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Why is this the right time to study Down syndrome?

- 400,000 people with DS in the U.S. alone. New knowledge could prove powerful
- Realization that DS touches so many different issues and conditions
- New tools
  - Induced pluripotent stem cells
  - Deep DNA sequencing
  - Sensitive new kinds of microscopy
What genes matter?

A few hundred on Chromosome 21 are in 3 copies instead of the usual 2.
Are the extra copies of a few of them causing the trouble?
Is the extra chromosome causing the trouble?
Is overexpression of proteins in general causing the trouble?
Perhaps all of the above?
Autophagy

• The cell’s way of rebalancing the system when too many proteins are made or fail to be properly folded up

• Is the extra protein from overexpressed chromosome 21 overwhelming the cell’s regulatory networks, and inducing autophagy?

• Chronic induction of too much protein may induce expression of systems needed to protect under normal circumstances, but chronic induction may cause trouble
Cool experiment

• Make aneuploids (one extra copy of one chromosome) in human cells (not chromosome 21)
• They all have similar cellular phenotypes
• In humans, most aneuploidy is lethal. Too much DNA? Too many different proteins?
• We call them miscarriages
What’s wrong at the cellular level?

- Induction of the stress response
- Slower cell proliferation
- Programmed cell death
My favorite idea

• Regulatory chaos
• Caused by imbalance between proteins on chromosome 21 and their partners from other chromosomes
• Transcription factor example
• Many genes on other chromosomes are known to be mis-expressed
Why muscle weakness?

- Muscle is normal
- Must be the neural connections
Mouse models

• None of them are perfect
• They all show cognitive defects, like in Down syndrome
• This says something basic about how easy it is to cause this phenotype
• 20 different treatments have been shown to improve cognitive functioning.
• None has been shown to work in people
Why?

• Mice aren’t people
• Human trials: don’t know when to treat or for how long or the right dosage
• Human trials have too few people in them to achieve statistical significance. Human trials are really expensive.
Cancer

• Certain leukemia’s are frequent, but they are not quite the same as in typical people
  - The competition idea

• Solid tumors are very rare
  - Induction of p53, a tumor suppressor by induction of the stress response?
  - Suppression of cell division by the same mechanism?
  - Starvation of tumor by restricted blood supply?
VEGF

• VEGF is needed for angiogenesis, production of new or increased blood supply
• Cancer needs a rich source of blood to thrive
  - Needed for out-of-control cell division
• Trisomy 21 reduces VEGF production
• Are solid tumors rare because they their cells can’t divide?
• Interesting question: Do people with Down syndrome get cancer at the normal rate, but the cancers aren’t detected because they usually never get big enough to cause trouble?
Biomarkers project

• Can we find proteins in the blood that predict severity of symptoms or so far undetected issues?
• Look for correlations between phenotypes and presence of proteins in the blood.
• Promising for Alzheimer’s disease
Deep sequencing

• Everyone with DS has the same extra chromosome: 21
• But there are thousands of genetic differences between any two individuals (except identical twins). Some are on 21.
• Can we sequence the complete genomes of hundreds of individuals with DS and find genetic changes that correlate with phenotypes?
Why are the characteristics of people with DS so incredibly variable?

After all, they all have the very same extra chromosome

• Genetic differences
• Environmental influences
• Chance