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BIOGRAPHY

Ken H. Young, MD PhD is an Associate Professor in the Department of Hematopathology at the University of Texas MD Anderson Cancer Center. He was Medical Director of Hematology at the University of Wisconsin School of Medicine and University East & West Clinic Laboratories, overseeing the laboratories at the University of Wisconin Hospital and Clinics Core Laboratory. He received his PhD from University of Lund School of Medicine and completed his MD training from Oregon Health Science University. He is board certified in Anatomic and Clinical Pathology and Hematopathology.

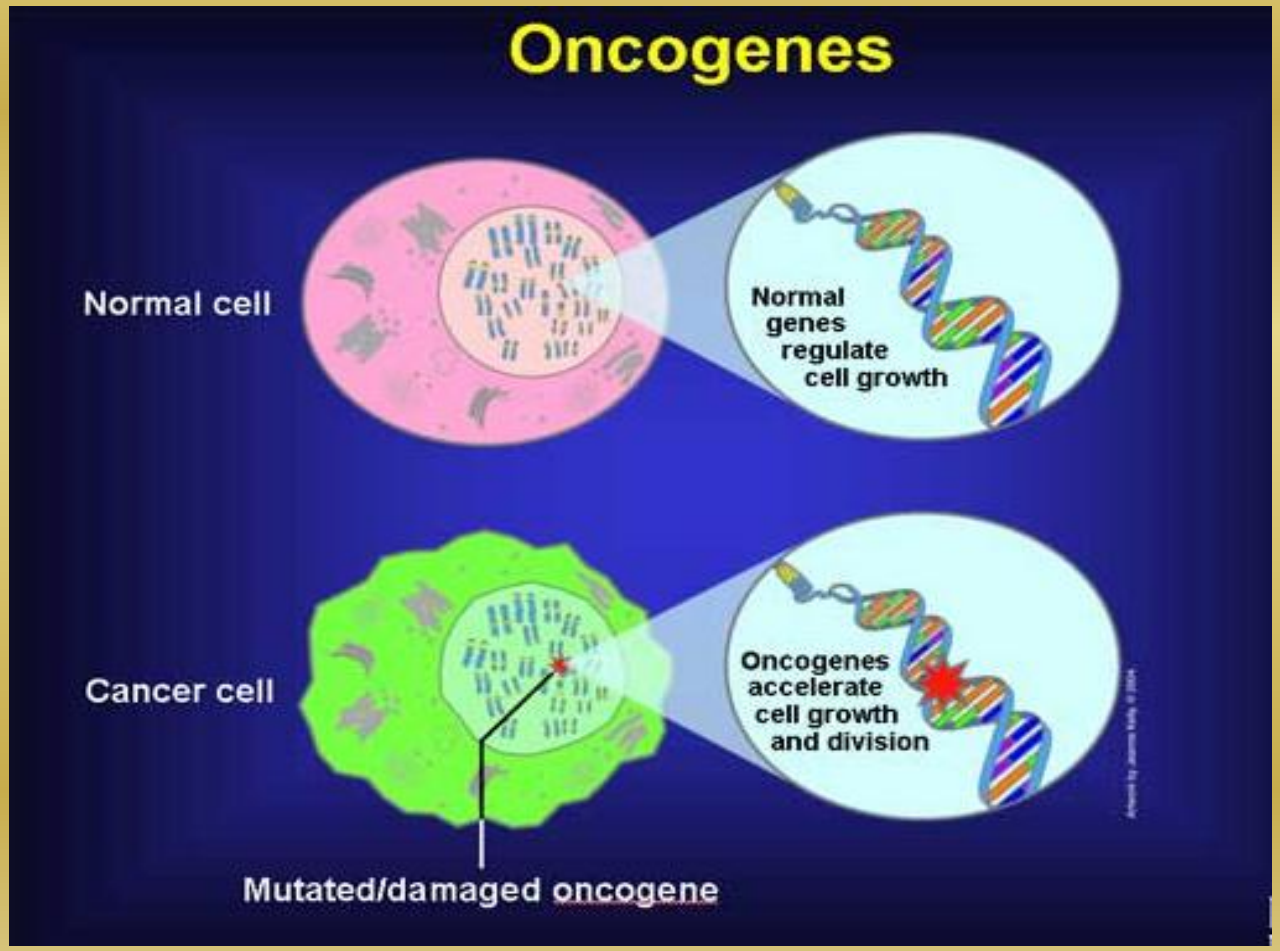
RESEARCH INTREST

- His interests are to characterize molecular defects in patients with leukemia and lymphoma by using gene expression profiling, immuno phenotypic method, methylation-microRNA-CGH arrays and current NGS molecular technologies with particular interest in tumor suppressor genes, oncogenes, p53 and NF-k B pathways. He has worked extensively on molecular diagnostics for human cancer and has obtained several novel discoveries valuable to predict treatment response, clinical outcome and survival in cancer patients.

PUBLICATION

- Jonathan Y-X L. Than, Lin Li, Hasan R and **Zhang X**. Excitation and modulation of TRPV1-, TRPM8- and TRPA1 Channel-expressing sensory neurons by the pruritogen chloroquine. *Journal of Biological Chemistry*. 2013, 288(18):12818-27.
- Lin Li and **Zhang X**. Differential inhibition of the TRPM8 ion channel by Gaq and Ga11. *Channels*. 2013. 18, 7(2): 115-8.
- **Zhang X***, Mak S, Li L, Martin AP, Denlinger B, Belmonte C and McNaughton PA*. Direct inhibition of the cold-activated TRPM8 ion channel by Ga_q. *Nature Cell Biology* 2012, 14(8): 851~8. (* co-senior author). Fan H-C,
- **Zhang X** and McNaughton PA. Activation of TRPV4 ion channel is enhanced by phosphorylation. *Journal of Biological Chemistry*.2009, 284(41): 27884-91.
- **Zhang X,** Li L and McNaughton PA. Pro-inflammmatory mediators modulate the heat-gated ion channel TRPV1 via scaffolding protein AKAP79/150. *Neuron* 2008, 59(3): 450-61.
- **Zhang X,** Huang J and McNaughton PA. NGF rapidly increases membrane expression of TRPV1 heat-gated ion channels. *EMBO Journal*, 2005; 24(24): 4211-23.

INTRODUCTION



TUIMOR SUPPRESSOR GENE

- DEFINITION:

- A protective gene that normally limits the growth of tumors. When a tumor suppressor gene is mutated (altered), it may fail to keep a cancer from growing.
- BRCA1, an example of a tumor suppressor gene, was the first breast cancer gene to be identified; mutated forms of this gene are responsible for some cases of inherited breast cancer, especially those that occur in younger women.

- Historically –suspected based on several lines of evidence:
  - Malignant phenotype suppressed by fusion with normal cells (presence of tumour suppressor in normal implied).
  - Chromosomal losses in hybrids caused reversion to malignant phenotype.
  - Introduction of single chromosomes into malignant cells:
    - e.g. insertion of chromosome 11(WT-1 gene) could suppress tumourigenicity in Wilm's tumour cell line.
- Some genes suppress tumour formation.
- Their protein product inhibits mitosis.
- When mutated, the mutant allele behaves as a **recessive**; that is, as long as the cell contains one normal allele, tumour suppression continues.
- (Oncogenes, by contrast, behave as dominants; one mutant, or overly-active, allele can predispose the cell to tumour formation

Example 1: RB - the retinoblastoma gene

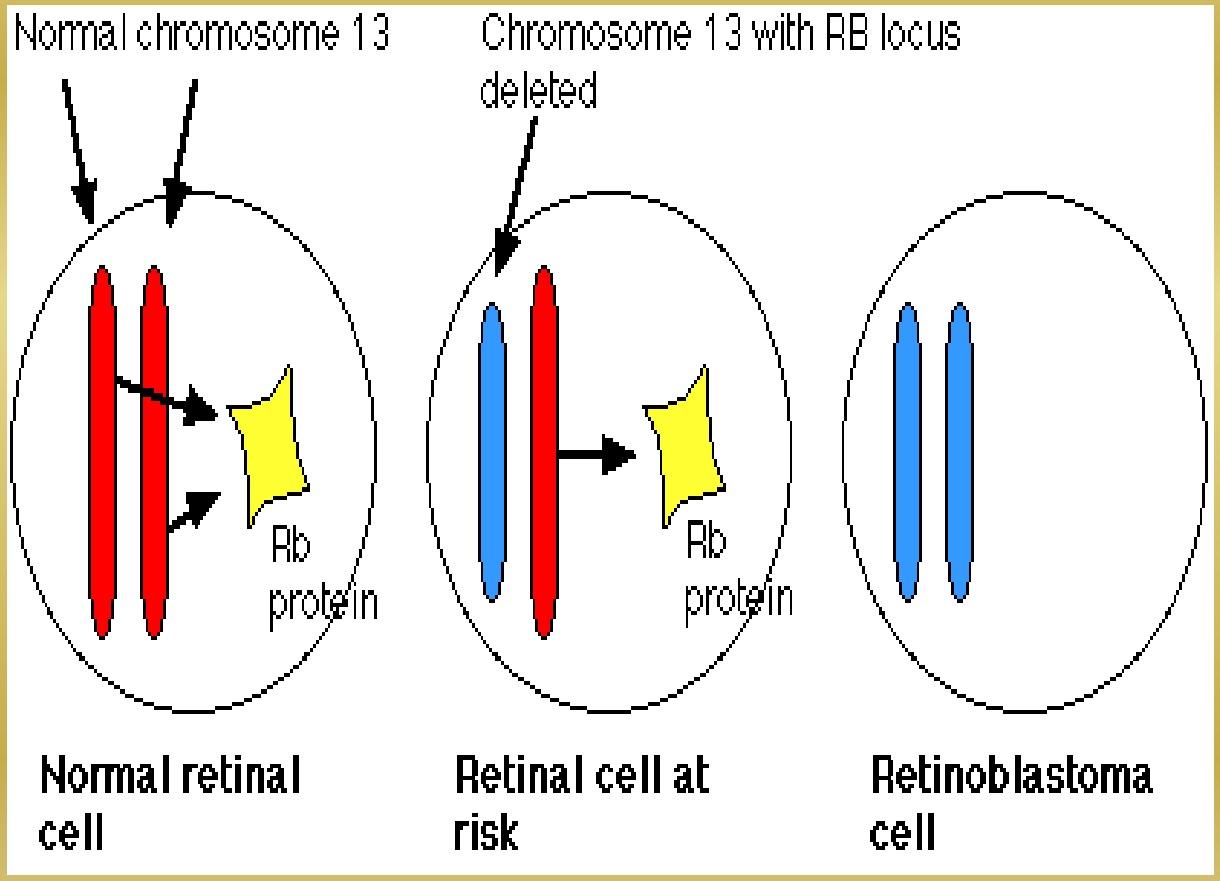
- Retinoblastoma is a cancerous tumour of the retina. It occurs in two forms:
  - Familial retinoblastoma
    - Multiple tumours in the retinas of both eyes occurring in the first weeks of infancy.
  - Sporadic retinoblastoma
    - A single tumour appears in one eye sometime in early childhood before the retina is fully developed and mitosis in it ceases.
  - Familial retinoblastoma
    - Familial retinoblastoma occurs when the fetus inherits from one of its parents a chromosome (number 13) that has its *RB* locus deleted (or otherwise mutated). The normal Rb protein prevents mitosis

Mechanism:

- The Rb protein prevents cells from entering S phase of the cell cycle. It does this by binding to a **transcription factor** called **E2F**.
- This prevents E2F from binding to the promoters of such proto-oncogenes as **c-*myc*** and **c-*fos***.
- Transcription of c-*myc* and c-*fos* is needed for mitosis so blocking the transcription factor needed to turn on these genes prevents cell division

Retinoblastoma

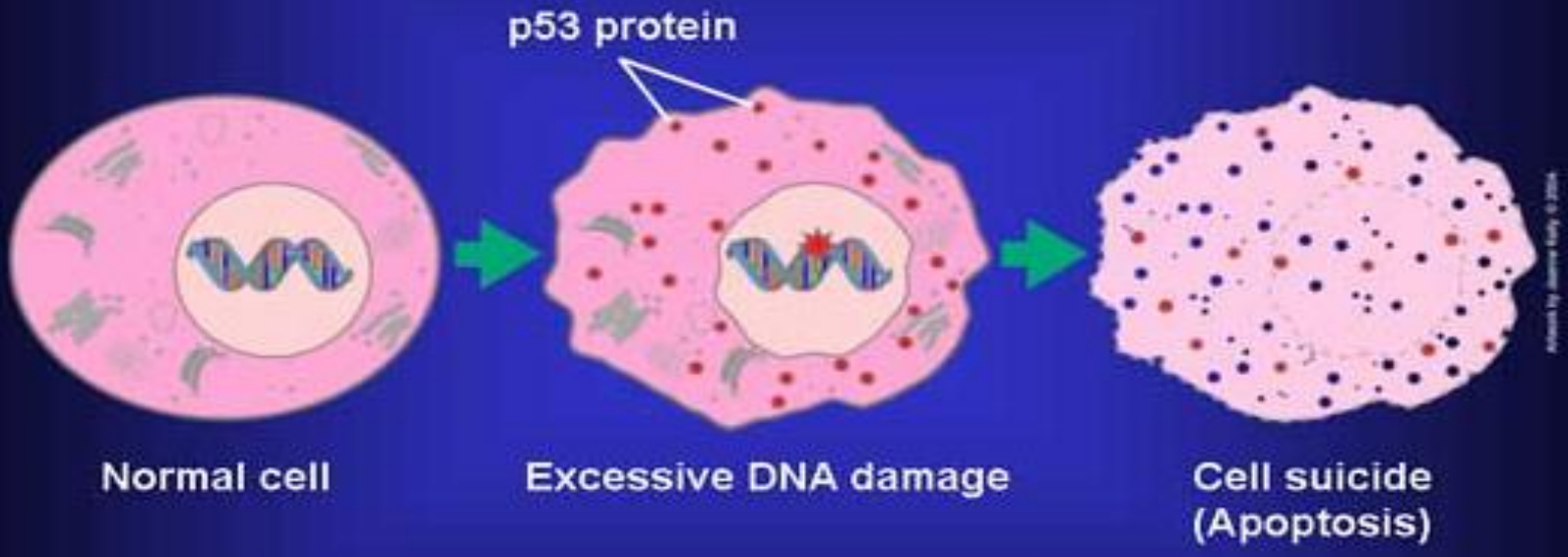
- A random mutation of the remaining *RB* locus in **any** retinal cell completely removes the inhibition provided by the **Rb protein**, and the affected cell grows into a tumour. So, in this form of the disease, a **germline** mutation plus a **somatic** mutation of the second allele leads to the disease.


Normal chromosome 13
Chromosome 13 with RB locus deleted
Rb protein
Rb protein
Normal retinal cell
Retinal cell at risk
Retinoblastoma cell

p53

- The product of the tumour suppressor gene ***p53*** is a protein of 53 kilodaltons (hence the name).
- The p53 protein prevents a cell from completing the cell cycle if
  - its DNA is damaged or
  - the cell has suffered other types of damage.
- When
  - the damage is minor, p53 halts the cell cycle — hence cell division — until the damage is repaired.
  - the damage is major and cannot be repaired, p53 triggers the cell to commit suicide by apoptosis

p53 Tumor Suppressor Protein Triggers Cell Suicide



- These functions make *p53* a key player in protecting us against cancer; that is, an important tumour suppressor gene.
- More than half of all human cancers do, in fact, harbour *p53* mutations and have no functioning p53 protein.

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