

stem cells. Carcinogens and random events that damage DNA, including viral infections and chromosomal translocation, can accumulate into a condition that allows upregulated cell proliferation and cellular transformation. Oncogenes are typically DNA sequences that encode proteins involved in promoting cell growth and proliferation, such as transcription factors, growth factors, or intracellular signalling molecules. Tumour suppressors act naturally as anti-oncogenes or inhibitors of cell growth and proliferation, becoming agents of transformation when they fail to function, such as during DNA repair or in blocking progression through cell cycle checkpoints. When the DNA sequences involved in apoptosis, or programmed cell death, are not functioning properly they can also aid in cellular transformation, encouraging the survival and proliferation of neoplastic cells.

Chronic inflammation and cancer

Chronic inflammation creates a pro tumour microenvironment. Sustained inflammatory responses increase cellular stress signals and can lead to genotoxic stress, increasing mutation rates in cells thus fostering tumorigenesis. The growth factors and cytokines secreted by leukocytes induce cellular proliferation, and during mutation events, nonimmune tumour cells can acquire the ability to respond to these growth stimulators. In this way, immune cells and the factors they produce can sustain and advanced tumour growth. Inflammation is proangiogenic and pro lymphangiogenic, increasing the growth of local vessels. This directs oxygen supplying blood vessels to the site of a solid tumour and aids tumour cell invasion into surrounding tissues via transport through newly constructed lymphatic vessels.

Virus induced cancer

Viruses can introduce oncogenes into the host cell, which were carried within the viral genome, eg. HBV infection which can lead to liver cancer.

Immunosurveillance

The immune system can recognise and destroy transformed cells, this is immunosurveillance. There is an increased incidence of cancer due to inefficiency of immunosurveillance due to; ageing and consequent immunosenescence, primary/inherited immunodeficiency such as that caused by lymphoma, secondary/acquired immunodeficiency such as that caused by several types of cancer, immunosuppression due AIDS, or immunosuppression due to immunosuppressive drug regimens post transplantation.

Tumour infiltrating lymphocytes

Tumour infiltrating lymphocytes (TILs) have been isolated from peripheral blood, lymph nodes and solid tumours of patients with cancer. In one multicenter study, the TILs from patients with metastatic melanoma were collected and expanded in the presence of IL-2 in vitro to overcome their anergic state. Following lymphodepleting treatments designed to create a niche for new cells to take hold, patients were infused with large numbers of these activated, autologous TILs. half the patients saw significant tumour regression, with 10% of the patients experiencing remission. However, half the patients showed little or no response. This divergent response could be influenced by an abundance of Treg cells in non-responding patients.

Therapeutic cancer vaccines are designed to redirect or enhance the anticancer response and use strategies like infusion of autologous dendritic cells with tumour antigens, in vitro stimulation and expansion of autologous cells, or presentation of hidden tumour neoantigens to the immune system. Sipuleucel T is a prostate cancer vaccine. Autologous dendritic cells are isolated from a patient's bloods and cultured with a fusion protein consisting of the prostate cancer specific antigen, PAP, and the APC activating cytokine, GM-CSF. Dendritic cells take up and process the antigens, after which they are infused into the patient in order to stimulate a T cell response against PAP expressed on tumour cells in the prostate. Other anti cancer vaccine strategies under development are exploring the possibility that occult tumour specific antigens (neoantigens) can be exposed and exploited. Neoantigens are unique epitopes that arise from mutations to DNA that generate non-self proteins which are not subject to immune tolerance. These neoantigens are thus unique to each individual and also highly specific to malignant cells.

Novel immune cell mediated therapies include; dendritic cell vaccines composed of ex vivo generated dendritic cells loaded with tumour specific antigens can be reinfused into cancer patients to incite a targeted T cell response; pro-inflammatory cytokine therapy can be used to reverse NK cell anergy in MHC deficient tumours; genetically engineered CAR-NK cells which may be a safer alternative to CAR-T cell therapy. Data generated from high throughput techniques have made bioinformatics a necessity in cancer research. The value of biomarkers and stromal gene signatures in predicting treatment response is well established and new approaches are developed every year. The commensal gut microbiota plays an important role in stimulating the host immune system. Researchers are characterising the patient gut microbiome to link composition to tumorigenic potential as well as to patients response to anti PD-1 immunotherapy.

Another form of cancer immunotherapy involves the utilization of immune sensitizing agents. For example, inhibitors of YY1 were shown to increase sensitization of human prostate carcinoma cells to chemotherapeutic drugs and to FasL and TRAIL-mediated apoptosis. Other small molecule inhibitors inhibit anti apoptotic pathway protein such as Bcl-2 family members. Other methods target the upregulation of tumour suppressors that exert suppressive activity on a wide range of protumorigenic molecules. Some drugs such as ReACp53 block p53 inhibition and restore its tumour suppressor activity.

Transfusion science

Blood group

A blood group is an inherited character of the red cell surface detected by a specific alloantibody. An alloantibody is an antibody formed to foreign antigens, but within the same species. Most blood groups are organised into blood group systems, each system represents a single gene or a cluster of two or more closely linked homologous genes. Of the 347 blood groups specificities recognised by the international society for blood group transfusion, 303 belong to one of 36 systems. Most blood group antigens are proteins or glycoproteins, with the blood group specificity determined primarily by the amino acid sequence. Some blood group antigens, including those of the ABO, P1PK, Lewis, H and I

haemoglobinuria, and hemosiderinuria, positive direct antiglobulin test within a few days of transfusion until incompatible cells are eliminated; and detection of antibody.

Haemovigilance

The goal of haemovigilance movement is to improve patient and donor safety and transfusion outcomes. Haemovigilance is a set of surveillance procedures covering the entire transfusion chain (from donation of blood and its components to the follow-up of recipients of transfusions), intended to collect and assess information on unexpected or undesirable effects resulting from the donation of blood and the therapeutic use of labile blood products, and to prevent the occurrence or recurrence of such incidents. Human error is the greatest potential risk associated with blood transfusion in the UK. serious hazards of transfusions (SHOT) is the UK independent, professionally led haemovigilance scheme. SHOT collects and analyses anonymised information on adverse events and reactions in blood transfusion from all healthcare organisations that are involved in the transfusion of blood and blood components in the UK. where risks and problems are identified, SHOT produces recommendations to improve patient safety. SHOT also monitors the effect of the implementations of its recommendations. The blood safety and quality regulations govern operation of blood establishments (establishments which collect, process and test human blood and blood products) and hospitals blood banks (hospital units which store, distribute and perform compatibility tests on blood and blood components for use in hospitals) the regulations include traceability requirements and notification of adverse reactions and events. The medicines and healthcare regulatory agency is a statutory body that determines laboratory and hospital conformance to the blood safety and quality regulations. Human errors which can lead to HTR include; blood sample drawn from the wrong patient, patient details recorded incorrectly on the sample request form, the incorrect unit is collected from the blood refrigerator, or incorrectly performed formal checks when administering blood. Transfusion of incorrect blood components is the most common cause of transfusion adverse effects.

Hypersensitivities

Hypersensitivity is an exaggerated immune response that causes damage to the individual. Immediate hypersensitivity reactions result in symptoms that manifest themselves within very short time periods after the immune stimulus. Immediate hypersensitivity reactions result from antibody-antigen reactions. Delayed-type hypersensitivity (DTH) reactions take 1-3 days to manifest themselves, and are caused by T-cell reactions.

Type I hypersensitivity reactions mediated allergy and atopy (genetic tendency to develop allergic diseases). Type I hypersensitivity reactions are mediated by IgE antibodies that bind to mast cells or basophils. The foreign antigen induces cross-linking of IgE bound to mast cells and basophils, inducing the release of vasoactive mediators. These reactions include the most common responses to respiratory allergens such as pollen and dust mites, and to food allergens, such as peanuts and shellfish. Typical manifestations of type I reactions include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, food allergies, and eczema.

Food allergens are a common type of atopy. The most common food allergens for children are found in cow's milk, egg, peanuts, tree nuts, soy, wheat, fish, and shellfish. Among adults, nuts, fish, and shellfish are the predominant culprits. Most major food allergens are water soluble glycoproteins that are relatively stable to heat, acid, and proteases and therefore, are digested slowly. Some food allergens are capable of acting directly as adjuvants and promoting a Th2 response and IgE production in susceptible individuals. Allergen cross-linking of IgE on mast cells along the upper or lower gastrointestinal tract can induce localized smooth muscle contraction and vasodilation, resulting in such symptoms as; nausea, abdominal pain, vomiting, and/or diarrhoea. Some individuals also have oral hypersensitivity, leading to tingling and angioedema of the lips, palate, and throat. Some individuals may develop hives when a food allergen is carried to sensitized mast cells in the skin. Basophils play a role in acute food allergy symptoms.

Asthma is an example of a localized hypersensitivity reaction. Allergic asthma is triggered by activation and degranulation of mast cells, with subsequent release of inflammatory mediators, contraction of the bronchial smooth muscles, mucus secretion, and swelling of the tissues surrounding the airway all contribute to bronchoconstriction and airway obstruction. With chronic asthma, over time more serious changes occur in the airway passages, including damage to the epithelial layers, thickened basement membrane, increases in mucus-producing cells and accumulation of inflammatory cells (neutrophils, eosinophils, mast cells, and lymphocytes). Intrinsic asthma is induced by exercise or cold, independently of allergen stimulation.

The most common localized hypersensitivity reaction is allergic rhinitis or hay fever, symptoms results from the inhalation of common airborne allergens (pollens, dust, animal dander, mold spores, which are recognized by IgE antibodies bound to sensitized mast cells in the conjunctiva and nasal mucosa). Allergen cross-linking of the receptor bound to IgE induces the release of histamine and other mediators from tissue mast cells, which then cause vasodilation, increased capillary permeability, and production of secretions in the eyes, nasal passages, and respiratory tract. Tearing, runny nose, sneezing, and coughing are symptoms. Allergic rhinitis affects 15-50% of the global population. The prevalence of allergic rhinitis is increasing due to; increasing airborne pollutants, rising dust mite populations, poor ventilation in buildings, increased time spent indoors, dietary factors changes in gut indigenous microflora, and increasingly sedentary lifestyles. Allergic rhinitis is associated with asthma. Family history of atopy is associated with progression of either allergic rhinitis or asthma to allergic rhinitis and asthma.

Atopic dermatitis (allergic eczema) is an allergic inflammatory disease of skin. Atopic dermatitis is frequently associated with a family of atopy. It is observed most frequently in young children, often developed during infancy. Serum IgE levels are usually elevated. The affected individual develops rash, erythematous skin eruptions that can fill with pus if there is an accompanying bacterial infection, the skin lesions contain Th2 cells and an increased number of eosinophils.

complex hypersensitivity reactions and can be induced by insect bites, as well as by inhalation of fungal or animal protein in individuals with antibodies to those antigens. Deposition of immune complexes in blood vessels can cause local and sometimes severe inflammation of blood vessels in the skin and other tissues.

Type IV hypersensitivity

Type IV hypersensitivity, commonly referred to as delayed type hypersensitivity, is the only hypersensitivity category that is purely cell mediated rather than antibody mediated. The hallmarks of a type IV reaction are its initiation by T cells, the delay required for the reaction to develop, and the recruitment of macrophages as the primary cellular component of the infiltrate that surrounds the site of inflammation.

The presence of a type III reaction can be measured experimentally by injecting antigen intradermally into an animal and observing whether a characteristic skin lesion develops days later at the injection site. A positive skin test reaction indicates that the individual has a population of sensitized Th1 cells specific for the test antigen. For example, to determine whether an individual has been exposed to M.tuberculosis, purified protein derivative from the cell wall of this mycobacterium is injected intradermally. Development of a red, slightly swollen, firm lesion at the site between 48 and 72 hours later indicates previous exposure.

Contact dermatitis is a type IV hypersensitivity response. Contact dermatitis occurs when a reactive chemical compound contacts the skin and binds chemically to skin proteins. Peptides with the modified amino acid residues are presented to T cells in the context of appropriate MHC antigens. The reactive chemical may be a pharmaceutical, a component of a cosmetic or a hair dye, an industrial chemical such as formaldehyde or turpentine, an artificial hapten such as fluorochromes, benzene, a metal ion such as nickel, or the active compound from poison ivy, poison oak, and related plants. A good example is the contact dermatitis induced by the toxins found in plants in the genus Toxicodendron including poison ivy and poison oak. The toxins, a family of related alkyl catechols, are known collectively as urushiol. Urushiol activates DTH-inducing Th1 cells, CD8+ cells, and Th17 cells. After oxidation in the body, urushiol binds covalently to skin proteins, which can be taken up by skin dendritic cells and carried to the draining lymph nodes, where they can be degraded into peptides, presented bound to MHC class II proteins, and induce the formation of Th1 cells. These sensitized effector cells can go back to the skin and release chemokines that recruit leukocytes to the site and cytokines, such as IFN-gamma and TNF-alpha, that activate macrophages to release inflammatory cytokines, lytic enzymes, and reactive oxygen species that cause tissue damage. Urushiol can also enter cells where it can bind to cytoplasmic proteins that may be degraded into peptides that enter the endoplasmic reticulum and bind to MHC class I. CD8+ T cells can be activated by the modified peptides bound to MHC class I and form effector cytotoxic T lymphocytes, which in the skin can be activated by skin cells expressing MHC class I with the urushiol-bound peptides to either kill those skin cells or release cytokines including IFN-gamma, a major macrophage activator. Th17 cells generate DTH responses to urushiol. Human CD1a expressed by skin langerhans dendritic cells binds urushiol and that complex activates Th17 cells. These T cells secrete proinflammatory cytokines IL-17 and IL-22, which recruit and activate neutrophils and macrophages which release inflammatory and tissue damaging mediators.

associated with regulatory T cells, which are generated both during central and peripheral tolerance.

Genetic factors and autoimmunity

Particular class I and II alleles or mutations are commonly associated with particular autoimmune disease, due to the role of MHC molecules in determining what fragments of antigens will be presented to T cells. However, two individuals can have exactly the same set of MHC alleles (monozygotic twins) and still be discordant for the development of autoimmune disease. This means that while genetics may predispose us to autoimmune susceptibility, one or more factors in the environment must still pull the trigger. The strongest association between HLA allele and autoimmunity is seen in ankylosing spondylitis (AS). AS is an inflammatory disease of vertebral joints, which is associated with expression of the allele HLA-B27. Other non-MHC immune genes are also associated with autoimmune disease. Inactivating mutations in two genes involved in establishing and maintaining tolerance, AIRE and FoxP3, have strong associations with systemic autoimmune diseases. Genes may have cumulative effects on susceptibility to autoimmune diseases. In some cases, a single gene can heighten susceptibility to multiple different disorders, for example a mutant form of PTPN22 has been linked to T1D, RA, and SLE. Genes for; cytokines and their receptors, antigen processing and presentation, C-type lectin receptors, signaling pathways, adhesion molecules, and co stimulatory or inhibitory receptors, have all been linked to specific autoimmune disease.

Environmental factors and autoimmunity

Autoimmune syndromes are more common in certain geographic locations or in particular climates. This suggests a link between environmental and/or lifestyle factors, and the development of autoimmune diseases. Environmental factors contributing to autoimmune susceptibility include obesity, smoking, infection, diet, and mucosa flora. Certain gut microbes or their secreted products make contact with immune cells in the intestinal mucosa and elsewhere on body surfaces, and regulate peripheral tolerance and suppress induction of autoimmunity. For example, tissue pathology following infection may result in the release of sequestered self antigens that are presented in a way that fosters immune activation rather than tolerance induction, or the molecular structure of certain microbes may share chemical features with self components resulting in the activation of immune cells with cross-reactive potential.

Th17 cells may be an important driver of multiple autoimmune diseases.

Causes of autoimmunity

Factors that may account for sex differences in autoimmune susceptibility, preferentially affecting women, include; hormonal differences between the sexes, differences between the sexes in terms of microflora, plus the impact of conception and pregnancy. The microbiome has a role in systemic immunity. Random (stochastic) events also contribute to autoimmunity. Exposure to carcinogens or infectious agents that favor DNA damage or polyclonal activation can interfere with regulation of self-reactive T and B cells and/or lead to the expansion and survival of rare T or B cell clones with autoimmune potential. Acquired mutations in genes that could favor expansion include those encoding antigen receptors,