Nature Communications*.

Approximately 25 per cent of the children who develop ALL have a form of leukaemia that is characterised by the diseased cells containing too many chromosomes, known as hyperdiploidy. Sometimes up to 67 chromosomes are found in a single cell.

"We have previously shown that the genes on the extra chromosomes control the development of leukaemia by becoming more active. This induces an imbalance in the cellswhich, for example, may then begin to divide faster", says Kajsa Paulsson, associate professor at Lund University and last author of the study.

However, the exact mechanisms at work have been unclear up to now. In the new study, researchers examined the activity in more than 8,000 genes and proteins—something that had never previously been done on this scale for this form of cancer.

The advantage of examining proteins is that it is more biologically relevant. If only the RNA level is examined and then translated to the protein level, the connection is not completely clear, explains Kajsa Paulsson.

"It is a newer field and examining the protein levels is more difficult, but the advantage is that it gives us a better picture of how the cell is controlled compared with only studying the genes," says Janne Lehtiö, professor at Karolinska Institutet and co-author of the study.

In the hyperdiploid leukaemias, the researchers noted lower levels of the CTCF protein and the protein complex cohesin, which control how the DNA string is folded in the cell, compared with the leukaemias that do not have extra chromosomes. The researchers therefore examined how DNA is folded in hyperdiploid leukaemia and were able to observe that a proportion of cases showed aberrant folding.

"How DNA is folded is important for the regulation of when genes are to be active or not. We could also see that the hyperdiploid leukaemias showed signs of dysregulated genes, something that probably contributes to the onset of the disease," says Paulsson.

Continuing research will focus on identifying the proportion of DNA that displays aberrant folding. The results of the study are important for understanding how hyperdiploid childhood leukaemia arises and what drives the cancer process.

"Today, there is a 90 per cent cure rate for children with ALL, due to extensive treatment using chemotherapy. In the future, we hope to be able to develop even better treatments that provide an even greater chance of a cure and fewer side effects," concludes Kajsa Paulsson.

https://phys.org/news/2017-05-great-mystery-dna.html

New study helps solve a great mystery in the organization of our DNA

May 18, 2017

After decades of research aiming to understand how DNA is organized in human cells, scientists at the Gladstone Institutes have shed new light on this mysterious field by discovering how a key protein helps control gene organization.

Humans have nearly 30,000 genes that determine traits from eye color to risk for hereditary diseases. Those genes sit along six feet of DNA, which are carefully organized into chromosomes and stuffed into each and every microscopic human cell. "The extreme compacting of DNA into chromosomes is like taking a telephone cord that stretches from San Francisco to New York, and stuffing it into a backpack," described

Benoit Bruneau, PhD, a senior investigator at Gladstone and lead author of a new study. "The organization of chromosomes is not random, but rather very complex, and it is critical for normal development. When this process goes wrong, it can contribute to various diseases."

How is our DNA organized?
Chromosomes are coiled into loops and then organized into many large domains called topologically associating domains, or TADs. Within each TAD, several genes and the elements that regulate them are packaged together, and they are insulated from those in neighboring TADs. MCFIP - Epigenetic modeling of CTCF identifies its role as binding to modulate alignment of cilia. Our findings are outlined in the document affixed to this article.

"Imagine TADs are like adjoining rooms: like the genes in each TAD, people in each room can talk to one another, but not to people in the next room," explained Elphège Nora, PhD, postdoctoral scholar in Bruneau's laboratory and first author of the study. "In previous work, we showed that TADs package genes together and insulate them from neighboring genes. The burning question then became: what controls this TAD organization?"

In the new study, published in the renowned scientific journal *Cell*, the scientists discovered that the key to organizing these TADs is a protein called CTCF.

"CTCF is a fascinating protein," said Bruneau, who is also a professor at the University of California, San Francisco. "It can be found at the boundaries of TAD domains, and was previously thought to be involved in many aspects of chromosome organization. We wanted to see what would happen to the structure of chromosomes if we removed all the CTCF from cells."

CTCF: observing a protein that is impossible to study
Researchers have struggled with studying the role of CTCF in the past, because it is absolutely essential to cells' survival. Therefore, completely removing CTCF would cause cells to die, making them impossible to study.

"We used a new genetic method to completely eliminate CTCF in mammalian cells," said Nora. "Using this technique, we destroyed the protein very quickly so that we could study the cells before they died. This allowed us to look at the entire genome in the absence of CTCF and observe the effects."

In collaboration with a team of computational biologists led by Leonid A. Mirny at the Massachusetts Institute of Technology, and a team of biochemists led by Job Dekker at the University of Massachusetts Medical School, the Gladstone scientists demonstrated the importance of CTCF for the insulation of TADs.

"We noticed that, in the absence of the CTCF protein, the insulating boundaries of TAD domains had almost fully disappeared, so that genes and regulatory elements could

now interact with those in adjacent TADs," added Nora. "This would be like removing the wall between adjoining rooms, so that people could now freely interact with others in the neighboring room."

However, the absence of CTCF had little effect on how genes connect within a single TAD. This indicates that CTCF is required for insulating TADs from one another, but not for packaging genes within these domains. This represents the first conclusive study to show that the two mechanisms are separate and controlled by different proteins.

Redefining our understanding of CTCF

Now that the scientists finally had a way of removing CTCF from cells, and disrupting the organization of TADs, they could start studying its impact on various aspects of the genome. They leveraged this new ability to examine other levels of chromosome organization.

"We looked at a level of organization called compartmentalization, which separates active and inactive genes within a cell nucleus," said Nora. "This helps the cell identify which genes to use. For example, skins cells don't need eye-related genes, so these genes would be tightly packaged in a compartment and put away, because the cell will never use them. We used to think that boundaries of TAD domains were a prerequisite for the organization of these compartments."

"To our surprise, we found that is not the case," said Bruneau. "When we deleted the CTCF protein, which caused TAD boundaries to disappear, we saw no effect on the organization of the larger compartments. This interesting finding revealed that CTCF and TAD structure are not required for compartmentalization but, rather, that an independent mechanism is responsible for this chromosome organization."

"Our findings redefine the role of CTCF in gene regulation and provide new insights about the fundamental processes that govern genome organization" added Bruneau. "With this knowledge, we can now start reevaluating the cause of several diseases, as chromosome organization-including TADs-is often disrupted in many cancers and involved in significant developmental defects, such as congenital heart disease."

Prior to its publication in the peer-reviewed journal *Cell*, a preliminary version of the study was posted on bioRxiv, an open-access distribution service for unpublished preprints in the life sciences, and downloaded nearly 5,000 times over the past few months.

"Websites like these offer new, exciting, and more direct ways to share research results," said Bruneau. "It also provided us with valuable input that helped shape our final manuscript and future research."

Explore further: Protein factors tie the genome up in a bow for gene expression

Journal reference: Cell

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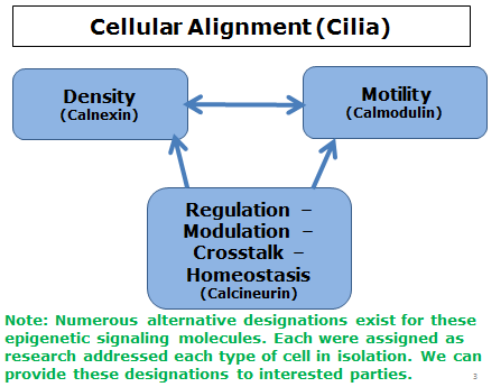
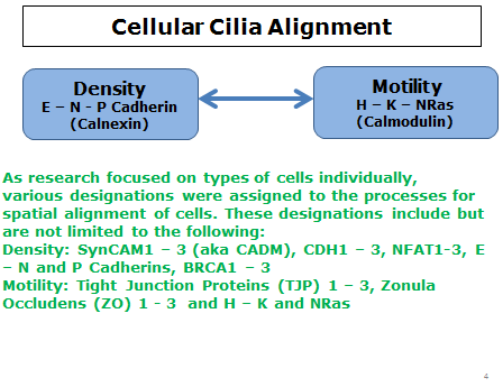
MCFIP – Our modeling of cellular adhesion indicates that, with near certainty, that an alternative for CTCF is calcineurin; a byproduct of IL-3 that functions as a crosstalk mechanism to regulate motility – density of cells.





30-year puzzle in breast cancer solved

May 2nd, 2014 in Cancer /

In a new study published today in *Cell Reports*, scientists at the Fred Hutchinson Cancer Research Center demonstrate that mice lacking one copy of a gene called CTCF have abnormal DNA methylation and are markedly predisposed to cancer. CTCF is a very well-studied DNA binding protein that exerts a major influence on the architecture of the human genome, but had not been previously linked to cancer.

Over 30 years ago, frequent loss of one copy of chromosome 16 was first reported in breast cancer but the gene or genes responsible remained to be identified. Dr. Gala Filippova, staff scientist at Fred Hutch and co-author of the study, originally cloned the human CTCF gene and mapped it to chromosome 16, within the same region that is frequently lost in human cancers. That same year, Dr. Chris Kemp of the Human Biology Division at Fred Hutch, co-authored a paper demonstrating that, in contrast to the predominant "two hit" theory on tumor suppressor genes, it was not necessary to lose both copies, one hit was enough. However, CTCF was ruled out as a candidate breast cancer gene on chromosome 16 simply because it did not conform to the "two hit" model.
"In this current study we explored whether loss of just one copy of the CTCF gene could trigger epigenetic changes and predispose to tumor development," said Dr. Filippova of Fred Hutch. The study demonstrates that indeed, loss of one copy of CTCF caused large scale epigenetic

changes and greatly enhanced tumor formation in multiple tissues. In addition, recent large scale analysis of the human cancer genome revealed that deletions or mutations in CTCF are one of the most common events in breast, endometrial, and other human cancers.

Collectively, these findings indicate that CTCF is major tumor suppressor gene in human cancer and highlights the power of the mouse models to prove that a candidate gene has a function in cancer. These results have implications for understanding the origin of DNA methylation alterations in cancer and suggest that epigenetic instability may both precede and accelerate the emergence of cancer. "This answers a 30 year riddle in cancer research", said Dr. Kemp. "And it shows once again, as we first showed in 1998, that one hit is enough".

Provided by Fred Hutchinson Cancer Research Center

"30-year puzzle in breast cancer solved." May 2nd, 2014. http://medicalxpress.com/news/2014-05-year-puzzle-breast-cancer.html