

Episode 2: The Chemistry of Life

(see <http://www.bbc.co.uk/programmes/b00m6nhq>)

Sponges – nylon sieve to obtain individual cells. Regrow.

Friedrich Miescher (Tubingen)

1868 Chemistry of white blood cells (WBCs). Wanted isolated nuclei – obtained WBCs from pus on bandages from wounded soldiers.

Slaughterhouse – pig's stomach to get mucus from stomach = pepsin.

Wash pepsin out of stomach and mix with pus – cells digested.

What did the nucleus consist of? Strange molecule – C, H, O & N but also P = different

Called molecule 'nuclein' = DNA

Sperm from frogs, calves and salmon – all contained same molecule

1870s salmon sperm DNA

Miescher's work went unnoticed at the time

Theodore Boveri (Bay of Naples)

Mediterranean – marine life, Bay of Naples scientific community

1888 Boveri, supported financially by Charles Darwin

Public aquarium to fund research.

Fish lay eggs direct into water, externally fertilised

Essence of life passed from cell to cell as they divide

Availability of new dyes allowed discrete rods to be seen within the nucleus: unravel, split in two, migrate to the ends.

Rods = chromosomes, "coloured bodies" only visible when a cell divided

Question: why divide in such a curious way?

Boveri expts using sea urchin. Large gonads inside, easy to harvest eggs and sperm

Shaking the urchins stimulates them to spawn – eggs collect on the bottom of beaker

Egg fertilised using sperm – the nuclei from the egg and sperm fuse then cells start to divide.

How important were the chromosomes? What would be the effect of adding extra sperm into the egg cell? Process of cell division disrupted. Led to mutant embryos, only a few cells in size.

Conclusion: a cell needed exactly one set of chromosomes from each of egg and sperm

Could the chromosomes be the way characteristics would be passed on?

Chromosomes must contain "the hereditary characters", a prediction of what we now call genes.

Thomas Hunt Morgan (Columbia University, New York)

Ex-Naples marine station

Drosophila melanogaster = fruit flies

A "mighty hero of biology"

Small, cheap, breed like flies. New generation every 10 days

Only 4 pairs of chromosomes.

Morgan looking for patterns of inheritance

White eyed male cross-bred with Red eyed females. In next generation some white eyed, but only male. Deduced that information for making white eyes had to be on sex chromosomes.

Moved on to map parts of chromosomes responsible for body shape, etc

1922 first chromosome map showing 2000 traits, used the word "gene" to describe these.

Chromosomes carry genes we inherit – but how?

Question: what *are* genes? What is the molecule that allows information to pass from generation to generation?

Fred Griffith (Ministry of Health, London) and Oswald Avery (Rockerfeller Institute, New York)

Both medical researchers studying pneumonia

Griffith: studying bacteria – why do some kill whilst others don't?

Using cocktails of bacteria strains and laboratory mice - looking for combination that would prevent pneumonia.

1. Harmless bacteria alone = fine
2. Lethal bacteria alone = killed
3. Heated lethal bacteria = fine
4. Mixture of lethal heat-treated with harmless bacteria = some of mice died, contained the lethal bacteria in their blood

Question: What had survived from lethal bacteria and transformed the harmless bacteria into killer cells?

Griffith never found out, he never realised he had offered a major clue regarding our understanding of genes and how cells work

Oswald Avery saw relevance of Griffith's results. Also expert on pneumonia bacteria. What was it that had the power to change one sort of bacteria into another?

At Rockerfeller looking at chemical soup within cells.

>9 years, tested every type of molecule, which was passing on the deadly traits?

Process of elimination: carbohydrates, lipids, proteins, DNA (an unlikely candidate)

Stripped of their DNA lethal bacteria could not transform others. Had discovered the molecule that genes are made of, that DNA controlling cells. Became crucial to know what it is and what it's for.

Late 1940s, chemistry of cell becoming clearer – chromosomes carry genes, genes made of DNA, but how did it control cells? Answer might lie in the structure of the molecule – how was DNA built?

Maurice Wilkins and Rosalind Franklin (King's College, London)

Most famous story in biology

After WWII quest began in earnest – physicists, ex nuclear weapons programme, included Maurice Wilkins. Using X-rays to probe structure.

Rosalind Franklin, new lab in basement. Authorities concerned that experiments could be dangerous, made Franklin and assistant work at night after students gone home. Skill to find right amount of moisture to prepare the strands, to tease out a single DNA strand.

X-rays scattered, collected on photographic film. Up to 90 hrs exposure. Projected onto wall. Picture 51. distinctive X-shape revealed the key.

James Watson and Francis Crick (Cambridge)

Wilkins gave photo 51 to James Watson. February 28th 1953 “We have found the secret of life”.

Double-helix model now most famous image in all biology. Bases A, C, G & T

A&T, G&C – split two strands, have all the info needed to replace the missing strand

Secret of how genes are reproduced, how an identical copy is passed on

How do you crack the code, the instructions to make the molecules within cells?

Electron Microscopes revealed sub-cellular structure.

Each human cell 3.4 billion letters of code (paper equivalent = 120 volumes). All cells same DNA – so how do you get a full human made of specialist cells? e.g. Wound healing requires specialist functions – nerve cells, white blood cells, red blood cells, replacement tissue cells. How does each know what it should be doing? How could same DNA make different sorts of cells?

Walter Gehring (University of Basel, Switzerland)

Freaky experiments! Using fruit flies. Rare mutant born with abnormality – perfect leg growing out of head in place of antennae. Isolated gene responsible for control of this process.

Found several similar genes on chromosome. Restriction map – a handful of identical genetic switches, each controlling one major section of fly's body. Homeobox genes – chain reaction of other genes.

Scientists looked for these genes in frogs, mice, humans. In every species they found exactly same switches, the same mechanism.

1995, student in Gehring's lab found gene for formation of eyes. Mouse and fly eyes very different. Mouse version of the gene inserted into fly egg – eyes all over its body. No way of controlling exactly where the mouse gene would end up. But they are fly eyes, not mouse eyes that are formed. Made headline news e.g. “With new fly, science outdoes Hollywood” (New York Times), “Scientists make fruit flies sprout eyes everywhere”, “Why all eyes are on the flies of Frankenstein”, “Really making eyes”, “Scientists grow eyes on flies' bodies: ‘master control gene’ may have been found”. Headlines missed real significance – shared switches and the ability to swap genes between species imply one common ancestor, as Darwin had predicted.

Shows we share common descent. Story of cell is story of evolution itself.