Genes as Instructions

- There are ~23,000 genes in the human genome

- Where they represent but a small fraction of the $6x10^9$ letter units or nucleotides that make up the full human genome

- In essence, each gene represents an instruction-in part or in full- delivered within and/or between cells.

- All manner of biological instructions are encoded in genes, including:

    - commands that promote cell and organ growth

    - commands that limit normal cell and organ growth and prevent cancer development.

- Commands that promote normal growth, can elicit abnormal, uncontrolled growth when they become corrupted/ abnormally accentuated.

- Commands that normally suppress growth, fail to elicit this effect when they become corrupted and underexpressed.

- Growth promoting genes when they secome superactivated= activated ONCOGENES

- Growth Suppressing genes that become corrupted= defective TUMOR SUPPRESSORS

• Many human tumors-common and uncommon-are the product of a combination of activated ONCOGENES and defective TUMOR SUPPRESSORS

• There are hundreds of oncogenes and tumor suppressors, and many of each have been shown to play a role in human cancer development.

• However, a very small number of each, and the same ones each time-e.g. Rb, p53, RAS, PI3K, c-myc-contribute to the development of most common tumors.

• Thus, a small number of the same, specific commands must be accentuated and eliminated for most tumors to develop.

•This suggests that cancer prevention could be enhanced by drugs that, specifically, kill cells in which these corrupted commands are being sent.

•New, genome- and chemical library- based screening methods make a search for such agents feasible.

Therapeutic strategy making

- In a tumor where a corrupted command(s)-ONCOGENE- is/are superactivated, it may also be necessary for the maintenance of tumor cell survival.

- Interfering with such a command should trigger cancer cell death-a clinically desired outcome and, thus, the basis for a generic therapeutic strategy.

Another rational strategy-synthetic lethality

- In tumor cells bearing an activated oncogene or loss of a specific tumor suppressor gene, loss of a third gene, which is not necessarily an oncogene or a tumor suppressor, may trigger cell death. Death only occurs in this special, multi gene- dependent setting.

- This is the concept of synthetic lethality, and drugs that elicit it in certain tumor cells can now be sought, also by novel screening methods.

Synthetic Lethality-example

In a given tumor

Oncogene A+ — No inhibitor available

Tumor suppressor B- — No activator available

a screen---> Gene C+ → A+/B-Tumor Cell Death

Specific inhibitor ↑

Breast Cancer Genes

- There are families in which some women in multiple generations develop breast (and/or ovarian) cancer.

- The frequency of disease is much higher than would be expected, if the disease developed at a ‘normal’ rate.

- The lifetime risk of developing the disease may approach 50-90% vs a normal rate of ~12%

- Sometimes the affected women develop the disease earlier in life than would normally be expected.

• The existence of such families prompted investigators to search for a mutant/corrupted gene in the germ line that could be ‘linked’ to disease development.

• The search yielded two such genes between 1990 and 1995- so-called BRCA1 and BRCA2.

• It was also shown that disease was linked to a loss of function rather than amplified or superactivated function of these genes (cf B. Ponder et al).

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• Thus, BRCA1 and 2 are tumor suppressor genes.

We now know that:

- The normal commands sent by BRCA1 and 2 are carried out in virtually all proliferating cells in most/all organs,

- but disease develops largely (BRCA2) or ‘almost always’ (BRCA1) in the breast and ovary.

- in BRCA1 families, the males who carry the mutant gene experience little or no abnormal effects thereof.

So, even though BRCA1 and 2 are ‘expressed’ as commands/instructions in most organs and proliferating cell types, loss of their function triggers disease largely/only in two organs and, in BRCA1 families, only in women.

WHY?

- there are multiple possibilities, including

-a role for estrogens in the disease mechanism

and

-a role for BRCA1 in normal mammary gland and/or ovarian development and function.

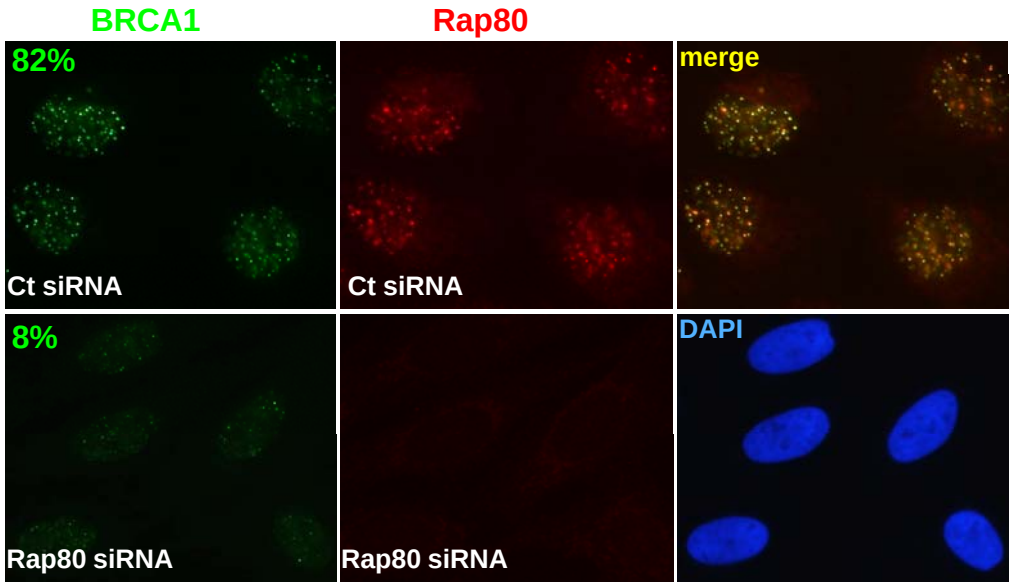
-?? a role for an abnormality of the X chromosome

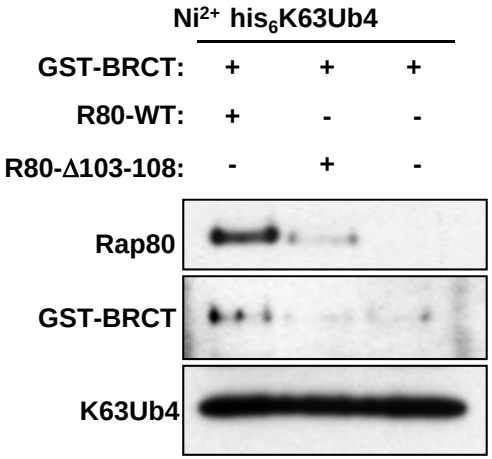
Progress in Deciphering the BRCA1 and 2 Commands

- Both genes operate by sending commands that direct a cell to repair, perfectly, damage that develops spontaneously in DNA.

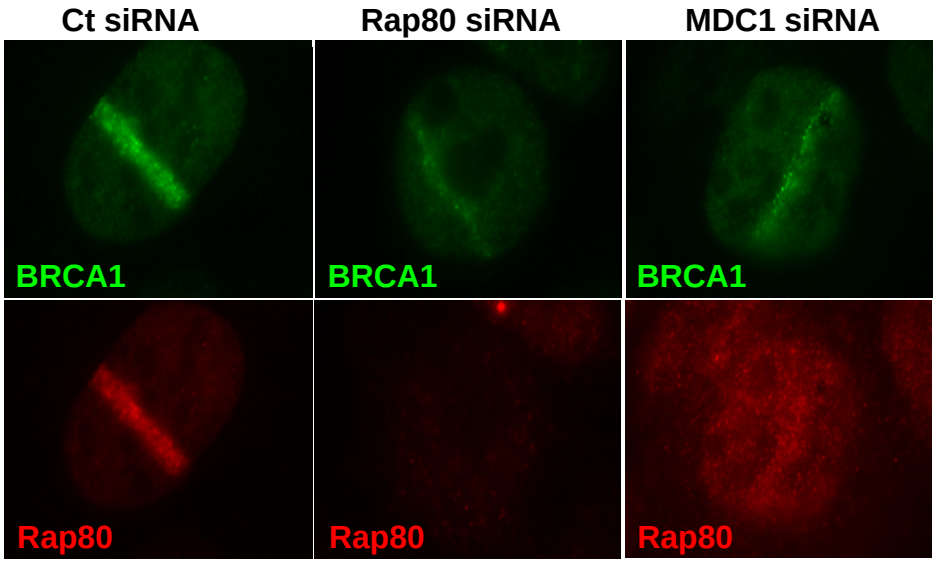
- Both genes also send instructions that promote proper cell division and the distribution of the right number of chromosomes, i.e. 46 to each newly divided 'daughter' cell.

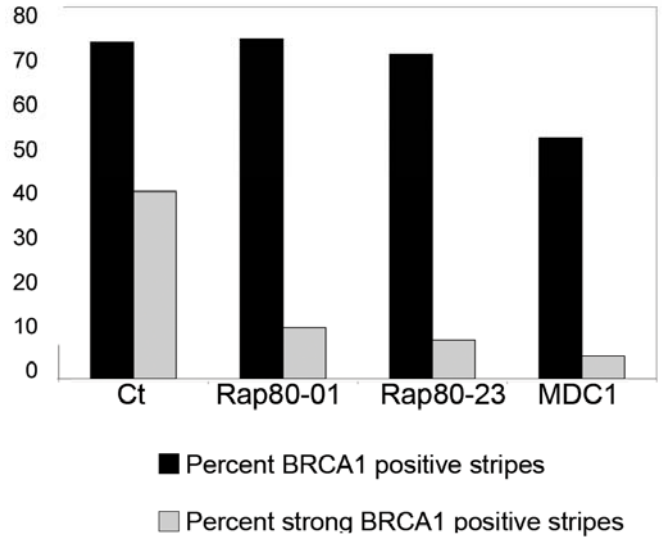
BRCA1 signals the presence of DNA damage





BRCA1 signals the existence of DNA damage





Progress in Deciphering BRCA1 and 2 Function

- Both genes operate by sending commands that direct a cell to repair, perfectly, damage that develops spontaneously in DNA.

- Both genes also send instructions that promote proper cell division and the distribution of the right number of chromosomes, i.e. 46 to each newly divided 'daughter' cell.

• when cells acquire DNA damage that is not fully or accurately repaired, cancer is an increasingly likely outcome, e.g. Xeroderma Pigmentosum, Fanconi Anemia, HNPCC.

• the more defective a cell is in its ability to repair DNA damage or to deliver its replicated chromosomes properly to its daughters, the more likely it is that cancer will develop.

•Thus, at the heart of BRCA cancer is an inability to maintain the integrity of the genome, one outcome of which is the development of additional genetic abnormalities, some of which also promote cancer development.

An inability to repair DNA damage, efficiently, also creates new treatment opportunities.

PARP1=an enzyme engaged in DNA repair

BRCA1/2= a different enzyme engaged in DNA repair

These proteins work together to eliminate DNA damage, but cell survival after DNA breaks develop requires only one or the other.

Farmer et al and Bryant et al Nature, 2005

DNA Breaks

activate

BRCA1/2+ PARP1---------> DNA repair

In the absence of BRCA1/2 or PARP1---> DNA is still repaired, and cells survive

In the absence of **both**------> inadequate DNA repair and cell death

Thus, PARP1 inhibition should be **synthetically lethal** with a BRCA1 or a BRCA2 mutation in a tumor cell.

Ashworth, A et al, Nature 2005;
S. Jackson et al

In the tumor cells of BRCA1 or BRCA2 mutation-bearing women, the relevant BRCA gene does not function.

In the non-tumor cells of these patients, one of the two copies of the gene still functions normally.

Thus, a PARP 1 inhibitor should kill tumor and not the non-tumor cells in such a clinical setting.

In BRCA1 or 2- Deficient Tumor Cells

- a small molecule inhibitor of PARP1 triggers death.

- In patients with advanced chemoRx-resistant, BRCA1 or BRCA2 breast or ovarian cancer, this agent led to significant disease regression and clinical improvement.

Fong, Tutt, Ashworth, deBono et al, NEJM, 2009

So, an interesting laboratory-derived concept has proven to be clinically valid and to have spawned the discovery and development of a new therapeutic strategy that is clinically useful in advanced cancers that are otherwise untreatable.

In addition, PARP1 inhibitors have not, so far, proven to elicit dramatic side effects at effective doses.