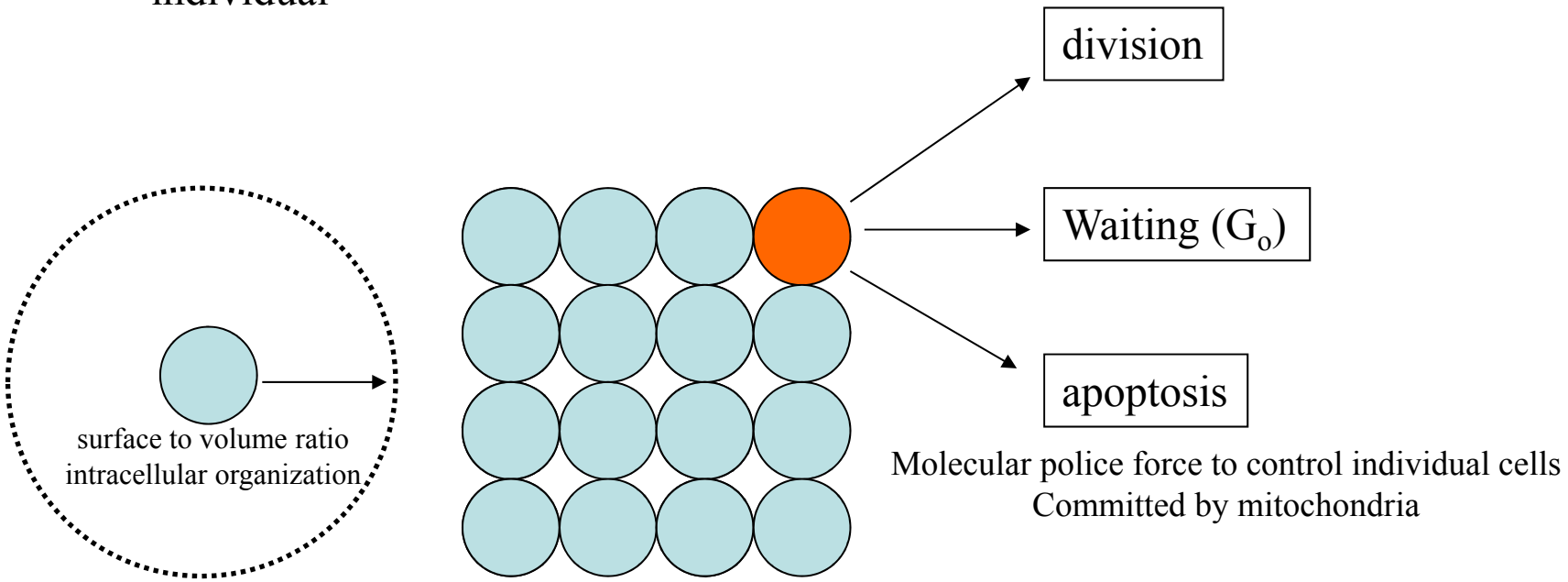
Part 5 Murder or Suicide
The troubled birth of the individual

unicellular
multicellular: independent (colony), dependent (differentiated)
individual



Natural selection upon

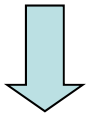
genes, individuals, groups of individuals, species?

<u>Species level might be plausible rather than individual</u>

Ageing: what do we gain from getting old and dying?

sex: twice as costly as clonal reproduction

genetic variation (meiosis)



Is it right?

If sex evolved in a species

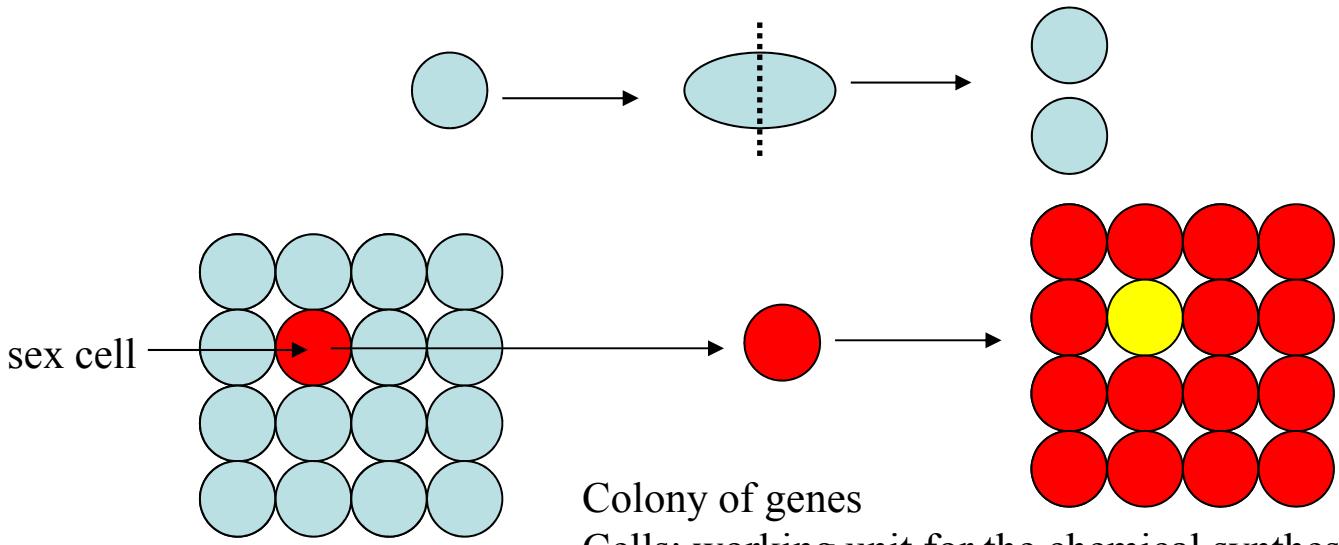
any possibility of tentative sex before being fully developed?

Darwinism
Natural selection → Neo-Darwinism
Darwinism+genetics → Ultra-Darwinism
Neo-Darwinism+selfish gene
Survival of the fittest gene

The unit of selection: cell or gene?

In multicellular organisms
Only the genes, not individuals, are transferred to the next generation
Inclusive fitness: altruism at the level of genes
selfish gene
living organisms are throwaway survival machines of their genes
disposable soma theory (soma disposable, germ eternal)

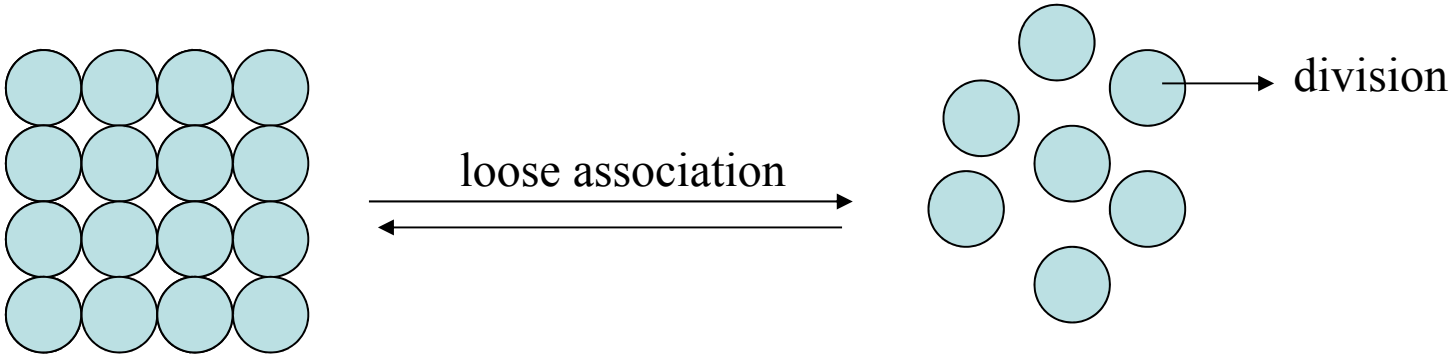
In asexual reproduction: individual cells are transferred
In sexual reproduction: individuals are not transferred
Body is the product of genes collaborating together to serve their own selfish end of being copied in ever greater numbers

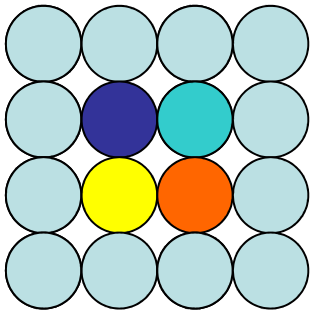


Colony of genes
Cells: working unit for the chemical synthesis of genes

What is their purpose?

Genes (in a cell) & Cells (in a body): reproduction





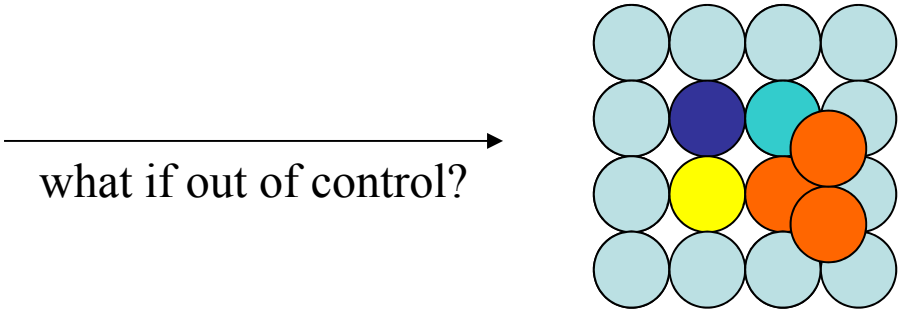
tight association

differentiation

common purpose: what?

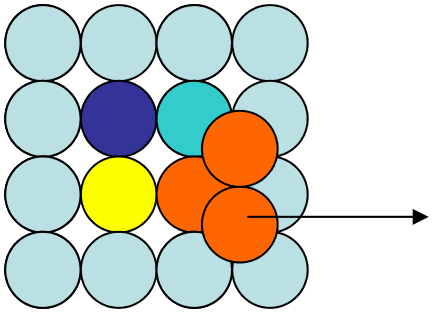
control is indispensable for the common purpose

no freedom to dissociate
no competition but cooperation



11. Conflict in the body

Cancer (out of control)



selfish growth?
for what?
return to bacterial growth

control

Apoptosis
Apoptosis in unicellular eukaryotes? yeast
Apoptosis in the first eukaryotes?

The history of apoptosis

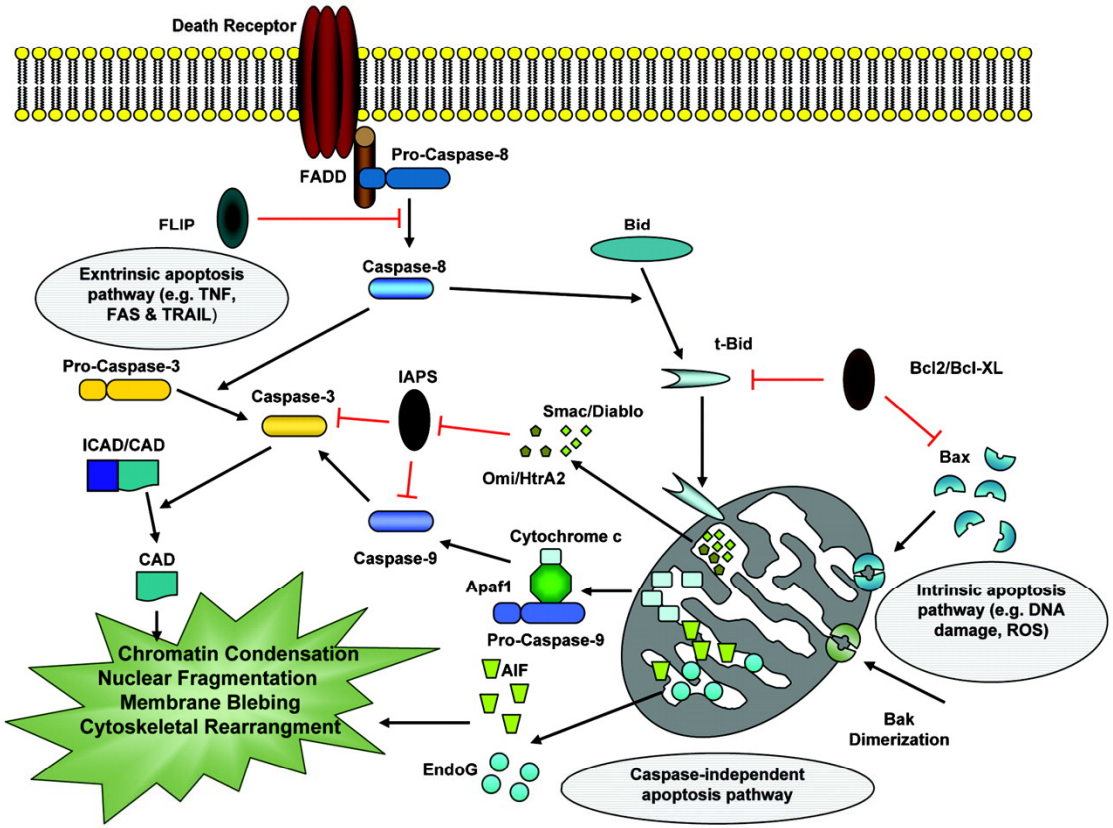
- Apoptosis & Necrosis
- Extrinsic & Intrinsic pathway: caspase cascade
- Apoptosis & mitochondria: membrane depolarization, ROS
- Mitochondria & cell connection: Cytochrome c & other proteins
- Permeability transition pore (mPTP)
- bcl-2 (B-cell lymphoma 2) family proteins: anti-apoptosis & pro-apoptosis

The central role of mitochondria in apoptosis

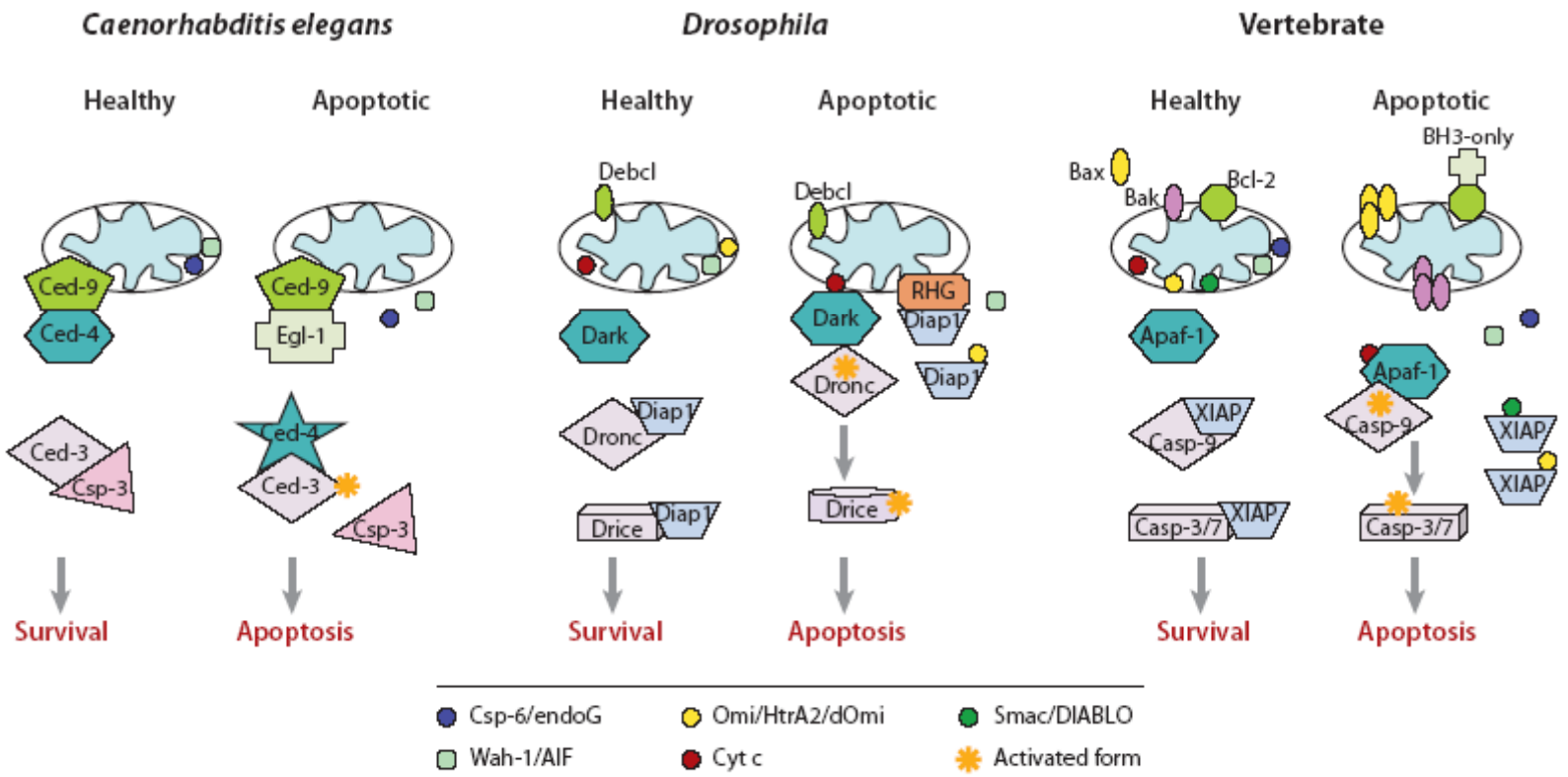
- Mitochondria brought with them the death machinary
- Mitochondrial origin of apoptosis proteins
- most of the proteins released from mito
- caspases
- bcl-2 family proteins

Apoptosis is not a suicide but a murder from inside

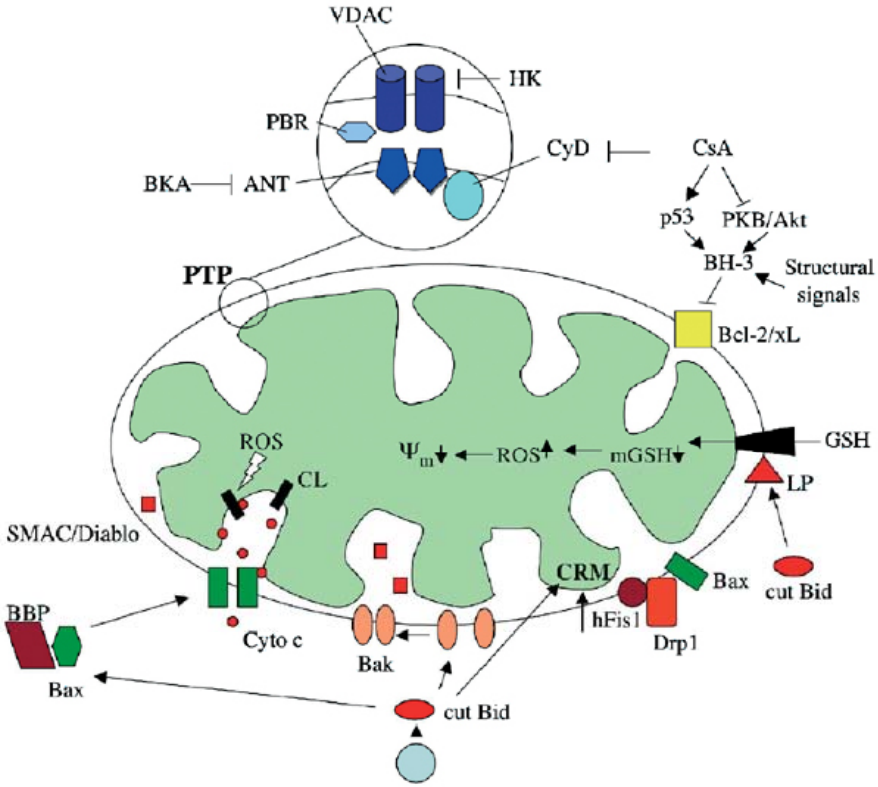
Apoptosis pathways can be initiated via different stimuli
—that is, at the plasma membrane by death receptor ligation (extrinsic pathway)
or at the mitochondria (intrinsic pathway).



Apoptosis and cancer: mutations within caspase genes
J Med Genet 2009;46:497-510


Caenorhabditis elegans
Drosophila
Vertebrate
Healthy
Apoptotic
Healthy
Apoptotic
Healthy
Apoptotic
Ced-9
Ced-4
Ced-3
Csp-3
Egl-1
Debcl
Dark
Dronc
Diap1
Drice
RHG
Bax
Bak
Bcl-2
Apaf-1
XIAP
Casp-9
Casp-3/7
BH3-only
Survival
Apoptosis
Survival
Apoptosis
Survival
Apoptosis
Csp-6/endoG
Omi/HtrA2/dOmi
Smac/DIABLO
Wah-1/AIF
Cyt c
Activated form

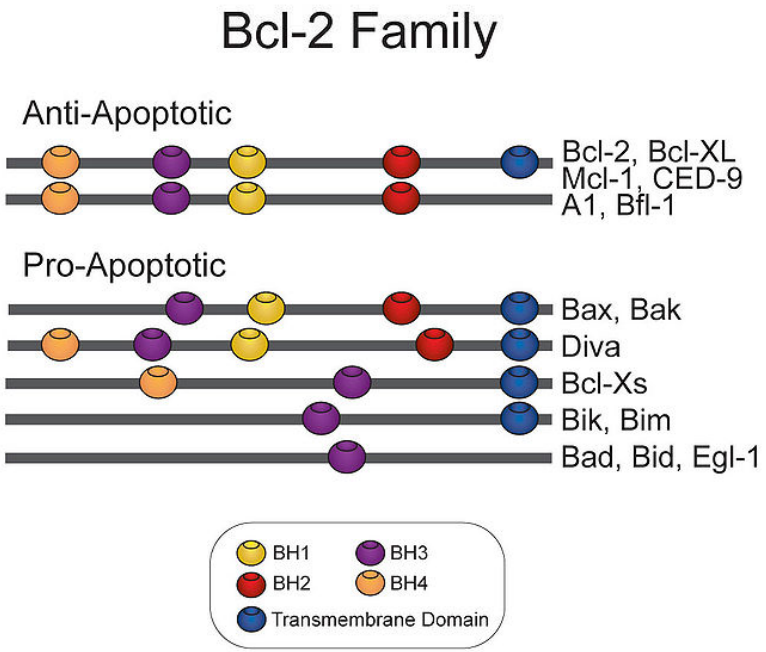
Role of mitochondrial membrane permeabilization in apoptosis and cancer



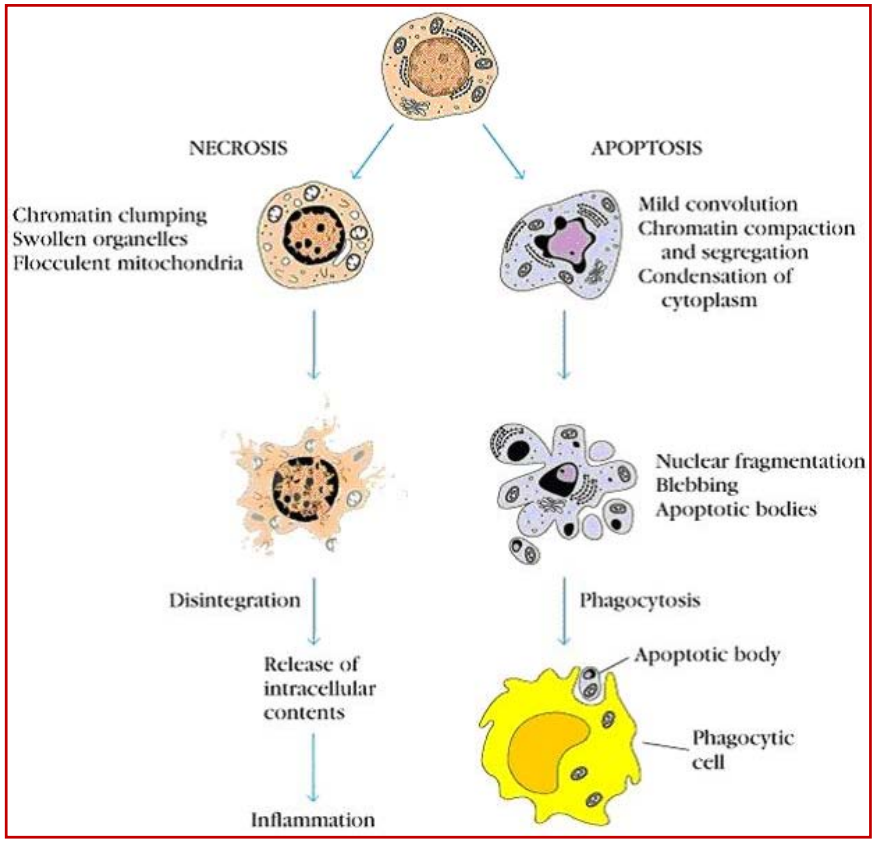
The Ca^{2+}-sensitive permeability transition pore (PTP) shown here in a proposed open configuration consists of the peripheral benzodiazepine receptor (PBR), the voltage-dependent anion channel (VDAC), adenine nucleotide translocator (ANT) and cyclophilin D (CyD). *Oncogene* (2004) **23,** 2850–2860

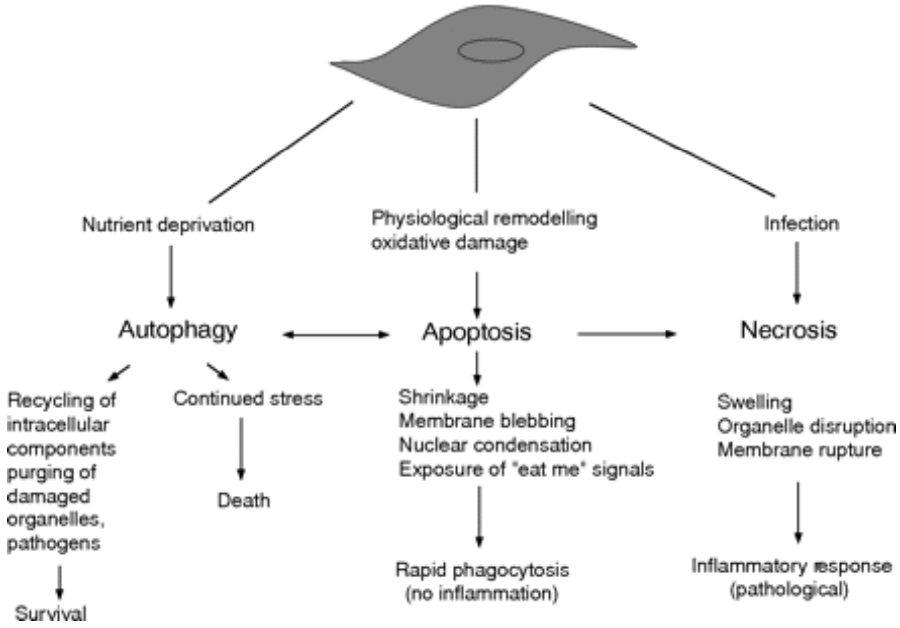
Apoptosis regulator Bcl-2, BH is a family of evolutionarily related proteins. These proteins govern mitochondrial outer membrane permeabilization (MOMP) and can be either pro-apoptotic (Bax, BAD, Bak and Bok among others) or anti-apoptotic (including Bcl-2 proper, Bcl-xL, and Bcl-w, among an assortment of others).

There are a total of 25 genes in the Bcl-2 family known to date, exerting their pro- or anti-apoptotic effect. This is achieved by activation or inactivation of an inner mitochondrial permeability transition pore, which is involved in the regulation of matrix Ca2+, pH, and voltage.



Necrosis & apoptosis

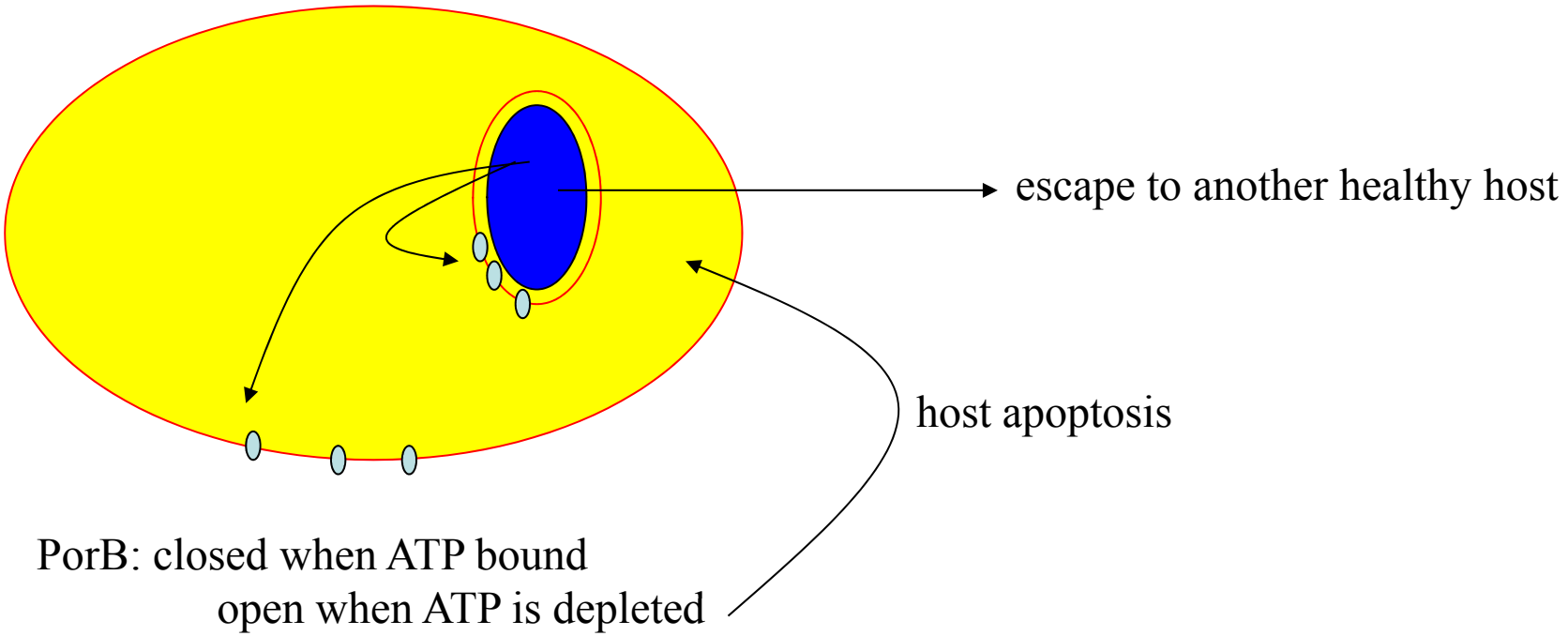




Evolutionary origin of apoptosis

Death machinary came from mito ancester: including caspases Proteins, except AIF, released from mito
Parasite War: José Frade & Theologos Michaelidis, 1997

Neisseria gonorrhoeae
Bdellovibrio



Can be applied to the first eukaryotes
But contradictory to the symbiosis of a peaceful metabolic cooperation
(hydrogen hypothesis)

12. Foundations of individual

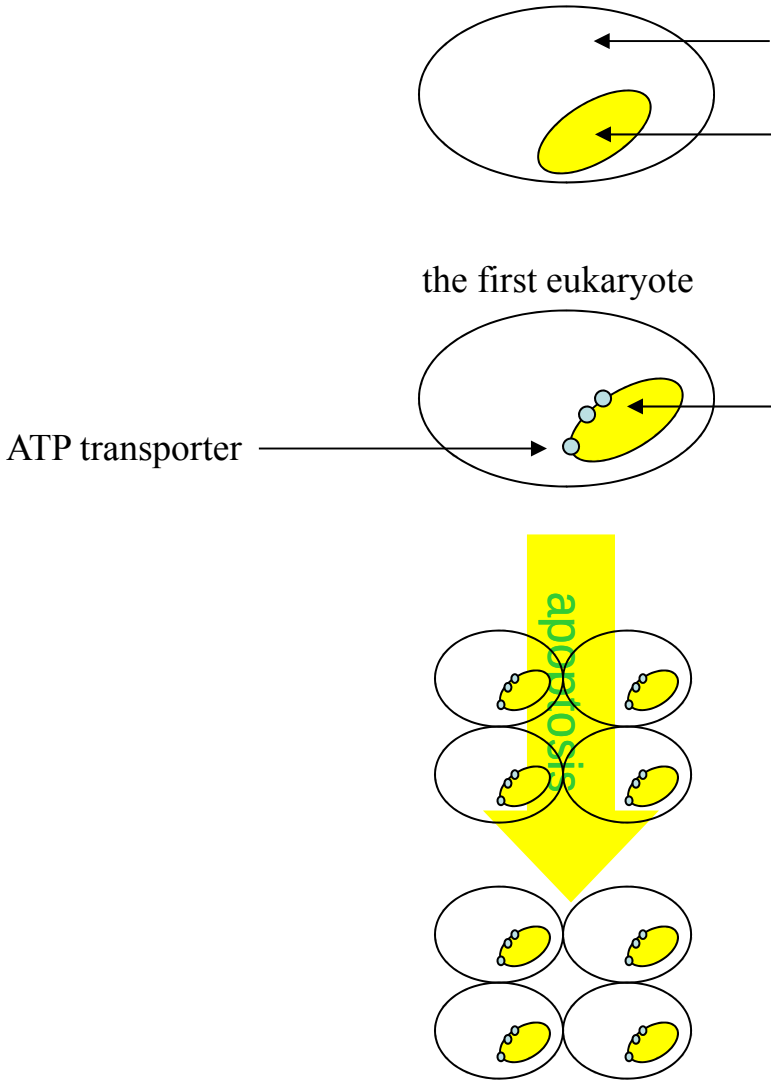
Parasite war & hydrogen hypotheses
Which is correct?

Bacterial porins: where did they come from?
    if parasite model is correct, they might share evolutionary origin with bcl proteins

<u>bcl proteins & bacterial porins: structural similarity but not genetic</u>
    probably the result of convergent evolution?
    bcl proteins from α-proteobacteria? insufficient sequence data
    bacterial porins from mitochondria (from the eukaryotic host)?

⇨ Not enough information, but probably does not support parasite model

Based on Hydrogen hypothesis



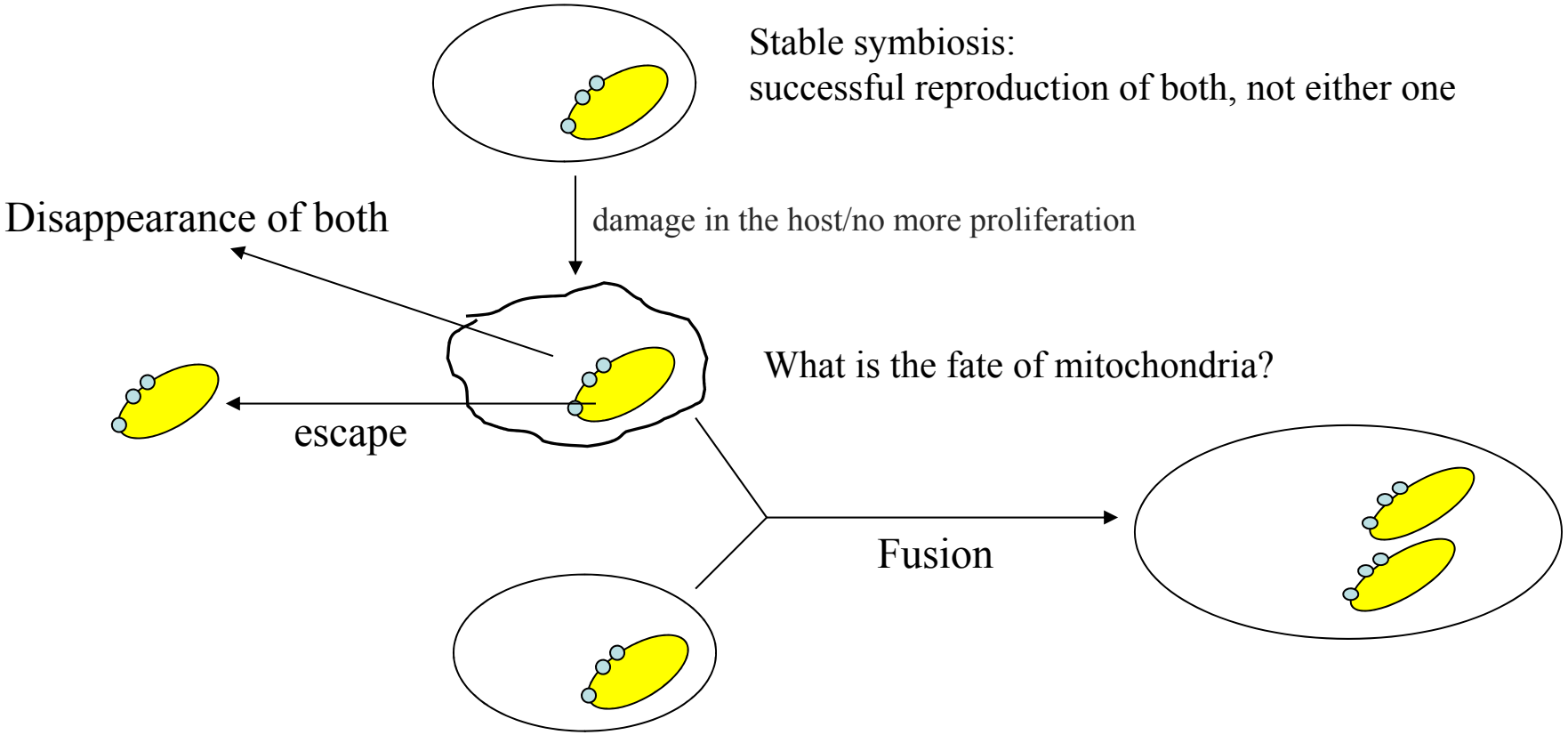
death machinery has no meaning
then, why is it remained?

multicellular: loose association

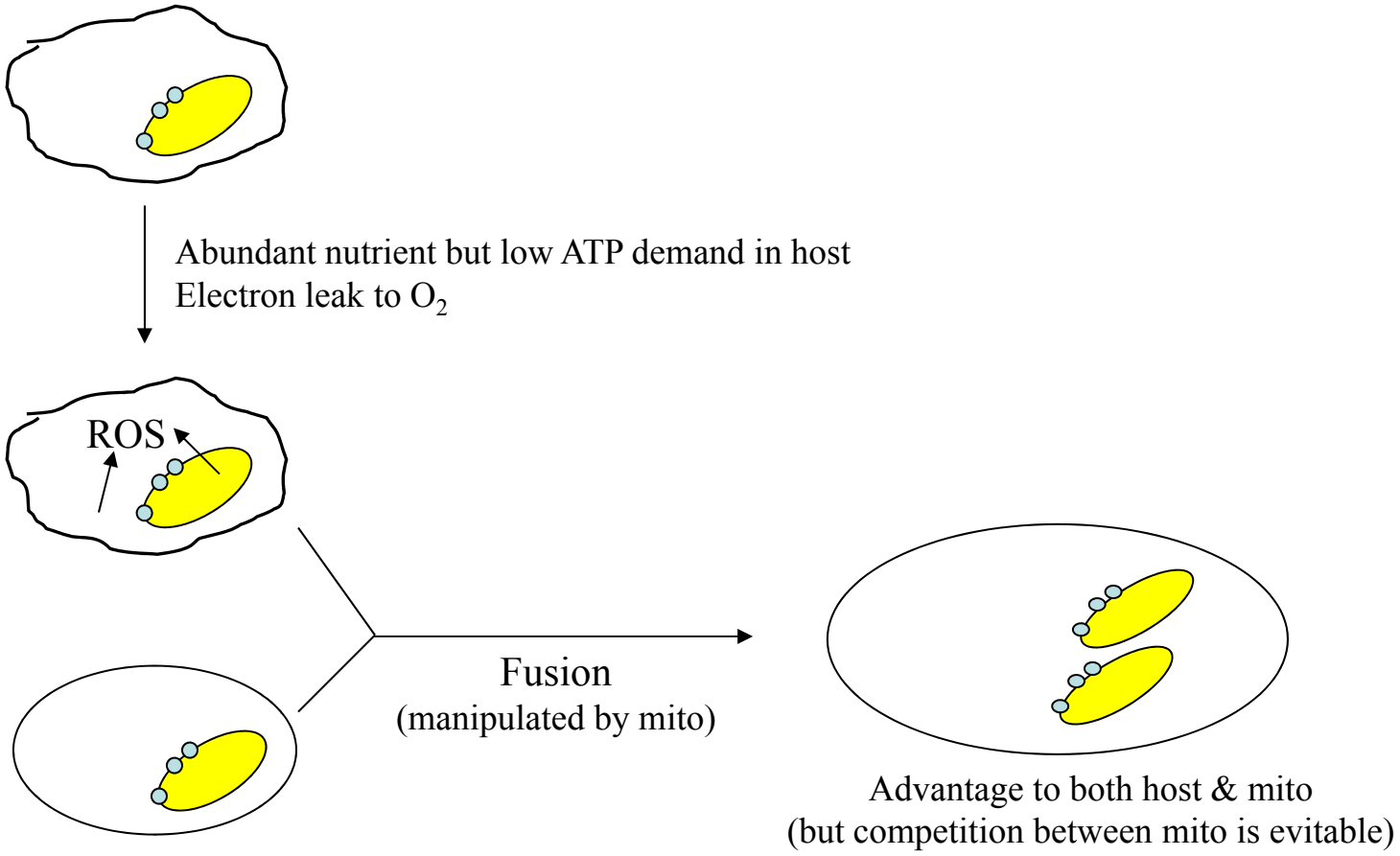
true multicellular

Sex and the origin of death

Neil Blackstone & Douglas Green, 1999



The role of ROS in sex



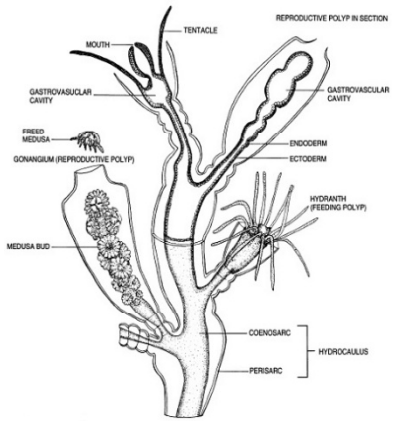
Yeast, Volvox: mating gene activation upon ROS increase, which caused DNA damage

First step to the individual
How sex turned into death?

Sex means genetic recombination to replace or mask damaged copy
Free radical in bacteria stimulate lateral gene transfer

Apoptosis means repair of damaged cells in a body (cost effective than fixing)
Similar to modern ‘throwaway’ culture

Blackstone
hydroid (asexual & sexual reproduction)
cellular colony
differentiated cells: a cellular ‘caste’ system
different environments (nutrients and oxygen)
different redox states
generation of ROS in individual cells
sexual reproduction or apoptosis?



The final hypothesis