Evolution of the Cancer Genome

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Overview

* Start with the obvious: cancer is not one disease; it has a huge array of causes
* The number and pattern of somatic alterations vary widely across cancers
    -- As few as 10 and as many as 50,000 somatic genome alterations in cancer cells
* Mutation rate may not be constant over time
    -- Sometimes, slow evolution; other times, “punctuated equilibrium”
* There are not many common alterations within and across cancer types
    -- Rare cases, such as TP53 – mutations are common across many cancers
    -- But even TP53 is found uncommonly within each cancer

Detecting causal genetic changes

* Because cancer cells don’t undergo mitosis, there’s no crossing over, (i.e. strong linkage), so GWAS doesn’t work within a single sample

* Hard to distinguish driver from passenger mutations

* As a result, we have to find correlations across individuals and across cancers

* …but then, if we don’t cluster them properly, each signal is lost in the overall noise

* A meta-test to see if there is a high ratio of non-synonymous to synonymous mutations detected

Susceptibility Mutations

* In many myeloproliferative neoplasms, JAK2 has the V617F mutation
* V617F mutations are frequently found in conjunction with a nearby JAK2 SNP
* The susceptibility SNP isn't actually cancerous, but seems to promote the cancerous mutation
* Two hypotheses:
    1) The susceptibility SNP makes it more likely that V617F forms (V617F found on several alleles)
    2) The susceptibility SNP makes it more likely that V617F-mutated cells live

Epigenetic Changes

* Loss of methylation is often associated with cancer
* But not the converse -- epigenetic abnormalities are common in healthy cells
    -- Epigenetic changes in mice 10x-100x more frequent than genetic changes
* There are many ways epigenetic changes can lead to cancer
    -- e.g., suppression of DNA repair genes, replication timing
* Cancer is often associated with mutations in DNA for epigenetic modifier enzymes

Tumor Heterogeneity

* Cells within a tumor may be highly heterogeneous
    -- Mono-clonal and poly-clonal breast cancers are equally common
* Poly-clonal tumors appear increase likelihood of negative clinical outcome
* Primary tumors and their metastases are commonly different clones, suggesting metastasizing ability evolves late
* One study showed that clones had a common ancestor

Why both hetero and homogeneous?

* Hypothesis: all cancers start with one (or a few) cells; heterogeneity depends onthe initial cancer cell being a “stem cell”

* Stem cells: can only produce non-reproducing “offspring”. Therefore, all cells are clones of the stem cell. Homozygous tumor.

    -- Supported by studies showing that in homozygous tumors, most cancer cells

    can not induce tumors when transferred into a new host

* “Clonal evolution” model: all cells can proliferate; natural selection takes over

Cells Resistant to Therapy

* Key question: are resistant cells detectable at time of diagnosis? Or do they develop only after therapy has begun?
* If we can find the resistant-cell needle in the tumor haystack, this has important implications for picking a therapy that is not resistant before it’s too late
* Limit: whole-genome sequencing of single cells is currently not possible

Study of other organisms

* Naked mole rats have an unexplained very long lifespan and high resistance to both spontaneous and induced tumors

* Initial studies show differences (w.r.t similar mammals) in protiens for telomere lengthening, DNA repair and replication, cell cycle and DNA torsion control

Holy grail

"The ultimate dataset will contain information on DNA sequence, copy number, DNA methylation, histone modifications, gene and protein expression as well as on chromatin architecture for the same sample, obtained from single cells over a time-course of several years, both before and after the administration of therapy."