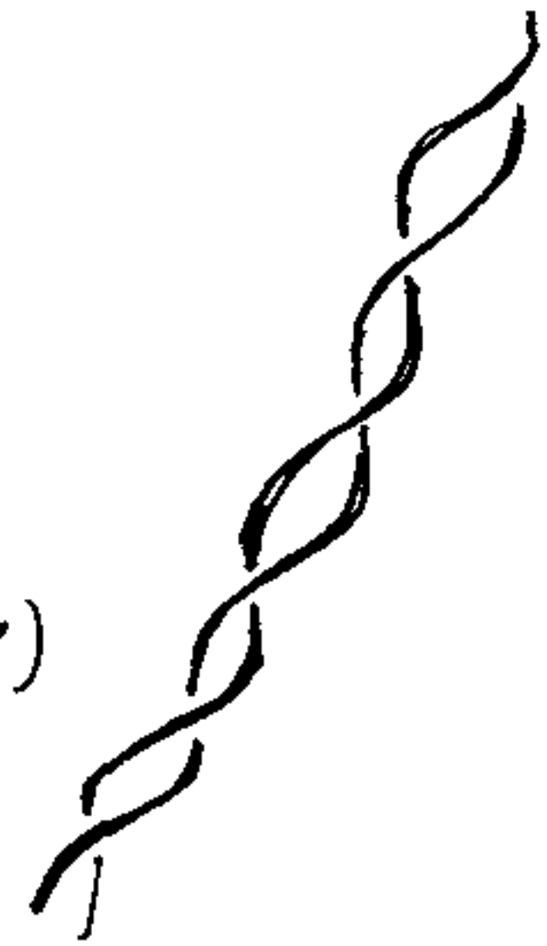
S. Wallace - Base Excision Repair of O_2 Damage 2.5.97

Free Radicals

- produced by ionizing radiation by the radiolysis of H_2O
- produced also by oxidants
- also produced during metabolism (superoxide + hydrogen peroxide)



metabolism → $SO \xrightarrow{SOD} H_2O_2 \rightarrow$ Hydroxyl radicals

Types of Damage

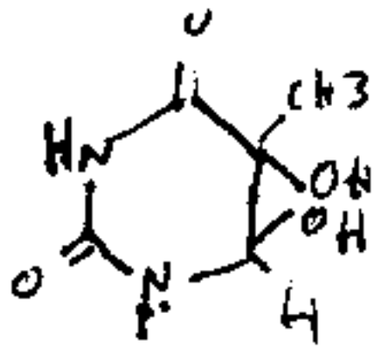
- strand breaks (after interaction of HO w/ C4 of deoxyribose)
- base loss (after HO attack on C1 or C4 or deacy of base)
- base damaged - many many types

Analysis

- chemically synthesize

Thymine products

thymine glycol



dihydrothymine

urea = ring opened product

UBA

Uracil Products

uracil glycol

dihydrouracil

5-hydroxycytosine

5-hydroxyuracil

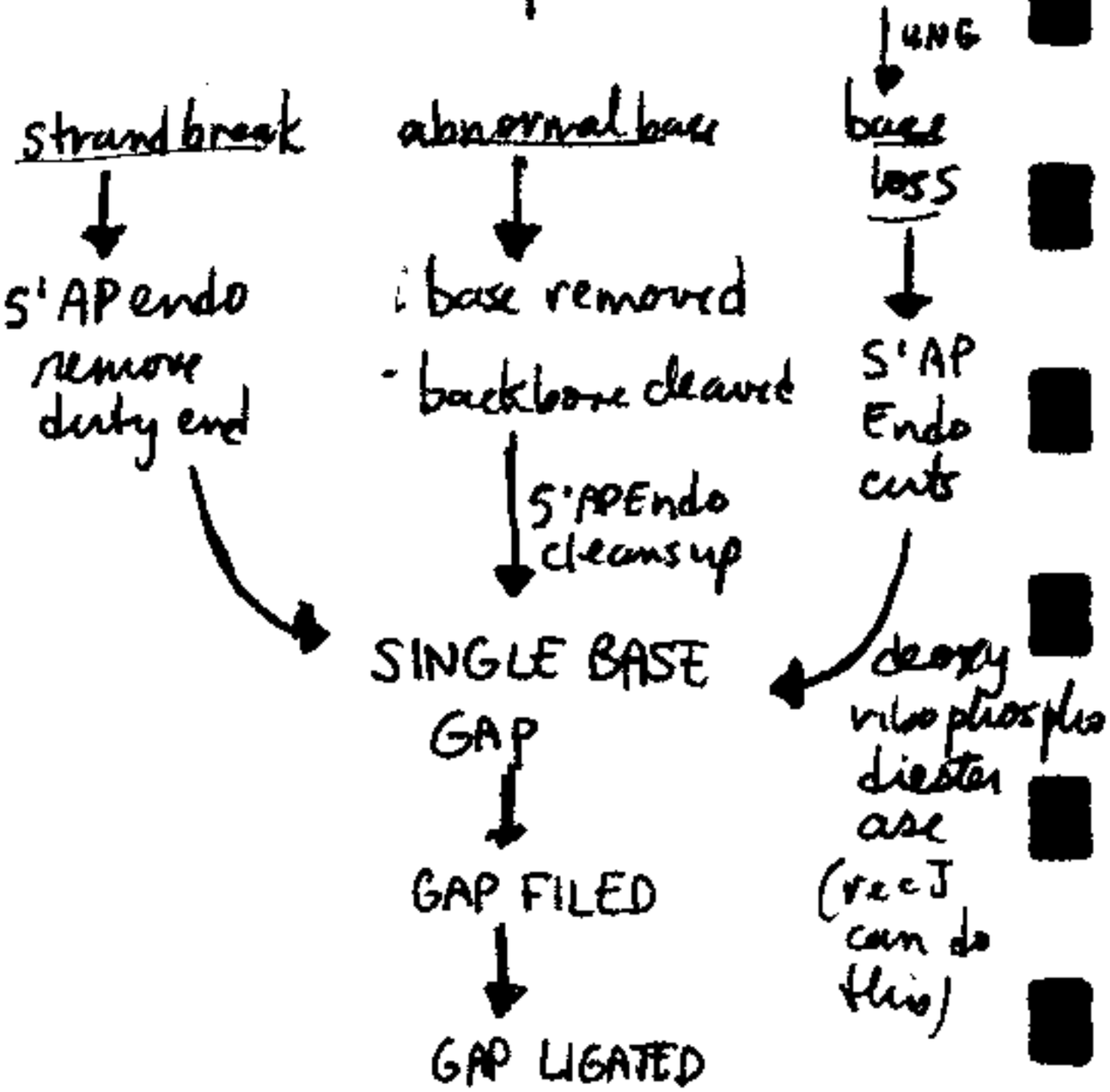
Purine lesions

8-oxoadenine

8-oxoguanine

All of these are STABLE

Base Excision Repair



Damaged Pyrumidines

endonuclease III = nth (but NOT endonuclease)

endonuclease VIII = nei

Overlapping substrate specificities including:

- TG, DHT, uG, 5OHC, 5OHU, HY, urea, LTU

Purine Damage Recognition

- fpg (MutM)
- will recognize 8-oxy-G } can recognize both purines and pyrimdines

For all 3 (fpg, nth, nei) the best substrate is an abasic site.

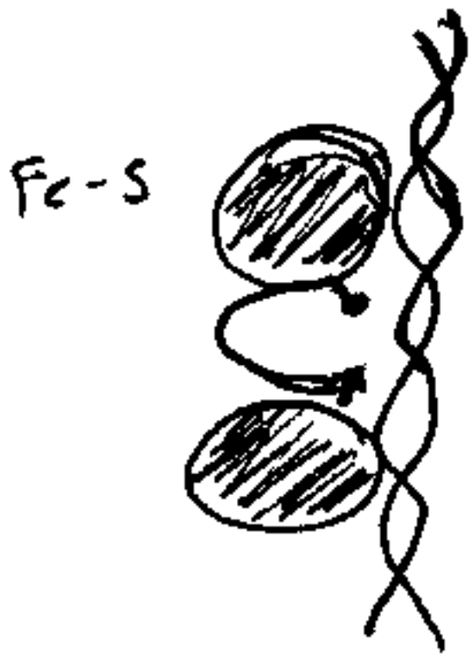
EndoIII

- V. similar to MutY
- both have iron-sulfur centers
- no overlap in substrate specificities
- both have β-lyase activity

Fpg + Nei

- V. similar to each other
- both have β-δ lyase activity
- both have "Drp ase" activity (deoxyribophosphodiesterase)

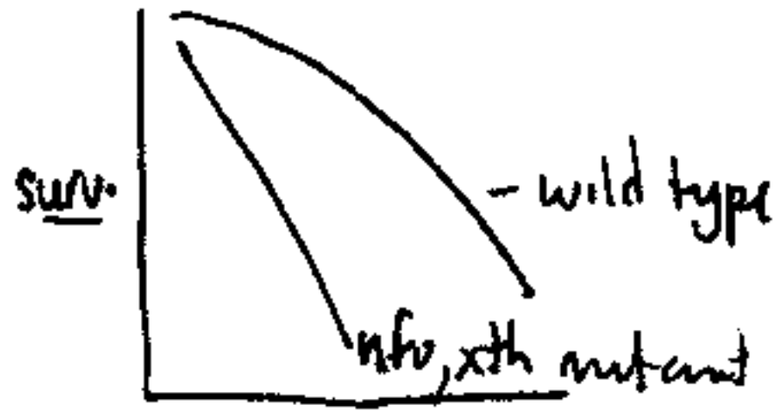
Unsolved issues



Many work by flipping a base into the pocket like the one - e.g. in Ung an aa. blocks thymine from flipping bec. of CH_3 group.

- endo III binds DNA in two places
- there is a pocket in between the two

Endo III
Exo III } Processing



- APE1 in mouse is lethal
- polB mutant mice are embryonic lethal.

These enzymes don't do exactly the same thing

- nfo ... induced by Superoxide (~10 fold in $SoxR^R$ regulon)
- xth ... normally more abundant than nfo