

3-15-9

Croce -

loss of gene function imp't in solid tumors

Protein tyrosine phosphatase
chron. 3 - somatic hybrid.

Most common chrom. loss is 3 in lung CA

bcl-2 in follicular lymphoma

Monitoring of CA by oncogenes - follow tx

Howley -

Papilloma Virus (PV)

~60 human PV

some PV found in carc. of genital - anal

DS circular genome

transferring genes, regulatory genes
↳ virus rep.

integration of virus into genome

PV prot. inhibit activity of RB gene prod.
↳ retinoblastoma

others may affect p53

Harris -

Multistep carcinogenesis being defined in molecular terms
P450s in activation

specific mod. in oncogenes from chemicals

p53 mutation spectrum in human CA

2023140366

are differences in mut. among tissues
CpG

Liver CA in China - aflatoxin + hep.
~50% w/ mutated p53

diff. spectrum in Japan - ~~problem~~ prob. no aflatoxin

Uhr -

Immunol., Tumor Dormancy

BCL-1 cells, mouse lymphoma

Liotta -

Invasion + metastasis

tumors heterogeneous - some cells v. metastatic

Adhesion, ~~protease~~ proteolysis, motility
matrix proteases - stromolysis ex.

Type IV collagenases

Balance of proteases + inhibitors (TIMP-2 ex)

NM23 - metastasis suppressor genes

↳ can bind to G proteins, + maybe regulate

Antman -

2023140367

Rosenberg -

Introduce TNF by lymphocytes.
↳ Tumor necrosis factor

Weinstein -

Cig smoking
states $\frac{1}{3}$ of CA due to cig.
smoking ↓ in OTs

Sat & CA
bact. in GI can convert lipids to DAG

Chemoprevention

Biomarkers

2023140368

942 - Codon 132 in p53
hot spot for point mutation
mutations will appear later 35 wks.

593 - Wistar Rats
SS+MS cond.
commercial blood 13 mg tar, 0.9 nic.
based nicotine
dose 1-3 g cigs worth
acetone PBS soln.

intestinal crypts
+ micronuclei SS+MS

1807 - 6/21 10 Non SC Thor
codons 163, 213, 247
exons 5-8

p.23 Poster Discussion

2023140369

974-

969-

Glucocorticoids

tx of lymphomas, inflammatory

receptors - cytosolic, related to estrogen + progesterone rec.

TPA effect on binding - ⁴⁻⁶ ↓ with peak at ~8h

Protein by AB - "

Paps - No TPA for 1 month, v. little rec.

CA

"

"

low level of r in CA + Pap cell lines

908-

2023140370

Nuclear Matrix Symp.
prots. cell specific

Cause or effect

Nickerson -

structure of nuclear matrix

CA a dis. of architecture

consists of pore / nuclear shell + internal matrix

RNA - imp't in struct. of matrix

↳ ribosome

Mab - to det. "cartography" of matrix

H1B2 - ser. prot. kinase

Berezny -

50,000 replicons / cells, DNA replication

loop structures organize replicons

Coffee -

van Driel -

isolation procedures Δ what results as nuclear matrix

2023140371

Molecular Epidemiology

Wogan - ^{type}
Biomarker slide

Tobacco exposure - BBDE, NNK, 4ABP

Diet "

Medicinal "

Occupational " aromatic amines, styrene ~~oxides~~

Oxidative damage - 8-OHdG, thymine glycol

Glycophorin, ^{marker} Bigbee 240:165

PCR - ras mutations

P53 Nature 350:1377

Vineis -

Epid links 50% of ♂ bladder CA to smoking.
black tob > blond

There are a variety of aromatic amines
4-ABP, aniline, & O-toluidine > in black than blond
& others

^{Haagbirk}
4ABP adduct > in black than blond tob.
also dose response w/ amount of cigs. smoked

large inter individual variability even controls for
type & number of cig smoked

Most var. can be explained by other metab dif.
Br. J. CA 61:534 (1976)

2023140372

N-acetyl transferase

Variation polymorphism w/ N-acetyltransferase
↑ N-act → ↓ risk, ↓ active mutagen

Adducts in exfoliated bladder cells
cancerogens 11:839, 90

? • ETS - published studies - some link
poor relation in their studies

- plateau in bladder ca also seen w/ adducts
- PAH adducts also
- alcohol + diet also looked at

Groopman - A. Slatore

Dev. of analytical + immunoassay approaches.

AFB - N⁷-G in urine

relation to p53 mutagenesis

Urine - mercapturic acid
guanine adduct
serum - lysine

monoclonal AB affinity chromatography

developed methods in rats

people in China w/ high liver CA incidence

Analyzed food samples for AFB1 for 10-15 yr
collected urine samples

day to day variation, must look @ exp over time

2023140373

some adducts (metabolites) in ~~my~~ urine don't correlate to exposure for good biochemical reasons

— studies in Gambia
low dose time of year for exposure

— How does adduct in urine predict cancer

testing in rats using chemoprevention
↳ oltipraz

olt. → ↓ N²-G add. but not to O
↳ liver + urine

get adducts even when no tumors

— Mutation in codon 249 in p53
GC to TA

— ? colon also

Bennett - p53

single copy gene 11 exons.
chr. 17 p13.1 in humans.

5 highly conserved regions Otagiri 51945, '90

mut in central region ↑ $T_{1/2}$ (20 min is normal)

Mutational hotspots 175, 248, 249, 273, 282
↳ how do hotspots arise

lung + esophagus - smoking
GC → TA in non small cell CA

2023140374

hot spot for liver CA -249 w/ Aflatox. exp

AB₁ → G add → G → C → T → A →

Esophageal

immunohist. screen for p53

Nitrosam.

Tob.

Hot water tea

Found p53 in early lesions esoph +
bronchial

Skopek -

Relationship of mutagen exposure to true risk

endogenous DNA damage vs exogenous

mutational spectrum to sensitivity

1) hemizygous gene - makes analysis

2) way to isolate mutation

HPRT -

on X chrom.

Mol. Biol. - cDNA / PCR

denaturing gel gradient electrophoresis

Sommardebye

get AT mutations
low level

2023140375

2023140376

Analyzing 2 mut. to handle a clonal expansion
of mut. etc.

Mol. Patho of Lung CA

Linnolla -

4 major type
adeno etc

Neuroendocrine cells
neuroepithelial bodies

hyperplasia can be intense in airways

Small cell Carcinoma

SCLC - 25%

Non " - 75%

Some Non-SCLC show certain markers of neuroend.

Other NSCLC

increase in adeno CA with time
↳ start peripheral airways

SAP35 imm cov w/ smoking

• Maybe virus for papilo-colum = adenocarc.
less associated w/ smoking

Harris -

Multistage stage process.

Breakout of oncogenes is diff by cell types

Oncogenes transform cells show tripartite dif.

wtD₂, N or H ras → SSC

Kras → adeno

Mye + raf → neuroendocrine

2023140377

tumor suppressor genes PTPy

Protein tyr phosphatase - function similar to the ty
cytoplasmic + receptor-linked

3p21 chrom. localized

allelic deletion in 8 of 12 lung CA

Loss of heterozygosity RNAS path.

p53 → mut.

BEAS2B cells - growth in culture

TGF β interact w/ p53

Mol. epidemiol of human CA risk

Molecular dosimetry

adducts, cytogenetics, mutational spectrum

Endogenous Risk Factor

p 450 2DG be debrizogane

G5H transposase defect

let.

Schaller -

DEN

NNK

ambient air vs hyperoxic cond.

2023140378

diff tumor type under various oxygen conditions
hypoxia & hyper $\rightarrow \uparrow$ NE

pub. NE cells controlled by acetyl choline, nicotine, O_2

Neuroendocrine cell line - nicotine receptor

Nicotine } $\rightarrow \uparrow$ cell prolif
NNN
DEN

& blocked by antagonists

Displacement of 3H nic bind in lysosync histone by cells
by DEN, NNN

Clara cells - secretion \uparrow by opioph

Nitrosomy strong mitogenic & effects reduced by
propanolol B ad. rec. antag.

Nicotinic receptor not involved here

Have not ~~tested~~ NNN

\hookrightarrow poor by tumor carcin

2023140379