免疫系統的基本觀念與對5070人的應用

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V1.1

Overview

- Why do we need an immune system
- Where is the immune system
- What are the key players in the immune system
- Immunity Tolerance
- Inflammation
- Immunotherapy
- Conclusion

Why do we need an Immune System

- External threat
  - Microbe (微生物 - H. pylori 幽門桿菌)
  - Pollution
  - Pet in your house (Allergic to fur)
- Internal threat
  - Apoptosis
    - Normal : Programmed cell death
    - Abnormal : Failure of normal cell death - Cancer
- Guard normal bodily functioning
  - Tissue clean up & Wound repair
  - Remove abnormal cells including malignant ones

Where is the Immune System

- 1st line human body defense (Non-WBC based)
  - Mechanical/Physical barriers
  - Chemical barriers & antimicrobial peptides
  - Microbiological competition
- 2nd line human body defense (WBC based)

  Innate (Non-Specific) Immune System
  - Complement system (Plasma protein tags bacteria for destruction)
  - Pattern recognition receptors/Toll like receptors (recognize general feature of the enemy)
- 3rd line human body defense (WBC based)

  Adaptive (Specific) Immune System
  - Humoral mediated immunity
  - Cell mediated immunity

1st Line Human Body Defense (1/2)

- Skin (physical barrier, fatty acids, commensals)
- Lysozyme (溶解酶) in tear and ear wax耳垢
- Mucous分泌黏液的membranes, Cilia纖毛 and Coughing
- Saliva (唾液)

1st Line Human Body Defense (2/2)

- Stomach acid (pH:1.5 ~ 3)
  - Composed by
    - Hydrochloric acid (HCl) (around 0.5%, or 5000 parts per million)
- Flushing of urinary tract (尿道)
- Low pH by commensals (共生菌 - 陰道乳酸桿菌分解「陰道黏膜中所產生的肝醣」，並製造乳酸) in vagina (陰道)

2nd & 3rd Line Human Body Defense (WBC based)

- Protect the body from infections by
  - 208 viruses (Cold, Flu, HBV, HIV ; AIDS - 愛滋病)
  - 538 bacteria (TB / Tuberculosis - 肺結核, Cholera - 霍亂, MRSA - 抗藥性金黃色葡萄球菌)
  - 317 fungi (菌類植物) (Athlete's foot by Ringworm 輪癬; 金錢癬)
  - 287 worms
  - 57 parasite protozoa (寄生的原生動物類; 單細胞動物類) (Malaria - 瘧疾)
- Guard normal functioning of the body
  - Tissue clean up & Wound repair
  - Remove abnormal cells including malignant ones
- But it can also cause disease when it is not doing the right thing (allergies, autoimmunity, transplant rejection, etc.)

Human Blood Function

- Transport
  - Oxygen
  - Carbon dioxide
  - Nutrients
  - Wastes
- Coagulate (clot) blood
- Combat infection (Immunity)

Human Blood Composition (1/2)

- Serum (血清)
  - Base liquid of blood (mostly salt water)
  - Includes all proteins not used in blood clotting
  - Contains all the electrolytes, antibodies, antigens, complement, hormones & any external substances (e.g., drugs, microorganisms, etc.)
- Plasma = Serum + Clotting factors (made by liver)
- Blood cell (originated from the bone marrow)
  - Red blood cell (RBC): Erythrocytes
    - Erythropoetin 紅血球生成素 is synthesized by the kidneys to stimulate RBC production
    - Erythropoiesis 紅血球生成-stimulating agent (ESA) is needed for ESRD dialysis patients (AMGN, JNJ ~ USD10B/year)

Human Blood Composition (2/2)

- Platelets (Plt): Thrombocytes 血小板
- White blood cell (WBC): Leukocytes
  - Phagocyte (Neutrophil (嗜中性白血球) ~ 60%WBC, Macrophage (巨噬細胞), Dendritic cell ~ less than 1% WBC)

    Responsible for eating foreign particles by engulfing them, and then breaking them apart
  - Eosinophil (嗜酸性白血球), Basophil (嗜鹼性白血球), and Mastocyte (Mast cell, 肥大細胞)
  - Natural killer cell (produced by Lymphoid stem cell)
  - Lymphocytes (淋巴球; 淋巴細胞):
    - Helper T cell & Cytotoxic T cell (both matured in Thymus);
    - B cell (produced by bone marrow, and activated by Helper T cell)

What are the Key Players in Immune System

- Sentinel cells in tissues
  - Dendritic cell, macrophage, mast cell
- Circulating phagocytes and granulocytes
  - Neutrophil, monocyte, eosinophil
- Lymphocytes: cells can recognize specific pathogens (but also can cause allergies, autoimmune diseases, transplant rejection)
  - B cell / B lymphocytes (15%)
    - Antibody
  - T cell / T lymphocytes (70%)
    - Helper T cell (Th)
    - Cytotoxic T cell (Tc)
  - NK cell / Natural killer cells (15%)
    - Kill virus infected cells

Immune System

- **Innate (Non-Specific) Immune System**
  - Pattern Recognition Receptor (~1,000 types) mediated immunity (Phagocyte recognizes the microbe through its Pathogen Associated Molecular Pattern)

http://www.hindawi.com/journals/cdi/2008/742810/fig2/

- **Adaptive (Specific) Immune System**
  - Humoral & Cell-mediated immunity

Immune System Overview and Tutorial - Innate and Adaptive (14:38)
http://www.youtube.com/watch?v=HAjIekQvnVU&feature=related

Innate Immune System (1/2)

- Immediate & 1st line defense
- Has cells and mechanisms defending the host in a non-specific manner
  - Cell
    - Phagocyte (Neutrophil~60%WBC, Macrophage, Dendritic cell)
    - Eosinophil and Basophil
    - Mastocyte (Mast cell)
- Natural killer cell (produced by Lymphoid stem cell)
  - Mechanism
    - Cytokine production
    - Complement cascade activation
    - Identification and Removal of foreign substance
    - Adaptive immune system activation

Innate Immune System (2/2)

- Not a long-lasting Protective immunity to the host
- Evolutionarily older defense strategy
  - Antibiotic resistance - a type of drug resistance where a bacteria is able to survive exposure to an antibiotic (抗生素)

病原菌	發病所需菌量			增殖速度
腸炎弧菌	1.00E+06	~	1.00E+09	7.5 ~ 8 分
抗藥性金黃色葡萄球菌 (MSRA)	1.00E+06	~	1.00E+09	90 ~ 120 分
肺結核菌	1.00E+01	~	1.00E+04	11 ~ 12 小時

  - Superbug (**M**ulti **D**rug **R**esistant **TB - MDRTB**)
    - TB patients were given
      - Wrong medicines, Wrong diagnostic (child), or Wrong doses,
      - None or Not completing treatment (~ 24 months time required)
    - WHO data on MDRTB: 0.5M (2012), ~2M (2015)

Adaptive Immune System (1/2)

- **Active immunity**
  - The body generates the antibodies and memorize them
  - Old antigen can be quickly recognized by the antibodies, and a person may never become ill from that invader (pathogen) again. This person is now immuned
  - New antigen takes the adaptive immune system longer time to identify, and a person remains ill until a new antibody can be crafted

Adaptive Immune System (2/2)

- Passive immunity
  - The body does not generate the antibodies
  - The transferred antibody takes effect almost immediately at 1st time
  - Transferred antibody will be removed later by the body
  - Examples:
    - Protection against tetanus破傷風 (in an exposed person not previously vaccinated)
    - Protection against snake venom毒液, therapeutic antibodies (Immunotherapy)
    - Mother provides immunity to fetus via chord blood, and to new born baby via breastfeeding

Active Immunity (1/3)

- The body produces the antibodies after being exposed to the antigen in the past either through
  - Infection

    Exposure to the disease-causing antigen ;

    You fight it, win it & remember it

  or
  - Vaccination (Fake infection)

Active Immunity (2/3)

- Humoral immunity
  - Antigen Presenting Cells match Class II MCH, T cells proliferate, produce Th cells (1st time infection)
  - Th cells release interleukins (and other cytokines), which stimulate B cells
  - B cells proliferate and produce B plasma cells
  - Antibodies released from B plasma cells, circulate through the body, bind to antigens
  - Stimulate natural killer cells and macrophages to destroy antigens
  - Produce memory B cells and memory T cells
  - Antigens bind to B cells (2nd time infection)

Active Immunity (3/3)

- Cell-mediated immunity (procedures controlled by antibodies)
  - Antigen Presenting Cells match Class I MCH, T cells proliferate, produce T_C cells (1st time infection)
  - Tc cells bind to infected cells & destroy them
  - Antigens bind to T_C cells (2nd time infection)

Vaccination

- Targeted antigens are deliberately introduced into the immune system to produce immunity
- Because the microbe has been killed or weakened, minimal symptoms occur
- It generally takes 1-2 weeks (Immunity response time) to become effective
- Side effects does occur occasionally

HIV / AIDS

- A retrovirus discovered in 1983
- Human Immunodeficiency Virus (HIV) targets and infected dendritic cells, macrophages, & Th cells (CD4+)
- HIV transmitted via sexual / blood contact
- Can take up to 10 years for any HIV sign to appear
- Aquired Immune Deficiency Syndrome (AIDS) is the late stage HIV infection, No cure but can be controlled
- HIV-infected women can pass the virus to their children during pregnancy, childbirth, breastfeeding

Immunity Tolerance

- Body health
  - Nutritious food intake
  - Regular exercise
  - Peaceful mind
- Living environment
  - Pollution
  - Toxic chemicals in home
- Working environment
  - Hospital-born illnesses

細菌的增殖速度和其引起感染症所需要的病原體量

病原菌	發病所需菌量			增殖速度
腸炎弧菌	1.00E+06	~	1.00E+09	7.5 ~ 8 分
霍亂弧菌	1.00E+05	~	1.00E+07	20 ~ 30 分
腸道出血性大腸桿菌O-157	1.00E+01	~	1.00E+03	20 ~ 30 分
痢疾桿菌	1.00E+01	~	1.00E+05	30 ~ 40 分
傷寒沙門氏菌	1.00E+01	~	1.00E+04	30 ~ 40 分
沙門氏菌	1.00E+06	~	1.00E+09	30 ~ 40 分
非抗藥性金黃色葡萄球菌 (MSSA)	1.00E+06	~	1.00E+09	50 ~ 60 分
抗藥性金黃色葡萄球菌 (MSRA)	1.00E+06	~	1.00E+09	90 ~ 120 分
肺結核菌	1.00E+01	~	1.00E+04	11 ~ 12 小時

Inflammation

- Part of the complex biological response of vascular tissues to harmful stimuli, such as: pathogens, damaged cells, or irritants
- A protective attempt by the organism to remove the injurious stimuli and to initiate the healing process
- Considered as a mechanism of innate immunity
- Conditions including swelling, redness, heat and aches and pains associated with the damaged tissue or organ
- Progressive destruction of the tissue would compromise the survival of the organism

Inflammation Types

- Acute inflammation
  - Mostly mediated by granulocytes such as: sterile inflammation (tissue injury but no infectious agent present)
  - A healthy response by the body to a harmful condition
- Chronic inflammation
  - Mediated by monocytes and lymphocytes
  - Can potentially damage healthy cells and consequently result in even more harm than the initial condition
  - Chronic, or silent, inflammation will invariably compromise the body's immune system as a result of the activating and re-activating of intermingled immunological responses (such as: Atherosclerosis, Hepatitis B)

哪些才是正確的傷口癒合方式

1. 傷口 (裂傷、挫傷、傷口縫合處、燙傷、褥創) 一定要消毒
2. 傷口不消毒就會化膿
3. 傷口因為化膿了，所以需要消毒
4. 要直接在傷口上貼紗布
5. 傷口絕對不可以弄濕
6. 傷口結痂就表示傷口已癒合了

皮膚缺損傷口(擦傷、燙傷、褥創)不可以覆蓋紗布

1. 紗布會使創面乾燥，延遲傷口的癒合
2. 紗布會將創面分泌的「細胞生長因子」吸盡
3. 紗布的網目會陷入傷口，當將紗布撕開時可能會破壞正要癒合的傷口

Chronic Inflammation (1/3)

- Chronic inflammation: if antigen persists, antigen-reactive T cells can drive continued inflammation, which can cause tissue damage (autoimmune diseases and inflammatory diseases)
- Atherosclerosis(動脈硬化症): Inflammatory process is implicated in the progression of atherosclerosis (elevated CRP level in blood is a risk factor indicator independent of Low-density lipoprotein, LDL)
  - CRP (C-Reactive Protein) is an indicator of inflammation in the body. It is secreted from the liver and can be measured with a simple blood test

Four Basic Types of Lipoprotein

- Chylomicron – from dietary (TG + CE)
- VLDL (Very Low Density Lipoprotein) – from liver (TG+CE)
- LDL (Low Density Lipoprotein) – Transport cholesterol
- HDL (High Density Lipoprotein) – Regulate cholesterol

Characteristics of LDL

- Major contributor of
  - Cell membrane component
  - Precursor of
    - Bile acid
    - Steroid hormone
    - Vitamine D
- Stay longer in blood stream than Chylomicron & VLDL
- Can be damaged by
  - Various toxins: cigaret smoking, etc.
  - High glucose level in the blood (10 hr. after taking meal)
  - Oxygen free radicals

Chronic Inflammation (2/3)

- Atherosclerosis in progression
  - Macrophages gobble up damaged LDL (Foam cell) & embed themselves in the artery wall
  - Long time accumulation of foam cell in the artery wall may lead to heart attack or stroke
- Aneurysm: 動脈瘤

Chronic Inflammation (3/3)

- Chronic systemic inflammation is a powerful hidden cause linked to numerous age related ailments such as
  - Arthritis, *heart disease*, diabetes, cancer, stroke, *autoimmune diseases*, allergies, Alzheimer's disease, anemia, fibrosis, fibromyalgia纖維性肌炎, systemic lupus, weakness and/or frailty, psoriasis牛皮癬, chronic pancreatitis, etc.

Immunotherapy (1/2)

- In the quest to cure cancer, many researchers have started looking beyond toxic chemicals and harsh radiation and instead are trying to harness the body's immune system
- Fewer side effects than existing drugs, including less potential for creating resistance in microbial diseases
- The active agents of immunotherapy are a diverse array of recombinant, synthetic and natural preparations, often cytokines

Immunotherapy (2/2)

- Therapeutical antibodies: Monoclonal antibodies
- Cell based immunotherapy (Dendritic cell etc.)
- Therapeutic cancer vaccine
  - Vaccine made to treat the body already has cancers
- Prophylactic Cancer Vaccine
  - Gardasil (June 8, 2006, Merck, USA) and Cervarix (Oct. 16, 2009, GlaxoSmithKline, UK) for cervical子宮頸cancer (The only two prophylactic cancer vaccines approved by FDA so far)
  - Prevent infection with certain species of human papillomavirus (HPV) associated with the development of cervical cancer, genital外陰部warts疣, and some less common cancers

Monoclonal Antibodies (單株抗體) (1/2)

- Antibodies recognizing constituents tumors can be produced using recombinant DNA methods
- These antibodies, when injecting into the patients, are safe and well tolerated, and are becoming standard adjuvant treatments for several types of tumors
  - Herceptin (trastuzumab) (Movie: **Living Proof**)
    - Anti-HER2/neu antibody (Tumor-associated antigen: HER2/neu)
      - HER2+ : Human Epidermal Growth Factor Receptor (EGFR) 2 - positive
    - FDA approved for breast and gastric胃的cancers
    - Peak sales forecasts: ~ $6 billion worldwide
    - Developed by Genentech, Owned by Roche now

Monoclonal Antibodies (單株抗體) (2/2)

- Avastin (bevacizumab)
  - Anti-VEGF antibody (Tumor-associated antigen: VEGF)
    - VEGF stands for "Vascular Endothelial內皮細胞Growth Factor"
  - FDA approved for colorectal, lung, renal, and brain cancers
  - Off-label used for wet AMD (Age-related Macular Degeneration), breast cancer
  - Peak sales forecasts: ~ USD$7.5 billion worldwide
  - Developed by Genentech, Owned by Roche

- But each antibody recognizes only a single tumor constituent once, must be administered repeatedly over time, and is only partly effective

Conclusion

- Immune system prevents body from illness
- Maintain our immune system in good condition
  - Take nutritious foods (macronutrients, micronutrients)
  - Exercise regularly (lymphoid fluid circulation)
  - Keep peaceful mind (fight or flight)
  - Happy life
- Skin wound healed by the immune system
- Damaged LDL is the cause to atherosclerosis
- Chronic inflammation is a serious problem
- Immunotherapies will be given as adjuvant to current standards of care of chemotherapy, hormone therapy, radiotherapy and resection

Wish Life is Wonderful to all of us!!!