A

Mendel Lecture

Molecular Genetics : the present position

Honoured
Difficulty about title
Two aspects of molecular genetics.

from the genetic side

to genetic experiments which need a fairly detailed knowledge of molecular basis to interpret correctly.
(example : genetic interaction intragenic complementation.

from the molecular biology side

aim to explain biology (eg. fundamental processes) in molecular terms.
Then is needed as a tool.
example : co-linearity of gene + protein ——— S
Other tool is needed :

(1) NA is difficult to study (base sequence etc) by biochemistry
(2) in vitro systems in other molecule; also cell is complex.

note on the other hand that gene experiments now always been studied on whole cells : may be better to open cells and see on the "gene product" : protein.

B/

Merged Lecture
Molecular Genetics: The present position

~~Historical~~

Difficulty about title.

Too broad. Thus will omit

① recombination : breakage + rejoin, not copy choice repair mutagenesis.

can recombine between adjacent bases. ——— S

② Control mechanisms : ie can involve groups of genes

(ie of rate of gene action) group is polar (operon)

also polar mutants exist

(restricted type of mutation)

but situation is complicated, especially as

③ not sure if protein synthesis involved in mRNA production.

④ little known about mRNA destruction.

What are the basic problems of molecular genetics?

① What are genes made of?
② How are they joined together? chromosome structure.
③ How are genes copied? ~~and how do mutations occur~~
④ What are mutations? and how are they produced?
⑤ How do genes act? ie what is are the gene products.
⑥ What controls their rate of action?
⑦ What is mechanism of genetic recombination

C/

Second Restriction

to micro-organisms.

partly because ~~one~~ most of our knowledge comes from micro-organisms.

advantages because ① less populations + selective techniques.
② rapid growth - quick experiments
③ growth requirements simple.

Also because they are actually simpler
"chromosome" is simpler.
more like "enzymes in a bag" than higher cells.
i.e. less ~~interaction~~ spacial interaction.

Few side-references to higher organisms

Plan of Lecture

General survey : in broad terms.

Ref critical comments.

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Mendel Lecture

Title too wide : full coverage impossible.

Thus omit -- recombination (mainly) and control also replication

also mainly apply to microorganisms

but not the special mechanisms of microorganisms.

Plan

General survey first : to give picture in outline

Then critical evaluation.

importance of microorganisms :

(1) large populations + selection techniques

makes for fine genetic mapping

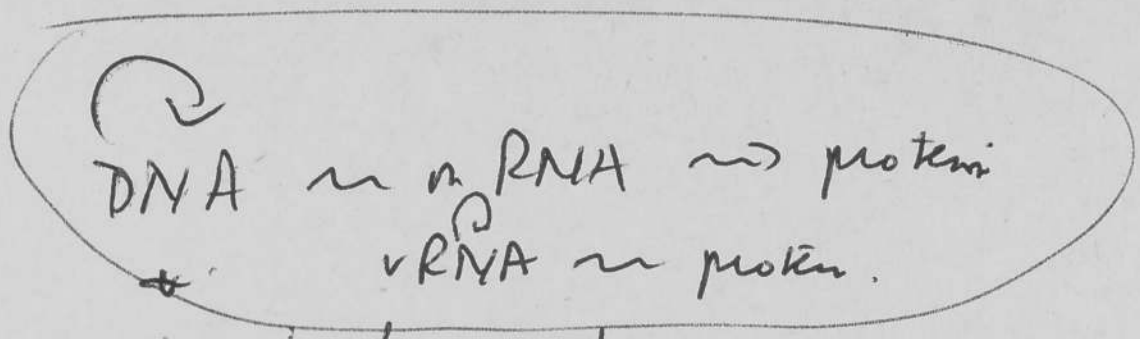
(2) rapid growth makes experiments quick

(3) "defined medium" helps in planning

experiments

(4) fairly easy to get at their proteins.

General Survey



Genetic material is nucleic acid.

usually DNA, but RNA in some viruses.

usually double-stranded, but occasionally single-stranded for some small viruses.

length very long compared with single genes.

Replication of genetic material

is by standard base-pairing mechanism. Normally

semi-conservative (define). for single-stranded, simpler a double-stranded replication intermediate

ie a rather direct, simple mechanism.

Expression of genetic material

by making an RNA copy of one strand

(unnecessary for single-stranded RNA virus)

and usually this RNA used as a messenger for protein synthesis. Then main function of genes is to control the sequence of proteins.

Protein synthesis

involves complicated biochemical machinery.

(eg. ribosomes, activating enzymes, tRNA etc.)

translate by means of a non-overlapping, ~~etc~~ triplet

code, most triplets standing for amino acids. probably universal.

~~Regulation~~

Protein folding

assumed to fold up itself (by and large)

3-D structure gives the specificity etc for enzyme action

or for use as structural components.

many proteins are aggregates of identical subunits.

[allosteric: idea that an <u>unrelated</u> small molecule can influence the configuration and thus the rate of an enzyme action]

~~Control mechanisms~~ poorly understood.

clear that ~~for~~ rate of gene action can be controlled

by small ~~control~~ molecules, ~~prob.~~ by means of a Moker.

~~that~~ genes are often switched in groups.

~~poly~~ polar effects

General remarks

① Central dogma.

② character of NA and protein.

NA – very limited function, but ideal for replication

protein – very versatile, but not so easy replication mechanism.

③ Basic plan

1D genetic information

→ 1D amino acid sequence

→ 3D protein structure.

④ Nature of genetic material — not outward state
— not plastic.

Detailed examination

(1) NA is the genetic material

(a) not crystal-clear what genetic material means.

prob. means material must simply replicated.

or contains all (most) information needed to make cell

need to borrow, some information, which is then paid back.

but must be self-consistent.

(b) cytoplasmic factors : probably due to special DNA

eg. mitochondria and chloroplasts.

shown to exist, but "rules" known about what

they do

(c) other factors eg. nucleation factors

probably exist. not clear how stable they

are alternatives would be ; nor how many

of them.

(d) is all NA "Genetic" ie (i) is it all copied.

no. no evidence that RNA is copied in most normal cells (but is in virus-infected cells) medical implications

(ii) does all DNA code for protein

no, some clearly codes for r RNA and t RNA

may be other examples.

however regulatory genes prob. produce protein (may be nucleoprotein)

but all DNA?

esp. DNA of eg. amphibians, newts

& crabs special AT DNA.

important because would like to estimate the number of genes. also other functions might be important.

7/

(2) Nature of the "chromosome"

E. coli: one long piece NA, often circular
Sometimes circularity permitted

E. Coli : one very long piece DNA, in form of a circle.

[Higher organisms
obscure : probable ~~several~~ circles
probably several per chromosome.
Arrangement unclear.
Role of proteins (histones) still
obscure]

Mc Dermott.

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DNA replication

Evidence for semi-conservative early good

Also in special cases can show chains come apart.

Here no increase replication of genetic DNA in test-tube

by known enzyme.

Also problem of direction of replication.

?

Is it a repair enzyme:

If so, what is the true enzyme like?

Is it specially located in the cell.

Surrounding problem still very unsatisfactory.

~~Title~~ AH ~~was~~ NA replication

Only one case in which increase of

biological activity + then mechanism controversial.

Also detailed action of enzyme ie base pairing, not yet

established.

making RNA for DNA

- reasonable evidence there only one strand is copied.

but don't know signal for start

- - - - - - stop

[only rather rough idea about control of rate]

don't really know if protein synthesis ribosomes

(i.e. protein synthesis) play a role in mRNA reading.

don't know details of mechanism (e.g. is there a

running loop?) or is double helix never untwisted.

but evidence does support complementary replication

(because will work a single strand)

So far no simple mutants (i.e. ones appear to

delete) which appear to give start or stop signals.

protein synthesis

Genetic code

— ~~don't~~ punctuation marks need further study

— what are minor tRNA's for ?

— is there ambiguity ?

— is there modulation (apart from punctuation mark effects.) ?

— is it really universal ?

Structure of code -- wobble

(origin of code ?)

intragenic ~~Pseudo~~ suppressor as error in protein synthesis.

General conclusions

We see that ~~the problems of~~ the problems of molecular genetics fall into two classes,

(1) Gene structure
Gene replication
Gene action
Nature of mutation
} all solved in outline

(2) gene control
recombination
} look as though they may be solved soon.

Future development

To extend to larger structures and higher organisms

eg. chromosome structure
"Evolution and "

To study (physical chemistry in more detail

eg replication process ; base pairing.