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Virus

- Cellular parasite
- Purpose
- Find a host cell and hijack the metabolic machinery to produce more copies of itself
- Components
- Genetic material
- DNA or RNA
- Very few genes
- Influenza is an RNA virus
- Only 11 genes
- Capsid
- Protein coat surrounding the genetic material
- Envelope (influenza only)
- Remnants of the cell's plasma membrane

Types of Influenza

- A
- Viral spikes
- Spikes are glycoproteins (protein with sugar attached) that help the virus enter the host cell
- Two types in Influenza A
- H spikes (hemagglutinin spikes)
- Assists with infecting the host cell
- 17 versions
- N spikes (neuraminidase)
- Breaks down mucus
- 10 versions
- B
- C
- D

Virus type / place virus isolated / strain number / year isolated (virus subtype)

A / Sydney / 05 / 97 (H3N2)

Characteristics of life

- Process energy and materials
- Maintain and internal environment
- Respond to stimuli from the environment
- Reproduce
- Adapt to changing environmental conditions

Three domains of life

- Bacteria
- Archaea
- eukarya

Giant viruses

- Some have protein-making machinery

Virus reproduction

Most viruses infect specific cell types via protein-protein interactions on the capsid and cell plasma membrane

Virus life cycle

- Two phases (pathways)
- Lytic cycle
- Utilizes the cellular machinery to make viral copies
- 5 stages
- Attachment
- Penetration
- Genetic material directly enters the cell
- Host cell engulfs the entire virus via endocytosis
- Biosynthesis
- Maturation
- Assembly of the virus
- Release
- Host cell bursts (cell lysis)
- Exit through the plasma membrane (exocytosis) creating an envelope
- Lysogenic cycle
- Integration into the host genome

- Delays reproduction until a later time
- 5 stages
- Attachment
- Penetration
- Same as above
- Viral DNA integrates into the host cell’s DNA
- Referred to as prophage
- Virus is inactive (latent) until an environmental factor signal reentry into the lytic cycle

It is estimated that 8% of our genome is viral in nature

RNA virus life cycle

- Problem: DNA is converted to RNA and translated to protein
- Viral reverse transcriptase can convert viral RNA into DNA
- Method used by HIV
- Viral RNA polymerase cna convert viral RNA into mRNA
- Method used by influenza

Epithelial cells

- Primary target of influenza virus
- In respiratory system
- Form boundary between body tissues and internal environments
- Respiratory system
- Digestive tract
- Skin
- Arranged in a thin layer of tissue called epithelium
- One cell layer thick
- Anything that enters the body must pass through an epithelial cell before reaching the bloodstream or other body tissues

Influenza A infection

- N spikes break down mucus membrane
- H spikes on flu A virus identify the specific glycoproteins/receptors on the surface of cells
- Infection can happen anywhere on the respiratory tract
- Replication cycle can happen within just a few hours
- Infection disrupts the normal function of the epithelial cells
- Symptom progression

- Epithelial cell function deteriorates
- Responsible for movement of materials into and out of the lungs
- Symptoms = fluid accumulation
- Epithelial cells die
- Immune system sends cells to fight
- Increases blood flow
- Symptom = tissue swelling, inflammation increase
- Large amounts of mucus are produced
- Symptom = cough and congestion
- TABLE 1.2
- Immune system releases cytokines, a protein meant to alarm the other organ systems of the body about the presence of a pathogen

Flu vaccine

- TABLE 1.3
- Quadrivalent vaccine
- 4 variations of the flu virus
- Viral particles have been killed and not capable of reproducing
- NOTE: nasal spray vaccine contains a weakened version of the flu virus
- How to choose the variations
- Begins a year in advance
- Global network of 100 influenza monitoring stations send clinical samples to influenza center
- Scientists review the data and determine
- The potential of each strain to cause a pandemic
- The ability of an effective influenza vaccine to be produced
- Manufacturers get 6 months to prepare the vaccine
- Challenge: virus evolves quickly and may change before the flu season

Using chicken eggs to make vaccine

- Inject virus into fertilized eggs
- Virus replicates inside the egg for a few days
- The liquid portion is extracted and the virus is killed
- The viral particles are isolated and purified
- Negative: long dev time

Cell-based method

- Inject virus into mammalian cells (outside of body culturing)
- Virus replicates
- Viral particles are inactivated, isolated, and purified

Recombinant process

- H spike protein is made using recombinant DNA tech
- Added to a virus that infects insect cells
- Insect cells produce large amounts of the H spike protein
- H spike protein is isolate and purified to make a vaccine
- Benefit: the complete virus is not produced.

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Evolution

- Change in species or population over time
- Individuals don’t evolve
- Occurs when heritable changes in the genetic information are passed from one generation to the next
- Changes occur over multiple generations
- Species are able to adapt to the environment
- Evolution is not debated among true scientists

Biology

- The study of life
- The study of our natural world
- Biologists have documented the history of life on our planet
- Life on our planet has progressively changed over time
- Results of a long evolutionary process

Evolution is a unifying theory in biology

Virus reproduce rapidly and thus are a good model of evolution

TABLE 2.1

Charles Darwin and Alfred Russell Wallace independently identified natural selection as the process by which evolution occurred

Charles Darwin

- Young naturalist on the HMS Beagle
- 5-year journey
- Collected fossils of extinct animals
- Examples: giant sloth and marine organisms high in the Andes
- Challenged the idea that the Earth was very young
- This would give time for organisms to change
- Organisms are related to each other

Similar environments had animals with similar appearances

Finch head beak variations adapted to food sources available

Alfred Russell Wallace had similar observations and shared them with Charles Darwin

Natural selection

- Individuals vary in their traits
- Example: beak shape
- Individuals struggle to exist
- Populations produce more offspring than can survive yielding competition
- Individuals differ in their fitness
- Those with favorable traits will survive at a greater rate than those without
- Those traits will be passed on to the next generation
- Fitness: reproductive success
- Populations become adapted to their environment
- Natural selection increases the frequency of the most advantageous trait
- In order for natural selection to influence a trait, variation must exist
- There are three different ways that natural selection can influence the variation of a trait in a population
- Stabilizing selection
- Selection favors the most common form of variation for the trait
- Extreme variants are selected against
- Directional selection
- Selection favors the variants at one end of the distribution
- Disruptive selection
- Selection favors variants at the end of the distribution (less common)

Central Dogma of Biology

- The information for a trait is contained within the individual nucleotides of the DNA molecule

- Proteins dictate traits
- Genes contain the information to make proteins
- Specifies the order of amino acids
- If the amino acid order changes the protein shape and function changes

Mutations

- Causes
- Radiation
- Chemicals
- Mistakes during replication
- Integrating viruses
- Effects
- Yield a nonfunctional protein
- It can be lethal to the host
- No effect on overall function
- Produce a slightly different shape and slightly different function
- Result: variation in the population
- Source of all variation
- Natural selection does not cause mutation
- Natural selection favors the variation that increases the ability of the individual to reproduce

Evidence for evolutions

- Transitional fossils
- Fossilized remains of a life form that exhibits traits common to both the ancestor and descendant
- When fossils are arranged and compared according to their age evolutionary change becomes apparent
- Comparative anatomy
- Organisms in different regions have similar structures that allow them to adapt to their environment
- Two types of structures
- Analogous structures
- Structures that have the same function but evolved independently
- Examples: wings of birds, bats, and insects
- Homologous structures
- Structures that are similar because they have been inherited from a common ancestor
- Examples: limbs of a mouse, bat, and whale

- Embryonic development
- homologous structures are evident
- Suggest descent from a common ancestor
- Genetic material
- The closer the genetic information is between two species, the more closely the two organisms are related

Fewer differences = less time for changes in DNA

How do viruses evolve

- Antigenic drift
- Viral enzymes frequently make mistakes when copying genetic material
- Reverse transcriptase of HIV
- RNA polymerase of influenza
- Result: genetic variation typically on surface spikes
- Variations can cause the virus to evade our immune system
- Consequence: vaccine effectiveness reduced
- Occurred during the 2017 - 2018 flu season

Antigenic shift

- Two different forms of the virus infect the same cell
- Often these two forms are from different animal hosts
- The host cell manufactures viral particles from both viruses and reassembles them into a new form with unique versions of H and N spikes
- Result: more rapid change in the virus
- Consequence: the immune system takes longer to respond to the virus
- Can cause a possible outbreak

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Immune System

- Protect our bodies from pathogenic infection
- Works closely with lymphatic system
- Routinely checks the fluid of the lymphatic system (lymph) for pathogens
- Performed in the lymph nodes

Lymphatic system

- Lymph vessels found in every tissue of the body
- Lymph is delivered to the right side of the heart
- Returns fluid back to the circulatory system
- Lymph nodes
- Some immune cells reside in the lymph nodes and kill pathogens
- Macrophages (type of white blood cells)

Table 3.1

Interstitial fluid

- Fluid outside the cell and outside the blood vessel

Our cells have special markers on the plasma membrane to allows immune cells to distinguish between our cells and foreign cells

Plasma membrane

- Phospholipids
- Proteins

Major Histocompatibility Complexes

- Glycoproteins on the plasma membrane of cells
- with a large sugar residue on it
- Abbreviated MHC
- Two forms
- MHC-I
- Found on every nucleated cell
- General self tag
- MHC-II
- Only found in immune cells
- Link between nonspecific and specific immune response

Antigen

- Substances that produces an immune response
- Proteins or large carbohydrates specific to a pathogen

Specific Immune Response

- Pathogens are ingested by macrophages and dendritic cells of the immune system

- A small portion of the pathogen is attached to the surface of the macrophage via the MHC-II
- Macrophage becomes an antigen-presenting cell (APC)
- Signals immune cells to attack the antigen

Autoimmune disease

- Immune system mistakes a self antigen as foreign and starts attacking its own cells

Non-specific immune response

- General defense
- Not specific for an antigen
- Referred to as innate defense
- Physical barriers
- Macrophages and dendritic cells (phagocytes)
- Protective proteins (complement)
- Cytokines (small protein involved in local response to pathogen

Table 3.3

Table 3.4

Complement Cascade Activation

- Two pathways
- Classical pathway
- C1 activated when bound to a pathogen
- C1 cleaves C2 into C2a and C2b and C4 into C4a and C4b
- C2b and C4b combine to form C3 convertase
- C3 conversate cleaves C3 into C3a C3b
- Alternative pathway
- Free antigens combine with C3b
- C3b combines with factor B, factor D, and properdin to form C3 convertase
- C3 convertase cleaves C3 into C3a and C3b

Inflammatory response

- First immediate action taken by the immune response
- Histamine causes fluid to leak from capillaries
- Slow movement of pathogens
- Increases blood flow to area delivering white blood cells

- Macrophages identify and destroy bacteria/viruses
- Neutrophils removes dead cells, wound debris, and pathogens
- Neutrophils release cytokines to recruit more immune cells
- Clotting factors close off the wound
- Creates pressure to build
- Causes redness, heat, swelling, and pain at damaged/infected area

Table 3.2

Adaptive immunity

- Target specific antigens associated with a pathogen
- Target cells infected with the pathogen presenting their antigen
- Response to free pathogens in the blood / interstitial fluid
- Provide memory of past infections
- Two forms
- Cell-mediated immunity
- Target cells that have been infected and are presenting the antigen
- Key player = T lymphocytes
- Made in the bone marrow
- Mature in the thymus
- Develop receptor to recognize a single antigen
- Helper T cells recognize the MHC-II bound to the antigen on APC cells
- Result: helper T cells become activated
- Cytokines activate cytotoxic T cells
- Cytotoxic T cells recognize the MHC-I bound to antigen on infected cells
- Cytotoxic T cell attaches to cell
- Releases perforin
- Granzymes enter cell
- Result: apoptosis (cell death)
- Cytotoxic T cells become T memory cells
- Antibody-mediated immunity
- Key player = B lymphocytes
- B cells can bind directly to an antigen or become activated by a helper T cell
- Once activated, B cells develop into plasma cells and produce large amounts of antibodies
- Antibodies are Y-shaped proteins that bind to a specific antigen
- Antigen clump around an antigen and inactivate it and/or flag the antigen for destruction by a natural killer cell

The flu vaccine works by generating active immunity by exposing an individual to an antigen specific to the pathogen without causing the disease (H spikes, unique to influenza virus)

Antigenic shift

- Two different forms of the virus infect the same cell
- Often these two forms are from different animal hosts
- Pigs and birds are reservoirs of the precursors of the influenza virus
- The host cell manufactures viral particles from both viruses yielding unique H and N spikes

Antigenic drift

- Viral enzymes frequently make mistakes when copying genetic material
- RNA polymerase of influenza

Antiviral medicine

- Molecules that target an aspect of the viral life cycle
- Result: prevent virus from multiplying inside the host
- Attachment
- Target the glycoproteins on the host cell the virus uses to invade
- Target the viral proteins the virus uses to attach
- Uncoating
- Target the viral enzyme that removes the genetic material from the capsid
- Release
- Target the viral enzyme that allows the newly made virus to escape the cell

Future directions

- Universal flu vaccine
- Made to provide immunity against other antigens that do not evolve as rapidly as the H and N spikes
- Example = core proteins (responsible for making the viral capsule)
- H1ssF_3928 is currently being evaluated in human clinical trials

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