Cancer Genetics 101 - a (Very) Basic Primer

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Genetics is the study of the structure and function of

genetic information inherited from

one generation and passed on to future generations

Genetics information is encoded in molecules of DNA.

This information specifies the structure and

function of proteins and the cells

that contain these proteins . . .

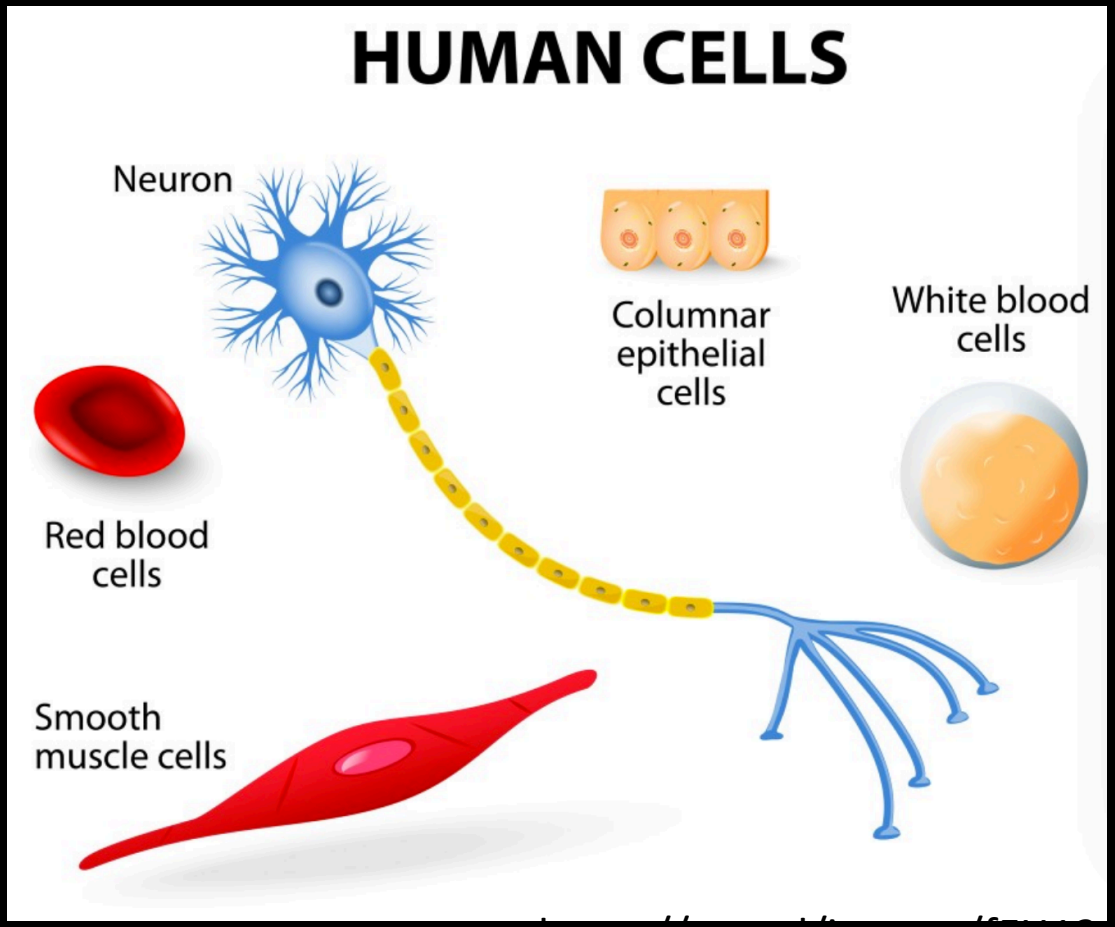
and ultimately, the structure and function of

whole organisms as well

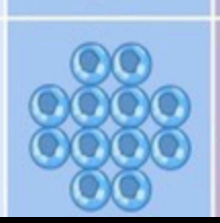
Cells are a structural and functional component

of all complex organisms, including humans

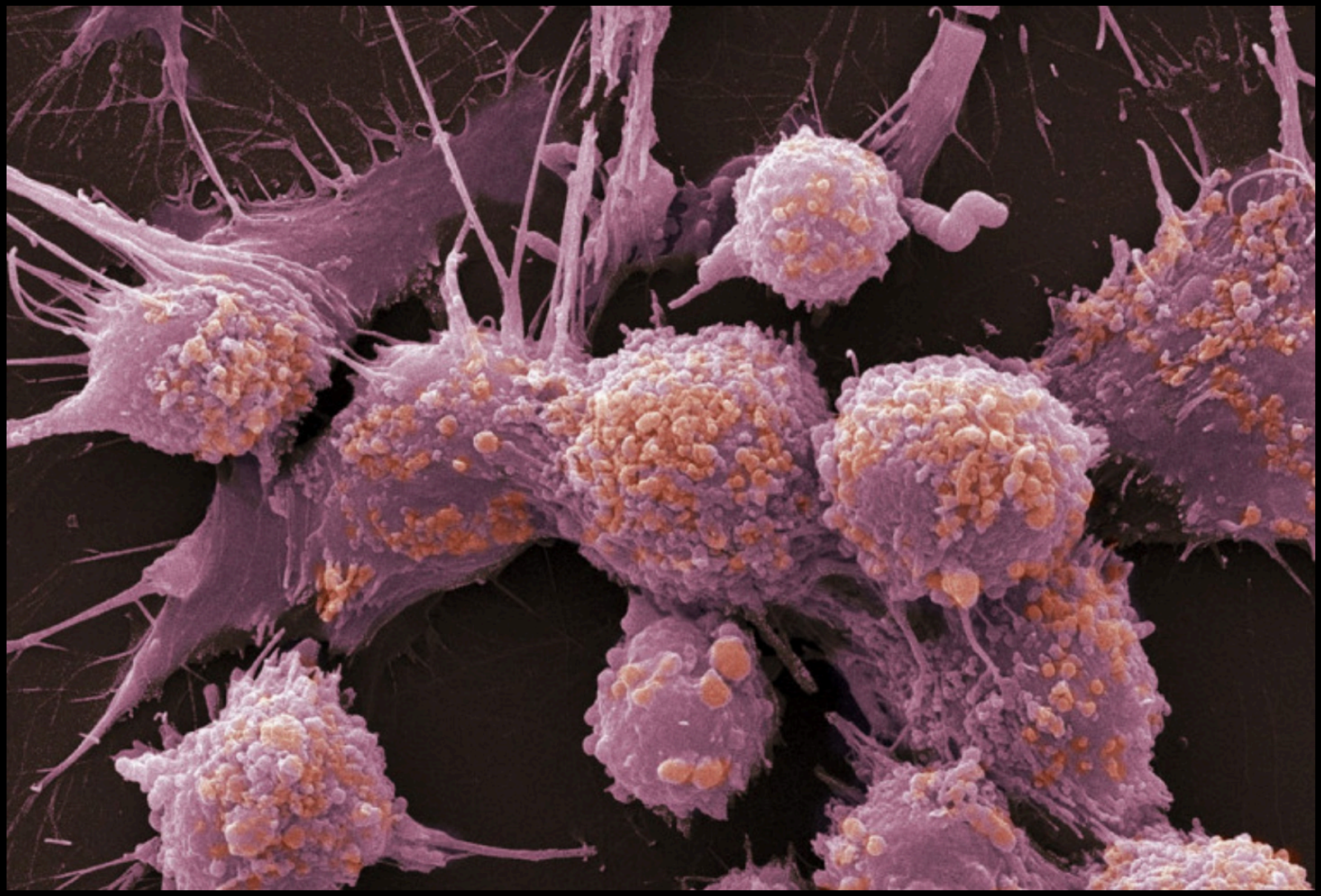
Cells have a variety of functions that are dictated by the structure and function of the proteins they contain



Due to mutations in the DNA of genes and the proteins they encode, the behavior and microscopic appearance of cancer cells is quite different from that of non-cancerous cells

Small, uniformly shaped nuclei Relatively large cytoplasmic volume		Large, variable shaped nuclei Relatively small cytoplasmic volume
Conformity in cell size and shape Cells arranged into discrete tissues		Variation in cell size and shape Disorganised arrangement of cells
May possess differentiated cell structures Normal presentation of cell surface markers		Loss of normal specialised features Elevated expression of certain cell markers
Lower levels of dividing cells Cell tissues clearly demarcated		Large number of dividing cells Poorly defined tumor boundaries

Cornell, B. 2016. [ONLINE] Available at: http://ib.bioninja.com.au. [Accessed 1/27/19]

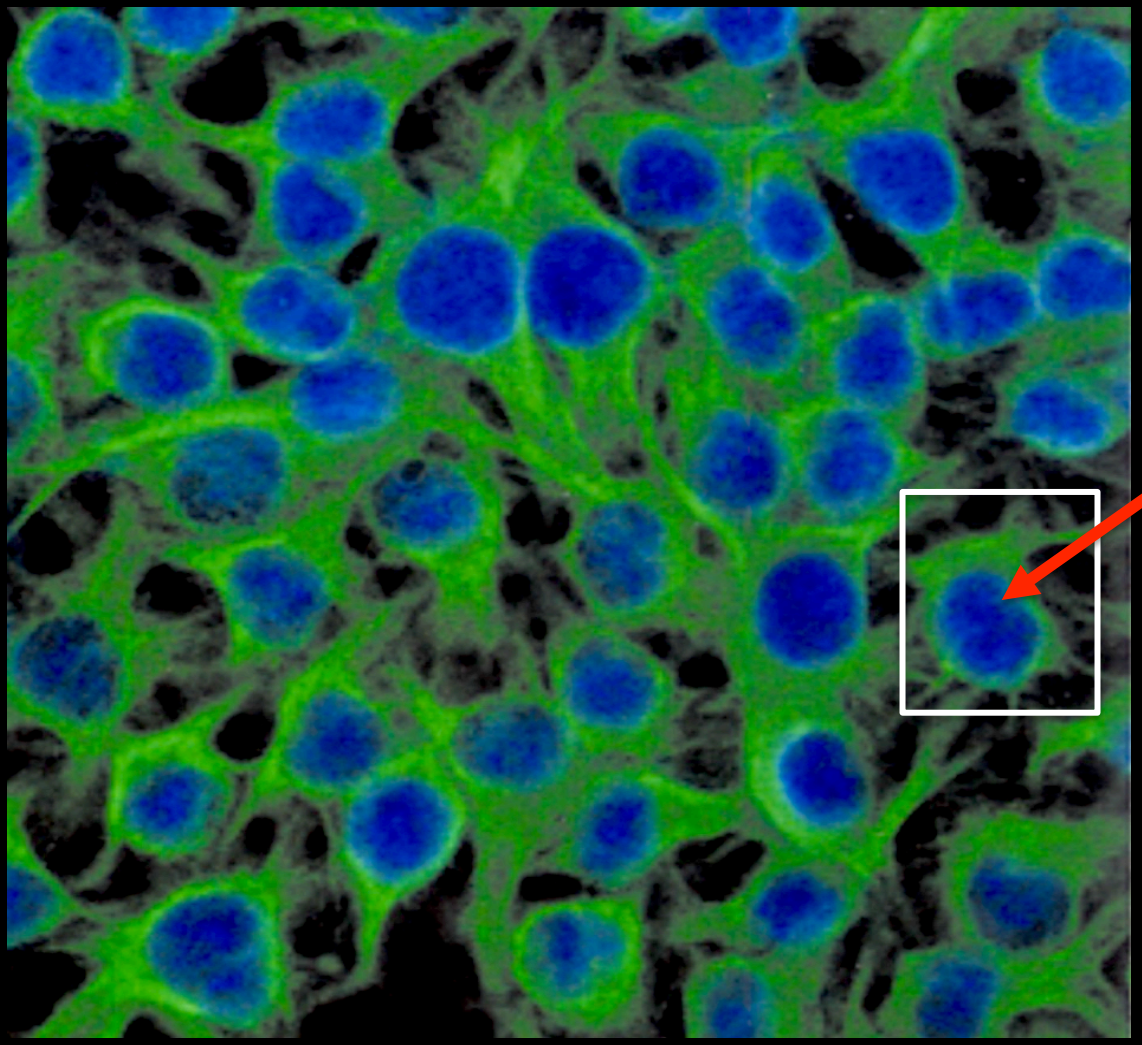


Scanning electron micrograph of prostate tumor cells that have prostate-specific membrane antigen (PSMA) on their surfaces

The most important feature of cancer cells

is their aberrant proliferation

Most cells are very small - prostate tumor cells, for example, are on average, about 8 micrometers – that is, 8 millionths of a meter - in diameter (a meter = 39.37 inches)

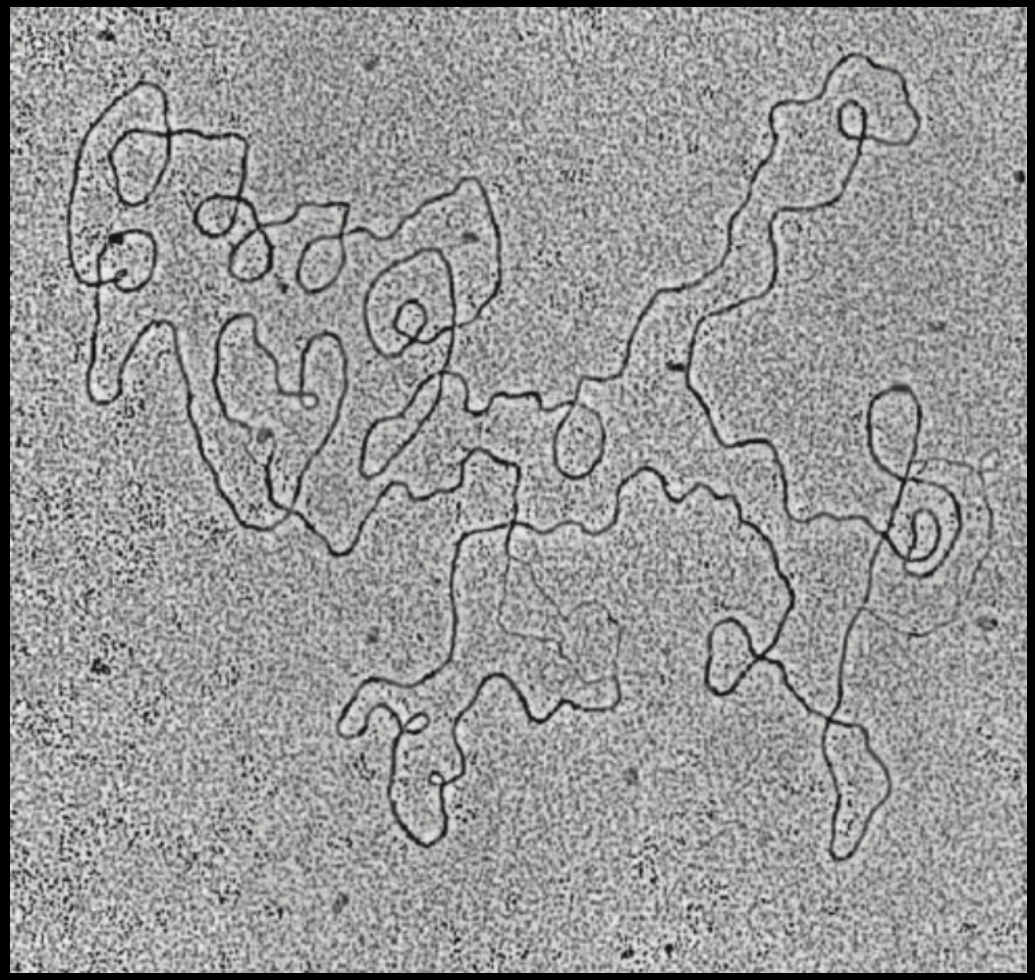


DNA (stained blue) in cell nucleus

Every adult human body has about 40 trillion cells. If the DNA molecules in all these cells were stretched end to end, they would span *twice the diameter of the solar system!*

What is DNA, and how does it encode genetic information?

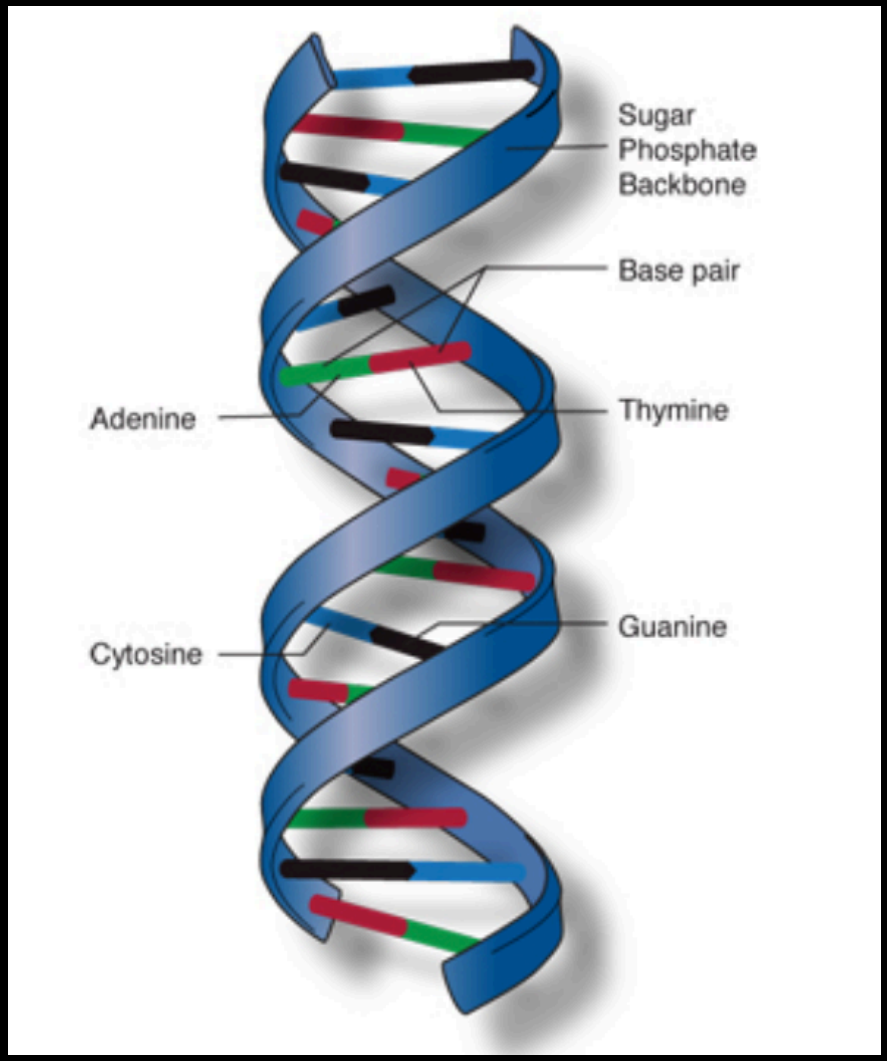
DNA is a linear molecule



The 46 molecules of DNA found in most human cells

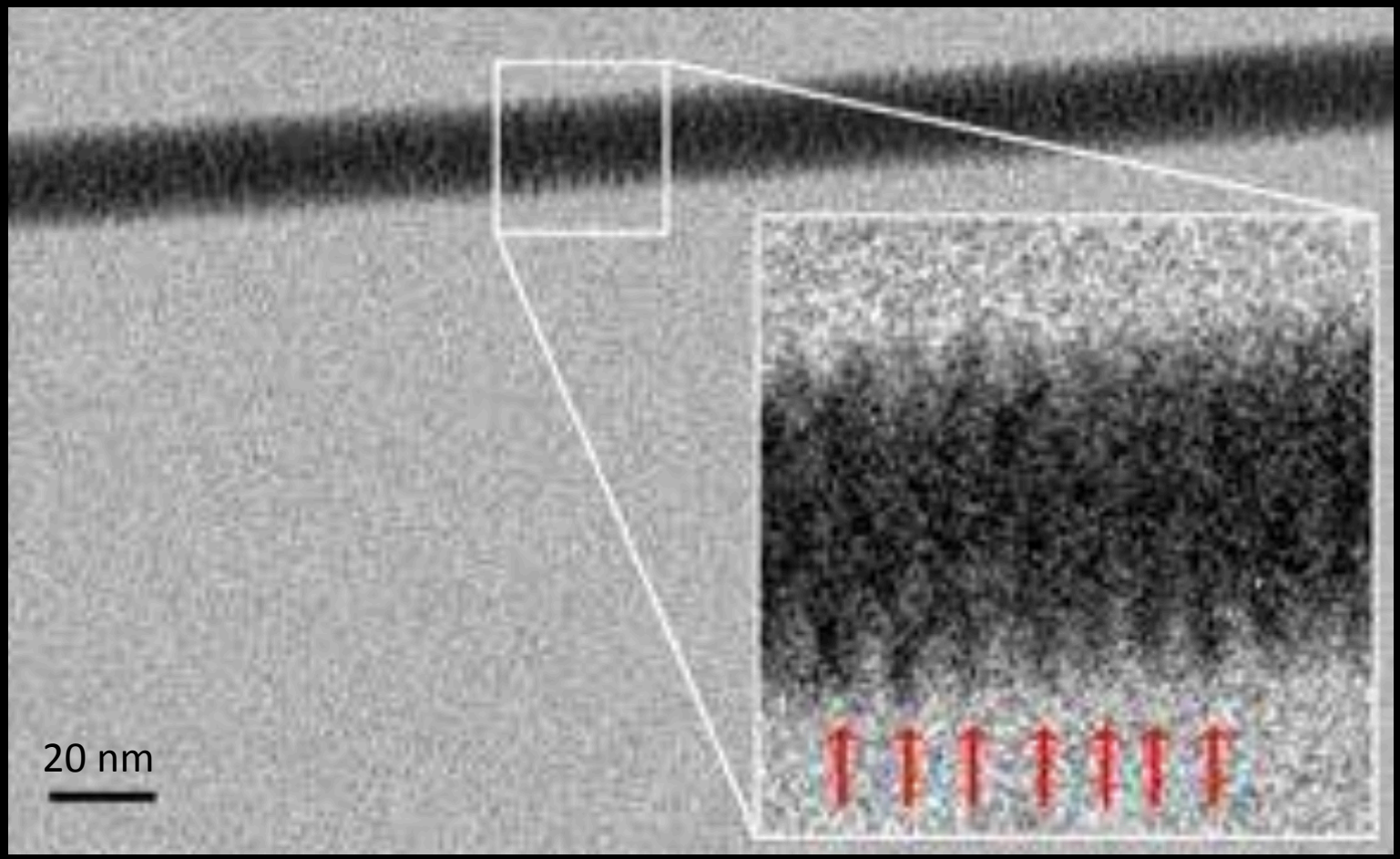
contain genetic information for approximately 19,000 genes

DNA = deoxyribonucleic acid



The double helical structure of DNA

visualized by electron microscopy

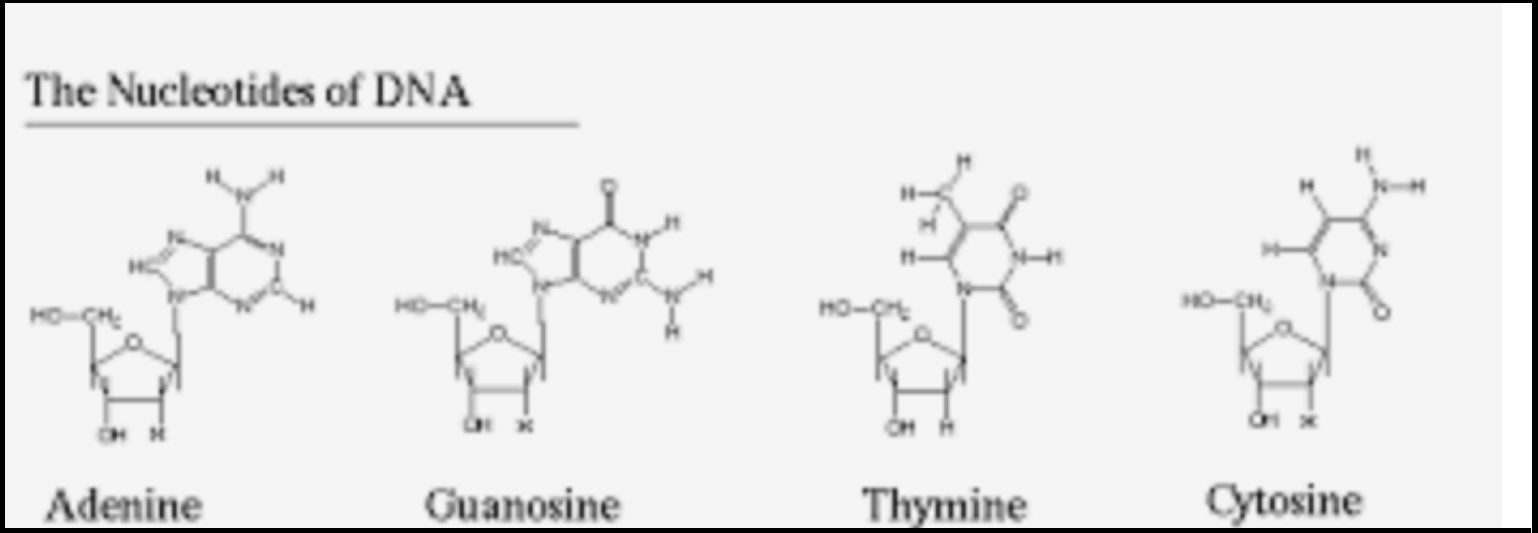


Nano Lett. 2012, 12, 12, 6453-6458

Linear DNA molecules consist of two strands of nucleotides, each of which corresponds to four different chemical “letters” designated A,G,T or C

ATGGGAGTTCCAGTGTGTGACAAGTACCATGTTCAAGTAGGAACAAAAGTTGACCTAGAGATTCCACC

TACCCTCAAGGTCACACATCTGTTCATGGTACAAGTCATCCTTGTTTTCAACTGGATCTCTAAGGTGG



What exactly is a gene?

A gene is a segment of DNA (or RNA) encoding information

that determines the structure of a protein

ATGGGAGTTCCAGTGTGTGACAAGTACCATGTTCAAGTAGGAACAAAAGTTGACCTAGAGATTCCACC

TACCCTCAAGGTCACACATCTGTTCATGGTACAAGTCATCCTTGTTTTCAACTGGATCTCTAAGGTGG

(gene encoding a specific protein)

The genetic information in a gene is determined by the *sequence* of As, Ts, Gs and Cs in the segment of DNA, corresponding to a gene

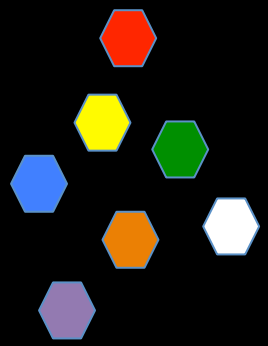
ATGGGAGTTCCAGTGTGTGACAAGTACCATGTTCAAGTAGGAACAAAAGTTGACCTAGAGATTCCACC

TACCCTCAAGGTCACACATCTGTTCATGGTACAAGTCATCCTTGTTTTCAACTGGATCTCTAAGGTGG

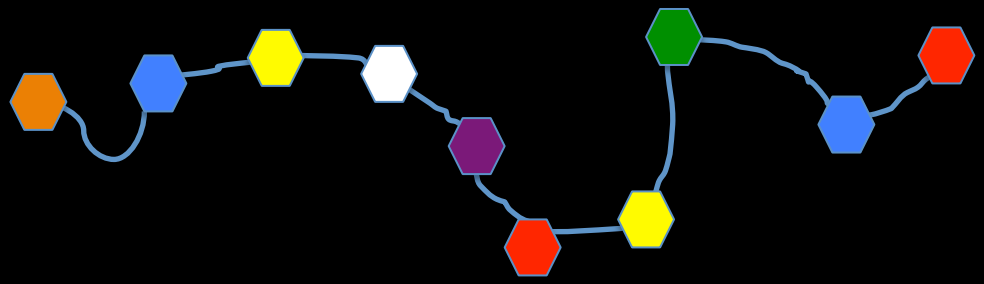
(gene encoding a specific protein)

Proteins are also linear molecules, and are made up

of 20 different types of amino acids,



= amino acids (20 different types)

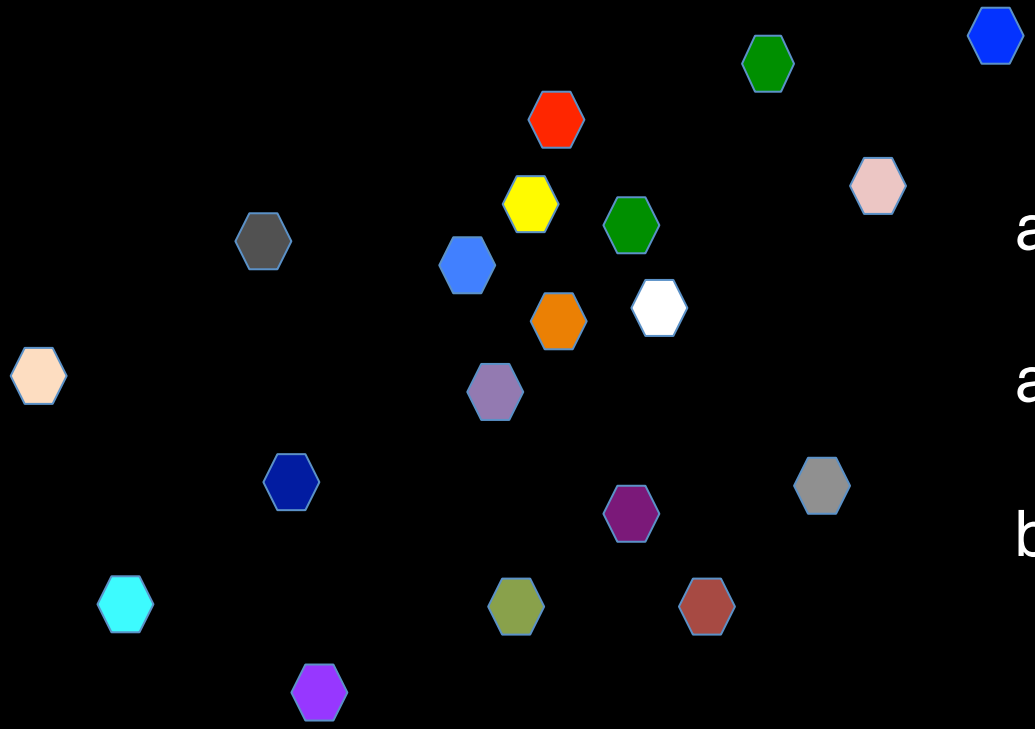


protein (specific sequence of amino acid building blocks dictated by DNA sequence)

The sequence of amino acids in a protein

Is determined by the sequence of nucleotides in the

gene it encodes . . .



amino acids

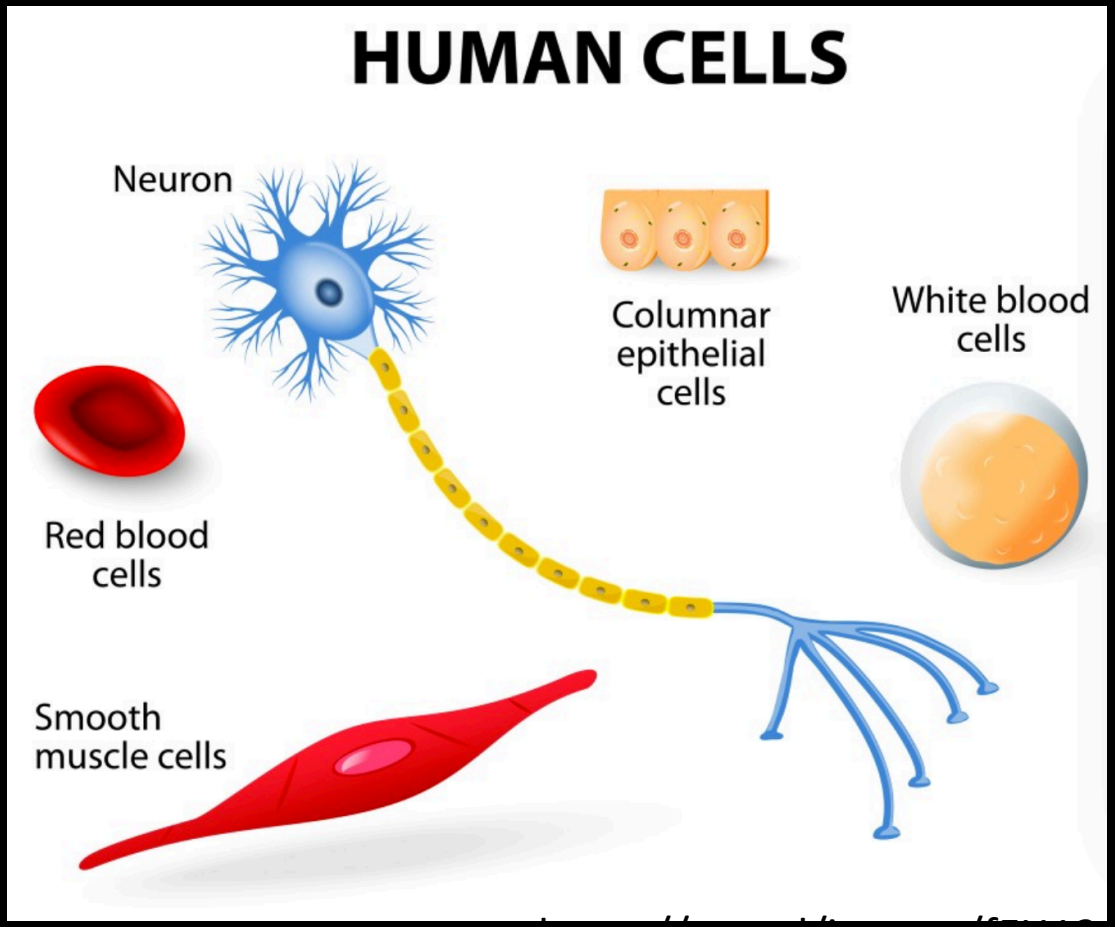
are the basic building

blocks of proteins

. . . and the sequence of amino acids in a protein determines its three-dimensional structure, which in turn determines its function

Cells have a variety of functions that are dictated by

the structure and function of the proteins they contain



How does DNA nucleotide sequence determine

a protein's amino acid sequence?

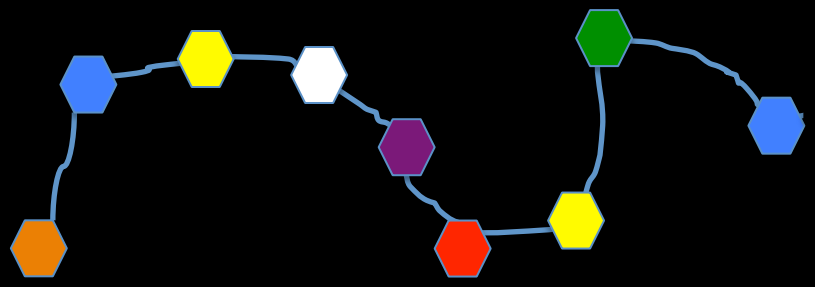
Every three “letters” in the DNA of a gene – called a *codon* - encodes an amino acid “building block” of proteins

ATGGGAGTTCCAGTGTGTGACAAGTACCATGTTCAAGTAGGAACAAAAGTTGACCTAGAGATTCCACC

TACCCTCAAGGTCACACATCTGTTCATGGTACAAGTCATCCTTGTTTTCAACTGGATCTCTAAGGTGG

gene

ATCTGTTCATGGTACAAGTCATCCTGT



Protein (specific sequence of amino acid building blocks dictated by DNA sequence)

What about mutations?

A “mutation” is a change in genetic information –

that is, *a change in the sequence of nucleotide letters in DNA*

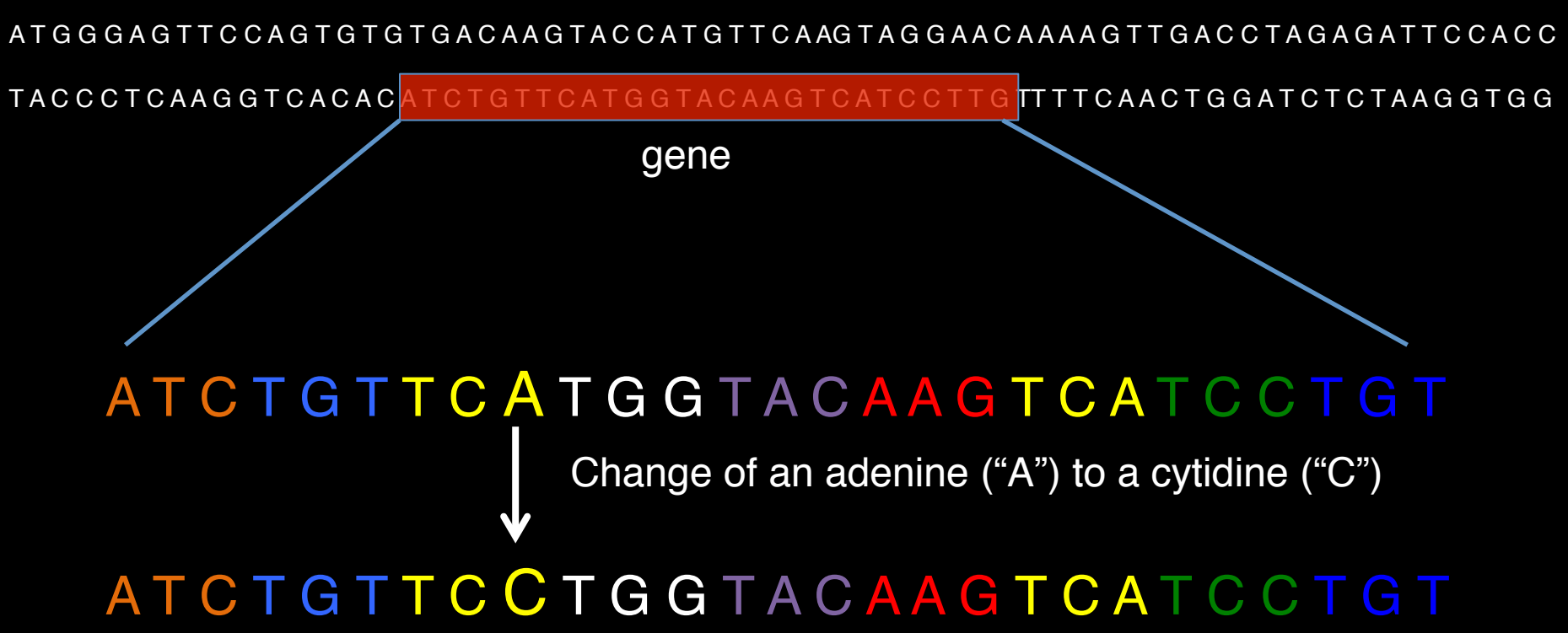
Mutations are caused by chemicals (including carcinogens that cause cancer), as well as by radiation and by mistakes in the duplication of DNA

When this mutation – i.e., nucleotide change - occurs in a gene,

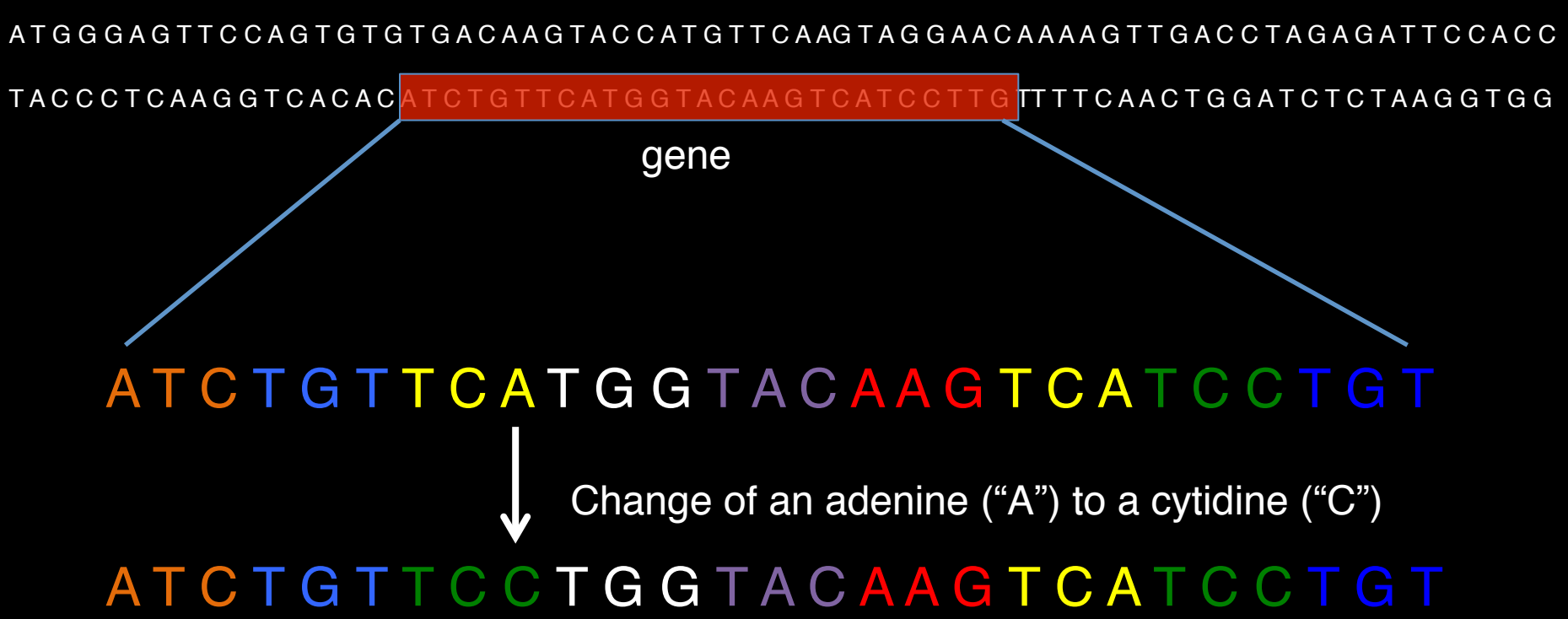
it can also change the sequence of amino acids

in the protein encoded by the gene

For example, a mutation of an adenine to a cytidine . . .



. . . alters the amino acid sequence of the protein encoded by this gene . . .



. . . by changing a “yellow” amino acid to a “green” amino acid

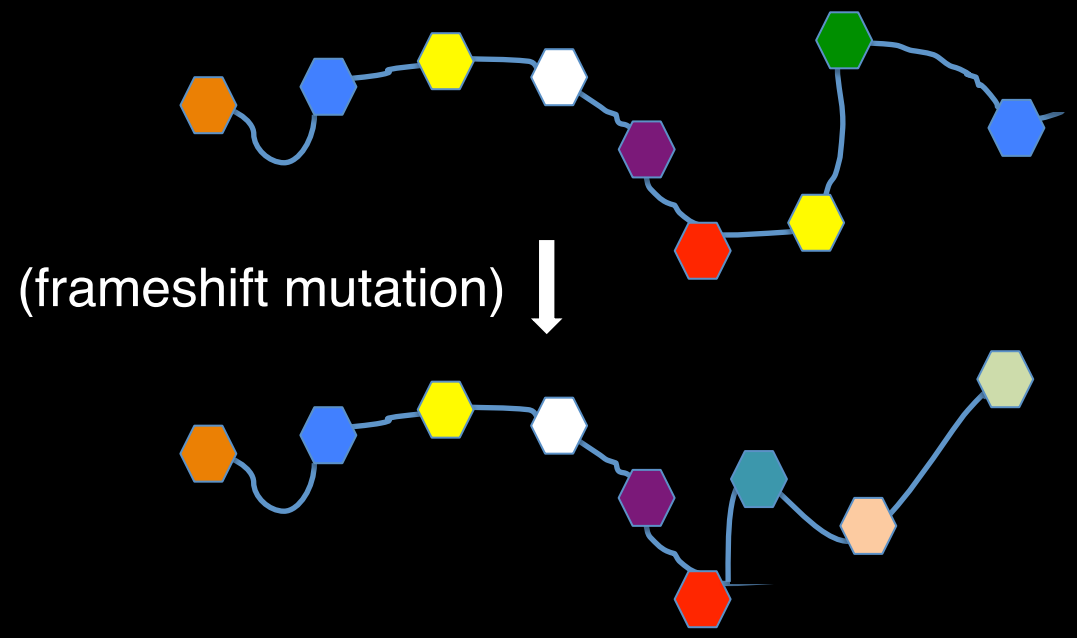
Mutations can also be caused by deletions of nucleotides,

which can also change the amino acid sequence of a protein

A T C T G T T C A T G G T A C A A G T C A T C C T G T T

Deletion of T

A T C T G T T C A T G G T A C A A G C A T C C T G T T

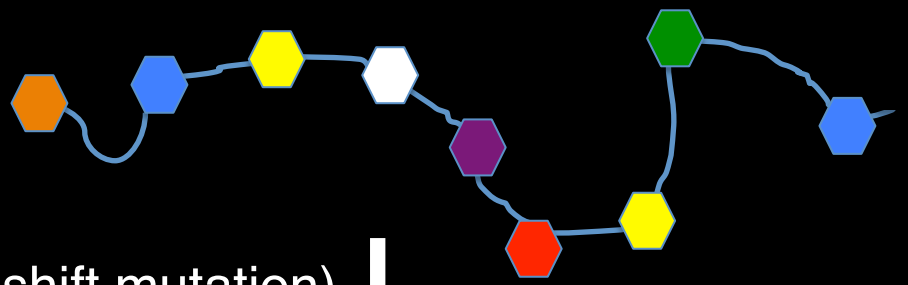


When this mutation occurs in a gene that encodes a protein that regulates cell proliferation, it can cause aberrant proliferation of the cell that suffered this mutation . . .

A T C T G T T C A T G G T A C A A G T C A T C C T G T T

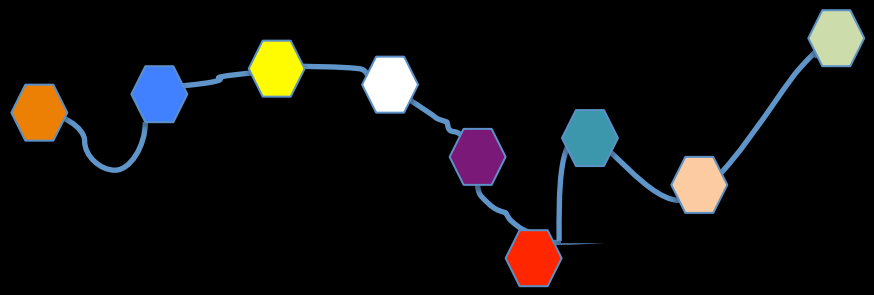
Deletion of T

A T C T G T T C A T G G T A C A A G C A T C C T G T T

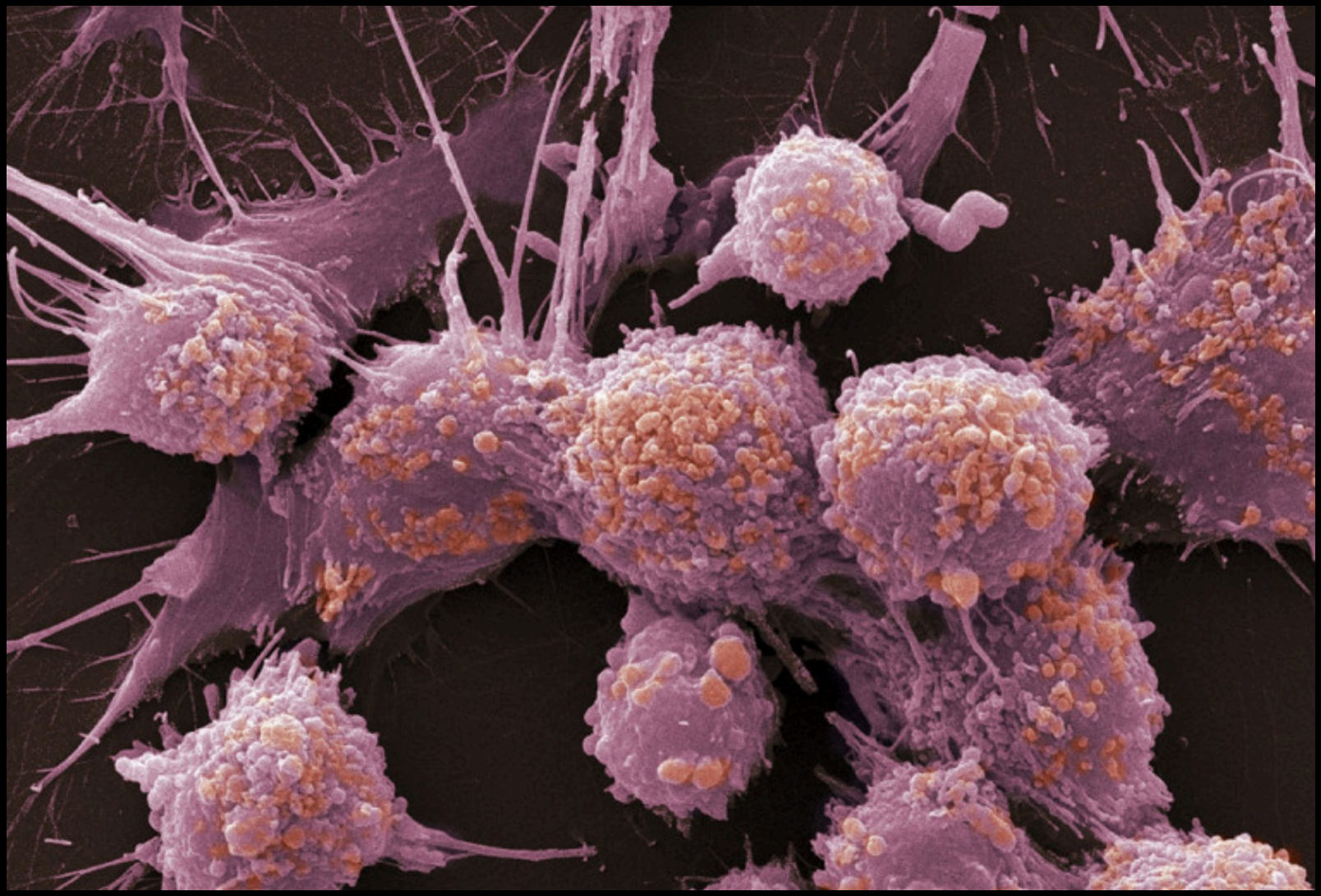


wild type protein

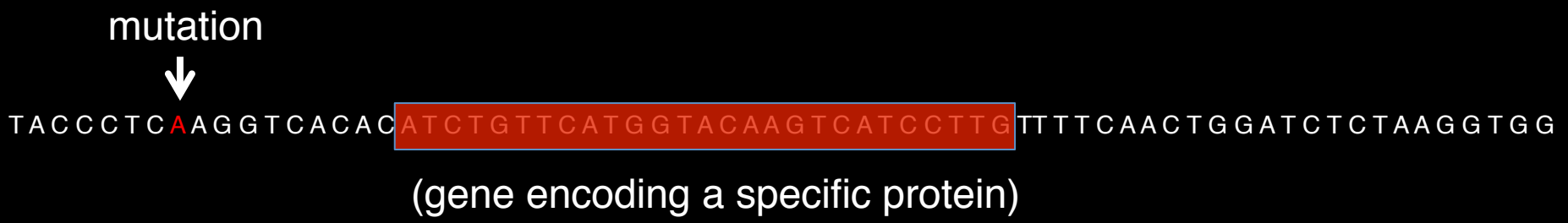
(frameshift mutation)



mutant protein



. . . as well as other changes that occur in cancer cells



Mutations that occur in DNA outside of genes (i.e., in “non-coding” DNA) can also cause cancer, by (for example) increasing the frequency with which genes are “expressed”, leading to elevated levels of proteins, or by decreasing expression and therefore reducing levels of proteins

Importantly, not all mutations are *pathogenic* –

that is, cause disease

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FINAL REPORT - 10/13/14

Ordered By Contact ID: 34385 Org ID: 05476

Physician: Iyer, Renuka V., MD
Ph: 716-845-8400 Fx: 716-845-5720

Client: Roswell Park Cancer Institute
Clinical Genetics Service
C & V Building, Rm. 233
Elm & Carlton Streets,
Buffalo NY 14263

Additional Authorized Recipient
Hutton, Mollie, MS, CGC Ph: 716-845-8400 Fx: 716-845-5720

Patient Name: **Burhans, William**
Accession #: **14-177584** Specimen#: 393318
Specimen: Blood EDTA (Purple top)
Birth Date: 04/02/52 Age: 62y 6m
Gender: M
MRN#: 393318 Collected: 07/22/14
Family#: 150110 Received: 07/23/14
Ethnicity: Caucasian Authorized: 07/29/14
Indication: Diagnostic/Family History

CancerNext: Analyses of 28 Genes Associated with Hereditary Cancer

PANEL RESULTS

BRCA2	**Pathogenic Mutation:**	**c.4638delT**
CDH1	Variant, Unknown Significance:	p.P537L
MLH1	Variant, Unknown Significance:	p.R389W

(genetic test report)

Recent studies have established that defects

in cellular responses to DNA damage, including

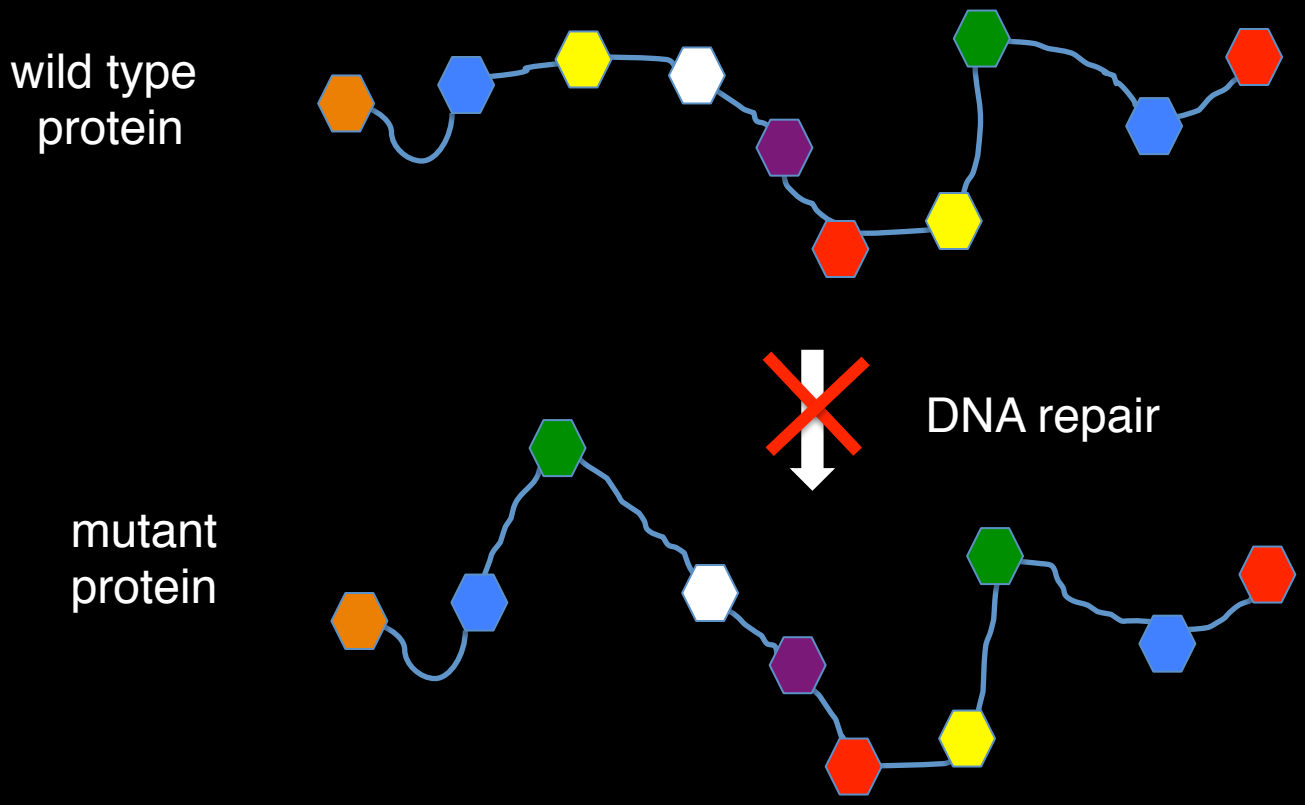
DNA repair, occur especially frequently in

prostate tumor cells

Repair of DNA damage maintains the integrity of genetic information,

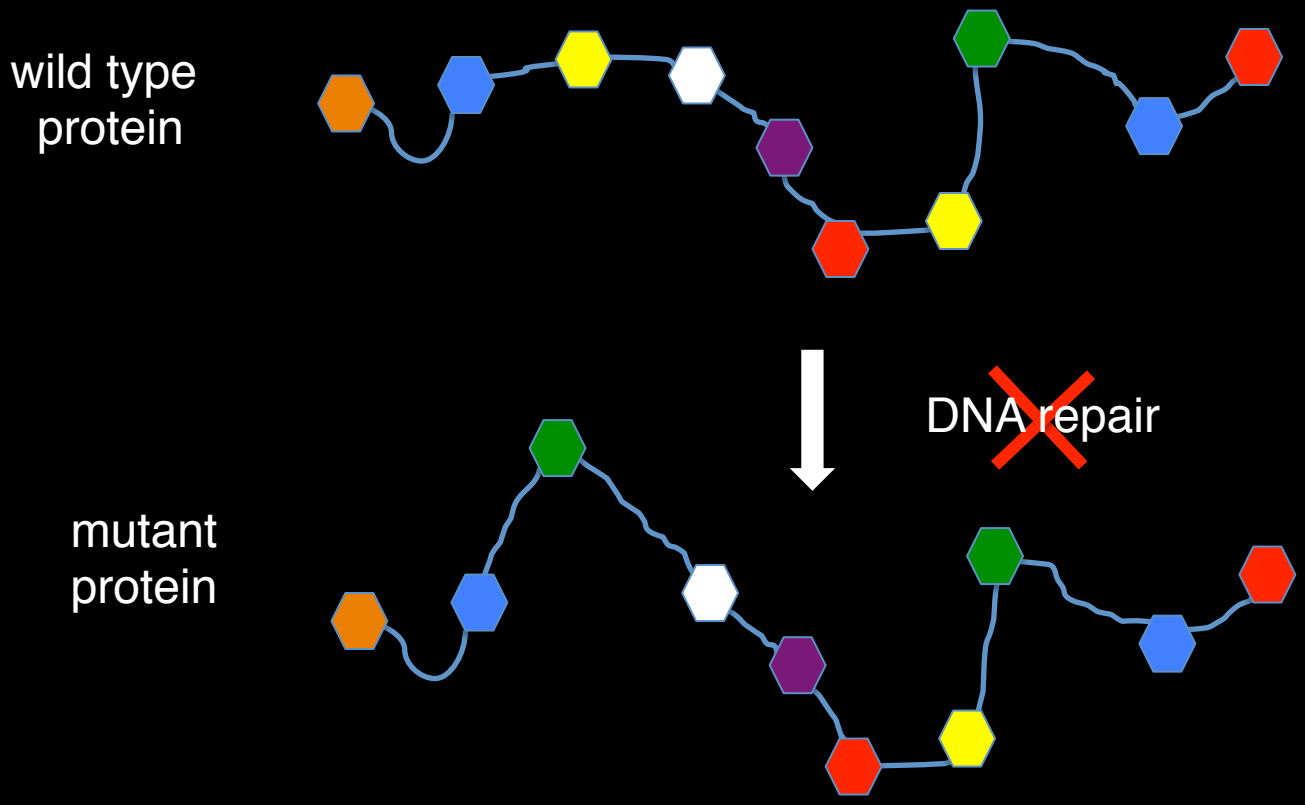
and therefore also maintains the wild type structure

and function of proteins



Conversely, defects in DNA repair can cause mutations

that can lead to cancer



The “breast cancer” *genes* *BRCA1* and *BRCA2* encode proteins

that are required for efficient repair of DNA damage,

especially during the duplication of DNA molecules

required to provide a complete set of genetic information

to new cells produced by cell division

Mutations that occur in germline cells are *heritable*,

meaning they can be passed on to the next generation

Inherited mutations in *BRCA1* and *BRCA2* genes that impact the structure and function of Brca1 and Brca2 proteins promote breast, ovarian, prostate and pancreatic cancer, as well as melanomas (which are a type of skin cancer)

DNA repair genes that when mutated in the germline are

also associated with an increase in risk for

cancer include, in addition to *BRCA1* and *BRCA2*,

the *PALB2, MLH1, MSH2, ATM,* and *PMS2* genes and others

"Genetic testing" searches for germline (i.e., heritable) mutations

in these and other genes that when mutated are known

to increase the risk for the development of cancer

Therefore, genetic testing for germline (i.e., heritable) mutations provides valuable information about the risk that individuals or their offspring might develop cancer

Prostate tumor and other tumor cells also frequently develop

"somatic" (non-heritable) mutations in DNA repair and other genes

Mutations that occur in *somatic* cells

- although they are NOT heritable by the *organism* -

can be passed on to

subsequent generations of somatic cells,

including tumor cells

These mutations as well as heritable mutations can create

opportunities for therapeutic intervention called “targeted therapies”

"Personalized medicine" leverages specific

information about a patient – including information

about specific mutations in germline or somatic tumor cells -

in the design of targeted therapeutic strategies for individual patients

For example, cells that have increased

levels of DNA damage due to

defects in DNA repair are often sensitive to drugs that

increase the frequency of DNA damage. This

Is because extensive DNA damage associated with

the combined effects of mutations in DNA repair genes and

the effects of drugs that block DNA repair can cause

tumor cells to die

Olaparib (trade name Lynparza), which is a drug that

inhibits the DNA repair activity of a protein called PARP,

causes DNA breaks to accumulate in cells that harbor mutations

In genes required for DNA repair (such as BRCA1 and BRCA2)

Genomic testing involves searches by DNA sequencing for these

and other mutations in somatic tumor cells

that can be exploited therapeutically in this fashion

Genomic testing involves searches by DNA sequencing for these

and other mutations in somatic tumor cells

that can be exploited therapeutically in this fashion

In 2006, my laboratory predicted that olaparib and other drugs that inhibit PARP might provide effective treatment for cancers caused by mutations in BRCA1 and BRCA2 genes

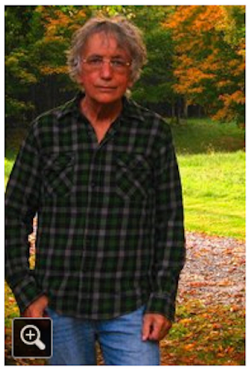
FUTURE PERSPECTIVES

The connections between DNA replication and cancer summarized here and in other chapters of this volume undoubtedly will drive the development of more effective diagnostic, prognostic, and therapeutic strategies for treating cancer. This includes "synthetic lethality" therapeutic approaches employing drugs that act synergistically with replication-related and other defects in cancer cells to specifically target these cells for elimination (Kaelin 2005). Two recent examples of this approach are the use of G_2 checkpoint-abrogating drugs to selectively eliminate cancer cells that accumulate DNA damage during S phase due to G_1 checkpoint defects (for review, see Kawabe 2004), and the increased sensitivity of BRCA1- and BRCA2-defective cancer cells to inhibitors of poly (ADP-ribose) polymerase (McCabe et al. 2005). Another effective approach may employ drugs that inactivate the initiation, rather than elongation, phase

"DNA Replication and Cancer", W.C. Burhans, G. Wahl and A. Carr

"A Researcher Becomes a Patient"

NY Times Magazine, May 15, 2016



William C. Burhans
BUZZ BURHANS

A Researcher Becomes the Patient

My laboratory at a major cancer center has spent many of the last 24 years studying DNA replication and DNA damage-response pathways that require BRCA proteins, which suppress tumors, as well as PARP (polyADP ribose polymerase) proteins. Ten years ago, I wrote a book chapter in which I predicted (based on preclinical studies) that PARP-inhibiting drugs would one day provide effective treatment of BRCA-positive breast and ovarian cancer. A few short months ago, a drug called olaparib became the first PARP inhibitor approved for treatment of ovarian or breast cancer. Three years ago, I was diagnosed with an aggressive prostate adenocarcinoma caused by a rare BRCA2 mutation, which was most likely inherited from my mother, who died of breast cancer when she was in her 40s. Radiation treatment and treatment with a number of anti-cancer drugs at the cancer center where I work has failed to stop the growth or metastasis of this tumor for more than a few months. My oncologists know very little about BRCA-positive prostate cancer, which is also rare, and had not heard of olaparib. This has occasionally resulted in an unusual and somewhat disorienting experience. Unlike most patients who sit in exam rooms and furiously scribble information relayed by their oncologists, my oncologists are sometimes scribbling information I relay to them, such as how to spell "olaparib"! After arranging mostly on my own for treatment with olaparib as an experimental drug almost one year ago, tumor progression has been halted, and recent bone scans indicate that my bone metastases are melting away. The success of my treatment reflects, in part, the extraordinary promise of personalized medicine that targets specific cancer-causing mutations, although the role I've played in my treatment perhaps takes personalized medicine to the extreme. ***William C. Burhans****, 64, Buffalo* ◆

RELATED COVERAGE

It's now clear that drugs that inhibit PARP,

such as olaparib, can be effective in the treatment of

the unexpectedly large fraction of prostate cancer tumors

that harbor defects in DNA repair pathways,

and not just prostate tumors

caused by mutations in BRCA1 and BRCA2

All of these findings have implications for

the role of genetic testing in

the management of prostate cancer

Perhaps most importantly, they suggest that

patients with advanced prostate cancer

would benefit from genetic testing and genomic testing

for both germline and somatic mutations,

even in patients that do not have a strong family

history of cancer

Some defects in DNA repair can also lead to a phenomenon called "microsatellite instability", ("MSI"), which is a marker for the potential efficacy of some types of immunotherapy

Consequently, patients contemplating these types of immunotherapy

should also undergo genetic testing for microsatellite instability


Thanks for your attention!