Autoimmunity

Introduction

- **Autoimmunity** is the failure of an organism to recognize its own constituent parts as ***self***, which results in an immune response against its own cells and tissues.

- Many people experience some type of **autoimmune reaction** during their lifetime.

- Mostly these autoimmune reactions are **short-lived, self-resolving** after-effects of infection.

  These are due to **cross reactivity** of antibodies produced against pathogens.

- However in **5%** of individuals the reaction is **chronic, debilitating** and **even (rarely) life-threatening**.

- These latter conditions where **serious immunopathology** occurs are usually considered as **autoimmune diseases,** e.g. **arthritis** and **glomerulonephritis**.

Natural autoimmunity

- **In the past**, any autoimmune response was perceived to be abnormal and considered to be connected with **human disease.**

- Now, it is **accepted that autoimmune responses are vital** to the development and functioning of vertebrate immune systems.

- This concept has been termed **natural autoimmunity.**

- The **natural autoantibodies** play vital role in **clearance of debris** of naturally dying cells.

Alloimmunity

- **Autoimmunity** should not be confused with **alloimmunity**.

- **Alloimmunity** (sometimes called **isoimmunity**) is an immune response to **non-self antigens** from members of the **same species.**

- These antigens are called **alloantigens** or **isoantigens**.

- Two major types of alloantigens are **blood group antigens** and **histocompatibility antigens** (responsible for tissue rejection).

Low-level autoimmunity

- A low level of autoimmunity may actually be **beneficial**.
- Firstly, low-level autoimmunity might aid in the **recognition of neoplastic cells** by CD8+ cells, and thus reduce the incidence of **cancer**.
- Second, autoimmunity is likely to have a role in allowing a **rapid immune response** in the early stages of an infection.

The autoantibodies which are **already circulating may** interact with invading pathogens.

Autoantibodies - cause or effect?

- Almost all patients presenting with autoimmune conditions have some **autoantibodies** present in their serum.

- However they also have **autoreactive T cells** present.

- It is not always known whether the autoantibodies play an important **role in the disease** or are a **secondary result** of the tissue damage which has been caused by the **T cells**.

- This problem is particularly difficult in many **organ-specific** conditions.

Genetics

- **Genetic susceptibility** plays an important role in almost all autoimmune conditions.

- The most significant influence is that of the **MHC genes**.

- The linkage between particular **MHC allotypes** and **specific diseases** has already been documented.

- Studies have shown that within the human population there are **multiple genetic loci** which are involved in susceptibility to common autoimmune conditions such as rheumatoid arthritis and some types of diabetes.

- Apart from the MHC, very few such loci have been **definitely** identified which are related to autoimmunity.

- Genes related to **Ig and T-cell receptors** which are involved in the recognition of antigens are **inherently variable** and **susceptible to recombination**.

- These variations enable the immune system to respond to a very wide variety of invaders, but may also give rise to lymphocytes capable of **self-reactivity**.

Allotypic Determinants

- differences in amino acids in C regions, which occur in some, but not all, members of a species

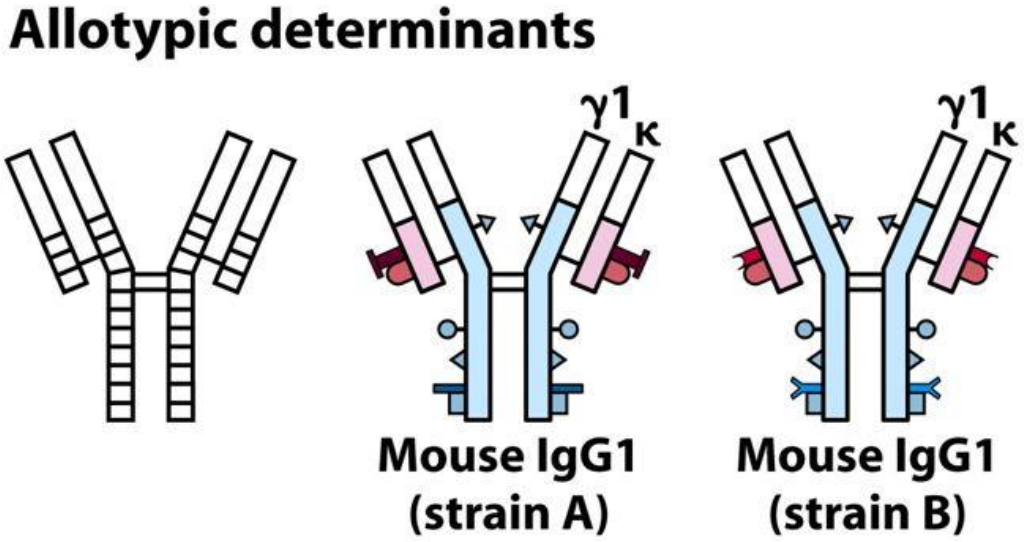

Figure 4-21b
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These changes are especially notable in kappa chain

Sex

- A person's sex also seems to have a **major** role in the development of autoimmunity.

- Most of the known autoimmune diseases have greater occurrence in **females.**

- The reasons for this phenomenon are **unclear**.

- Apart from inherent genetic susceptibility, several animal models suggest a role for **sex steroids**.

- It has also been suggested that the **slight exchange of cells** between mothers and their children **during pregnancy** may induce autoimmunity in mothers.

- Another theory suggests the female high tendency to get autoimmunity is due to an **imbalanced X chromosome inactivation.**

X-chromosome inactivation occurs in females to provide dosage compensation between the sexes (dosage compensation is the process by which organisms equalize the expression of genes between members of different biological sexes). X-chromosome inactivation occurs randomly for one of the two X chromosomes in female cells during development.

Diagnosis

- Diagnosis of autoimmune disorders largely rests on **accurate history** and **physical examination** of the patient, and certain **abnormalities** in routine laboratory tests (example, **elevated C-reactive protein**).

- In several systemic disorders, **serological assays** which can detect specific autoantibodies can be employed.

- Localised disorders are best diagnosed by **immunofluorescence** of **biopsy** specimens.

C in C-reactive protein represent "c" carbohydrate antigen of the capsule of pneumococcus.

Treatments

- Current treatments for autoimmune disease are usually **immuno-suppressive, anti-inflammatory**, or **palliative** (relieving pain).

- Non-immune therapies, such as **hormone replacement** in DM (Diabetes mellitus) Type 1 tone down **auto-aggressive** response.

- Dietary manipulation limits the severity of **celiac disease** (gluten sensitivity).

- **Steroidal treatment** limits inflammatory symptoms of many diseases.

- More specific immunomodulatory therapies, such as the **TNFα antagonists** have been shown to be useful in treating **rheumatoid arthritis.**

- The **levels of autoantibodies** are measured to determine the progress of the disease.

These immunotherapies may be associated with **increased risk of adverse effects**, such as susceptibility to infection.

Environment

- It is clear that environmental factors also **play a role in autoimmune disease.**

- It is only about **20-40%** for common autoimmune diseases such as diabetes, SLE and rheumatoid arthritis that **identical twins** both develop a disease.

- This makes it **highly likely** that environmental factors must also be important.

- While factors such as diet play a role, **infectious organisms** are the most significant environmental factor.

- An interesting **inverse** relationship exists between infectious diseases and autoimmune diseases.
- In areas where multiple infectious diseases are **endemic**, autoimmune diseases are quite **rarely seen**.
- The proposed mechanism is that the parasite **weakens** the host immune response in order to protect itself.
- This may provide **benefit** to a host that also suffers from autoimmune disease.

- On the **contrary**, there is **strong association** of certain microbial organisms with autoimmune diseases.

  For example, **coxsackie virus B** has been strongly correlated with DM Type 1.

- This has been explained by the tendency of the infecting organism to produce **super antigens.**

  Super antigens are capable of **polyclonal activation** of B cells, and production of large amounts of antibodies of **varying specificities**, some of which may be **self-reactive**.

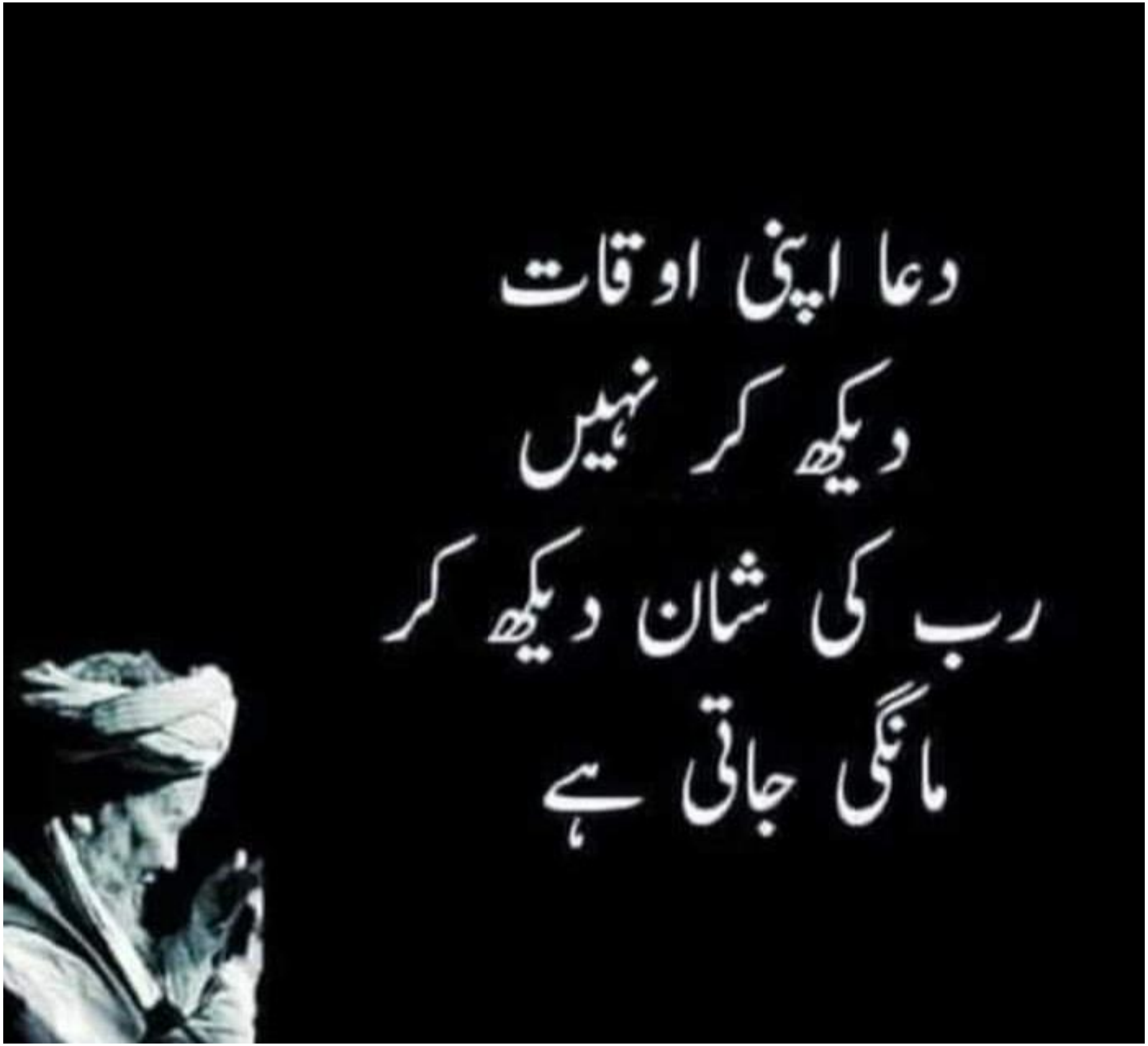
Effect of drugs

- Certain **chemical agents** and **drugs** can also be associated with autoimmune conditions, or conditions that simulate autoimmune diseases.

- The most striking of these conditions is the **drug-induced lupus erythematosus.**

- Usually, **withdrawal** of the offending drug (e.g. chlorpromazine) **cures** the symptoms in a patient.

- Overexposure to **pesticides** and **toxins** may also induce autoimmunity.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Snow festival Harbin, China

Veryovkina Cave Georgia

The deepest cave (2 kilometers) in the world.


Thank You!