Immune System

- Lymphocytes can secrete thyrotropin, growth hormone, and prolactin.
- Interferons interfere with viral replication (anti-viral, antineoplastic, anti-bacterial). Produced by leukocytes, T-lymphocytes, fibroblasts, and macrophages. They enhance natural killer cell activity, and activate macrophages.
- Immune suppression in Leukocytes = decreased proliferation, decreased ability to lyse other cells, and decreased release of cytokines.
- androgens (ie.testosterone) suppress B-cell (lymphocytes) function and macrophages.
- Natural Killer Cells = CD16, CD56
- immune cells use glut-1 with exercise training
- the increae in glut-1 is accompanied by and increase in immune cell function
- exercise decreases beta receptors on immune cells, thus decreasing adrenal hormone induced downregulation
- glucocorticoids can cause osteoperosis
- unloading causes and increase in glucocorticoid receptor density in osteoblasts and decreases IGF binding proteins in osteoblasts
- ventral medial nucleus of the hypothalamus decreases immune cell activity by sympathetic nerves (norepinephrine) that enter the spleen.....lymphocyte activity can be decreased by norepinephrine
- Immune cells have beta adrenergic receptors on their cell surface. Activation of the receptors leads to production of cAMP which is an inhibitory signal for immune system cells.
- lymphocytes egres from blood into lymphoid tissues...requires the interaction of adhesion molecules on lymphocytes with corresponding counter-receptor molecules on endothelial cells. Post cappillary venules in lymphoid tissues are lined with specialized endothelial cells which allow lymphocytes to bind and migrate into the tissue.
- at local inflammatory sites, endothelial cells are induced by pro-inflammatory cytokines (TNF, IL-1, etc) to express increased levels of adhesion molecules. Catecholimines can alter lymphocyte-endothelial cells interaction by reducing adhesion.

immune system cells

- produce neurotrophins
- production induced by exercise.....BDNF, p75NTR, Bcl-xL, hsp90, hsp27
- humoral factors and metabolic products modulate and regulate
    --- endocannabinoids....group of bioactive lipids serve as secondary modulators
    --- increase or decrease immune functions

Immune Cell Adhesion

- selectins and integrins are necessary for initial tethering, and endothelial migration of lymphocytes
- inducible cell surface glycoproteins =
    --- Interacellular Adhesion Molecule-1 [ICAM-1]
    --- Vascular Cell Adhesion Molecule-1 [VCAM-1]
- IL-1beta activates VCAM-1 production
- Gamma Interferon causes ICAM-1 production
- Gamma Interferon induces T-cell adhesion
- exhaustive exercise increases integrin receptors on granulocytes to help them adhere to endothelial cells to facilitate tissue infiltration
- oxidants induce adherence of leukocytes to endothelial cells
- antioxidants down-regulate inducible cell adhesion molecule expression as well as cell-cell adhesion
- vitamin C prevents leukocyte adhesion to platelets

immunoglobulins

- intravenous immunoglobulin (IVIg) is successfully used in the treatment of autoimmune diseases involving self-reactive CD8+ T cells.

B Cells

- during inflammation they cause restriction of transendothelial migration of T cells in during inflammation
    -- process is compromised in autoimmunity
- during inflammation and in response to adiponectin, B cells tonically inhibit T cell trafficking by secreting
    -- produce peptide called PEPITEM.....derived from 14.3.3 zeta delta protein
- binds cadherin-15 on endothelial cells, promoting synthesis and release of sphingosine-1 phosphate, which inhibits trafficking of T cells

T Cells

- T lymphocytes kill cells by way of FasL-Fas interactions
- can produce VEGF
- have receptors for LDL and oxidized LDL [NK, macrophages, lymphocytes]
    --- 5-HT1A-mediates promotion of cell survival and proliferation T and B lymphocytes through nuclear NF-B production
- T cells can find tumors expressing antigens even in deep tissue beds
- memory can be generated, stimulating antigen specific T-cells causing destruction of tumors that bear those antigens if the tumors re-occur

- 2 ways of stimulating tumor specific immunity.....a cancer vaccine, or infusion of T-cells pre-exposed to tumor antigen
- lower naïve T cell numbers associated with low thymus function
- lower naïve T cell numbers associated with advanced age in the elderly
- sjTREC….a marker of T cell proliferation
- elderly have reduction in CD8 naïve T cell number
- elderly preferentially have CD4 thymocyte production in thymus
- T cells with increased self-reactivity and marked by high expression of the negative regulator CD5 differ in gene-expression patterns and are poised for greater bursts of proliferation when they encounter foreign antigens.
- tumour-associated antigen -specific cytotoxic T lymphocyte
- CD4+ CD25+ FoxP3+ T cells referred to as T regulatory [Treg] cells = natural T regulatory (nTreg) cells
- induced Treg (iTreg) cells
    --- another class of CD4+ Treg cells involved in regulatory function in the periphery
- peripherally induced Treg (pTreg) cells
- protein kinase C [PKC] needed to activate and proliferate T lymphocytes
- nitric oxide synthase can activate or inhibit apoptosis
-- aerobic glycolysis regulates T cell function
    -- primary cancer alters T cell glycolytic metabolism and affects tumor immunity in cancer patients
    -- ovarian cancers imposed glucose restriction on T cells and dampened their function
        ----- via maintaining high expression of microRNAs miR-101 and miR-26a
        ----- which constrained expression of the methyltransferase EZH2
        ----- EZH2 activated the Notch pathway by suppressing Notch repressors Numb and Fbxw7 via trimethylation of histone H3 at Lys27
        ----- consequently, stimulated T cell polyfunctional cytokine expression and promoted their survival via Bcl-2 signaling
        ----- small hairpin RNA–mediated knockdown of human EZH2 in T cells elicited poor antitumor immunity
        ----- EZH2+CD8+ T cells were associated with improved survival in patients

T-cell classification
- cytotoxic CD8 [directly kill cells expressing antigen, or cytokine producing CD4 T-cells]
- CD4 T-helper [Th]...can induce or inhibit CD8 cells
- Th-1...produce type 1 cytokines such as interferons [ie. gamma interferon], stimulates CD8 cells
- Th-2...produce type 2 cytokines such as interluekins, inhibit antigen presenting cells, stimulates eosinophils and granulocytes
- newly discoveredTh-17 produces IL-17....causes tissue inflammation in autoimmunity

CD4 T-Cells
pool is maintained by division of mature cells, rather than by stem cell diferentiation in the thymus/bone marrow. Thus, HIV infection is able to affect the main source of CD4 production. Immune system cells have receptors for neurotrophins which have proliferating effects (explains the decreased immune function and control that comes with decreased neurotrophins “with age”.
- have melatonin receptors
- attack bacteria/virus in vagina and cervix
--- CD4+ Leu8+ cause production of CD4+ Leu8[negative] & CD8+ Leu + cells…then the CD8+ Leu8+ cells cause production of CD8+ Leu[negative] cells.
--- CD4+2H4+ T cells are responsible for production of CD8+ suppressor T cells
--- CD4+4B4+ T cells…..”true” helper/inducer cells
--- CD25 is the IL-2 receptor alpha chain
--- Foxp3 suppresses the secretion of cytokines by activated CD4+ T cells

T-regulatory cells
- IL-2 Is required for proliferation of regulatory T cells
- CD4 regulatory cells
    - produce IL-4, inhibits differentiation of naïve T-helper cells
    - express CD25 receptors = receptors for IL-2, TNF
- CD25 CD4 comprise 5 – 10% of peripheral CD4 cells
    - can suppress both T helper cells one and two
    - IL-2 is required for development of CD25 CD4 cells
- accumulate in dermis
- suppression causes auto-immune disease
- stress can cause suppression via glucocoticoid receptors
    - GITR [glucocoticoid induced receptor-related protein]
    - reduces their activity in suppressing other immune cells
    - may be a mechanism of acne
- CD4 FOXP3
    - T regulatory cell....[Treg]
    - inhibits development of adaptive T-cell response against self-molecules via immuno-suppressive cytokines [ie. IL-10] or via direct inhibition of antigen presenting cells

CD4 helper cells
-- target cancer cells

-- antigens they recognize on tumor cells
-- peptides encoded by mutated genes in human melanoma
--- TH1 = cell mediated immunity…..TH2 = humoral immunity, antibody production
--- overtraining may cause upregulation of TH2, and suppression of TH1.
- T1 cells… regulates asthma, allergies, skin issues
- cell surface ligand Tim-3 on T1, not T2 cells
- Tim 3 [similar to an immune-globulin] binding to Tim-3 ligand inhibits T1 function
- Th-1 facilitates cell mediated immunity
-- T helper 1 (Th1)……..cellular
-- Th1 cells releasing mainly interferon- (IFN-), aside from other cytokines including interleukin-2 (IL-2) and tumor necrosis factor- (TNF-), become activated in response to intracellular viral and bacterial challenges and support various cellular (type 1) responses, including macrophage activation and antigen presentation.
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- T2 cells… inhibit autoimmunity
-- T helper 2 (Th2)……..humoral
- Th-2 produces cytokines necessary for antibody production
-- Th2 immunity, IL-4 as well as IL-5, IL-10, and IL-13, tend to drive humoral (type 2) defense via stimulating mast cells, eosinophils and B cells against extracellular pathogens.
stimulate various aspects of humoral defense, such as a B cell switch to the production of IgG1 and IgE, and, thereby, these cytokines are known to be involved also in some forms of allergic responses
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CD8 T-Cells
- suppress immune system functioning
- meditation decreases their number following strenuous exercise
- toxic function…….produces
-- gamma interferon
-- TNF-alpha
-- lymphotoxin
- controlled by CD4 cells
- turns off response by CD4's by down regulation of CD4's and by causing decreased production of IgE
--- Supressive Factor [SF] stimulates suppressor CD8 cells.

Natural Killer Cells
- NKtolerant
- NKcytotoxic
- NKregulatory
- divided into different subsets based on expression of the surface markers
-- CD27
-- CD11b
-- CD27+
- Inhibitory NK Cell receptor [iNKR]…….cell surface receptor on CD8 T-cells
- expressed in greater number during HIV infection
- there are more than 30 natural killer cell receptors [NKR's], the inhibitory ones interfere with T-cell activation
- iNKR's may raise the threshold of T-cell activation….protecting against autoimmunity, turn off primary immune response
-- NK cells are abundant cytokine producers
-- numerically in the minority in human peripheral blood
-- large population of NK cells in cord blood, spleen, tonsil and decidua tissues
-- Type I and type II NKT cell subsets recognize different lipid antigens presented by CD1d, an MHC class-I-like molecule
-- Most type I NKT cells express a semi-invariant T-cell receptor (TCR)
-- major subset of type II NKT cells reactive to a self antigen sulphatide use an oligoclonal TCR.
-- TCR-α dominates CD1d-lipid recognition by type I NKT cells
-- TCR-α and TCR-β contribute equally to CD1d-lipid recognition by type II NKT cells.
-- type I NKT cells can promote pathogenic and regulatory responses, they are more frequently pathogenic
-- type II NKT cells are predominantly inhibitory and protective from such responses and diseases.
-- profound suppression of NK cell cytotoxicity by glucocorticoids
-- endogenous or exogenous elevated corticosterone levels can suppress NK cell cytotoxicity levels
----- prolonged exposure to stress
-- NK-suppressing impact of epinephrine
- Defined by the absence of T cell receptor/CD3 complex and presence of CD56 and/or CD16 on their surface.

- Natural Killer Cells = CD16, CD56
- NK cells are commonly defined by the expression of a CD3- CD56+ surface phenotype

- cAMP in NK cells is artificially elevated by caffeine….is a potent inhibitor of NK cytolytic function…glucose decreases cAMP
- in normal situations, cAMP is a “turn off” signal to NK cells, so they can stop lysis, replenish their lysing chemicals, and reset their receptors
- NK cells can kill virally infected cells and antibody coated cells
- Are the earliest, and possibly the primary tumor defence
- Responsible for limiting the spread of blood born metastases
- They are able to lyse cells without prior sensitization
- Necrosis is mediated by perforin, found in cytotoxic granules, which primarily causes membrane damage
- activated by IL-2, IL-12, IL-15

NK cells express inhibitory and stimulatory receptors that regulate cytotoxicity and cytokine secretion.

A second family of receptors includes „killer immunoglobulin-like receptors‰ or KIR. KIR isoforms have 2 or 3 immunoglobulin-like domains (called 2D or 3D, respectively). KIR expression is genetically determined, and KIR molecules may be either stimulatory or inhibitory

he cytotoxic activity of NK cells is thought to be determined by a balance between stimulatory and inhibitory signals, with activation of NK cells occurring when stimulatory signals exceed inhibitory signals

Inhibitory KIR have also been shown to impair NK cell adhesion to target cells, thereby allowing NK cells to release from cells expressing „self‰ major histocompatibility complex (MHC) class I ligands. This frees them to attach to more appropriate targets and protects normal cells from NK killing

T cells with NK-associated receptors have also been found in higher frequencies among patients with autoimmune diseases and atherosclerotic plaques and chronic infections

Inhibitory KIR have been shown to inhibit the activation of tumor-specific CTL, thus impairing T-cell function, including cytolytic activity and cytokine production

On both T and NK cells, inhibitory receptors generally outnumber stimulatory receptors

--- KIR and CD94/NKG2 receptors may be part of regulatory pathways by which stress effects on lymphocytes are mediated. Expression of both families of NK-associated receptors is more likely to be inhibitory than stimulatory
--- Distress was associated with significantly higher percentages of T cells expressing both….NK-associated receptors CD94 and KIR
--- individuals with higher levels of distress would have higher percentages of both KIR and CD94 receptors
--- distress was associated with significantly lower percentages of NK cells bearing KIR receptors.

Dendritic Cells

- located at pathogen entry sites into the body
    1. take up antigen
    2. moves in lymph vessels to lymph nodes
    3. activates helper and cytotoxic T-cells, interacts with B cells
- blood dendritic precursor cells = CD11c…….differentiates into peripheral epithelial or non epithelial CD1a
- stimulation of differentiation
    - products from the pathogen
    - mechanical stress
    - pro-inflammatory stimuli
- have ability to produce large amounts of alpha-interferon
-- DCs display peptide antigens for the initiation of immune responses
-- DCs are capable of shutting lymphocytes off
--- involves DC cell attachment to inhibitory receptors PD-1 and CTLA-4 on T cells
    --- resting dendritic cells (DCs) are thought to mediate self-tolerance
    --- activated DCs can break tolerance to self
    --- inflammatory mediators….generated DCs that supported CD4+ T cell expansion…..failed to direct T helper cell expansion
    ---pathogen components resulted in fully activated DCs that promoted T helper expansion
-- DCs can be immunogenic or tolerogenic depending on the context

CD40

- glycoprotein, antigen on surface of B-lymphocytes, macrophages.
- in brain, expressed by microglia in lesions of multiple sclerosis (and a variety of brain insults, including Alzheimers).
- up-regulated by gamma interferon [microglia production of it]

Neutrophils
Neutrophil granulocytes are primary defense cells. The are for killing of invading organisms by the liberation of reactive oxygen species (ROS) and microbial damage by enzymes liberated into the phagosome. Through this mechanism in early inflamation, ROS may contribute to wound healing. ROS are also known to activate nuclear factor-kB, the transcription factor in the cytosol that controls transcription of cytokine genes including interlukin-2 and TNFa. TNFa promotes angiogenesis, a process critical to wound healing.
- capable of inducing considerable injury to tissue by releasing ROS and cytotoxic proteins
- number increases during and after exercise for several hours
- have greater numbers after eccentric than concentric exercise

Macrophages
- monocytes differentiate into macrophages
- can produce ROS and cytotoxic proteins, as well as a large assortment of enzymes capable of degrading and remodeling
- responsible for resorption of neutrophils in necrotic tissue
- have cell surface expression of Major Histocompatability Complex (MHC) class II molecules (mechanism of cell adhesion)
- degree of immune responsiveness is proportional to the % of MHC class II molecules on the cell surface
- n-3 fatty acids suppress expression of MHC class II molecules
- prostaglandin E2 (PGE2) is released due to muscle damage
    - causes increased sensitivity of pain receptors
    - macrophages can synthesize PGE2
    - neutrophils can provide essential products for synthesis of prostaglandins
    - during tissue repair, fibrinogen is converted to fibrin which activates prostaglandins
- cortisol can impair macrophage function
- 2 subpopulations of macrophages…….ED1….infiltrate muscles within 12 hours postdamage…remove damaged tissue and generate cytokines…….ED2…..invade within 24 – 48 hours postdamage…..stimulate satillite cell activation
--- Liver X receptor [LXR]…….essential for moving cholesterol out of macrophages
--- macrophages sense pathogens through their……Toll-like receptors [TLR's]
    -- TLR3
    -- TLR4
--- TLR3 and TLR4 inhibit LXR gene expression…….and can thus inhibit cholesterol efflux….causing foam cell formation

Mesenchmal cells
--- bone marrow derived fibroblast cells
--- differentiation into adipocytes, osteoblasts, chondrocytes
--- can expand mesenchmal stem cells and infuse back into someone
--- can get them from a donor without rejection or side effects
--- mesenchmal cells important for growth factors related to blood cell prodution
--- can be immunosuppressive, via direct inhibition of T cell proliferation
--- can achieve long lasting immunosuppressive effect via 3rd party donors of mesenchmal cells

Lymphoid cells
-- population of innate lymphoid cells in the tumor microenvironment.....
    --- limits T cell expansion and cytokine production
    --- associates with early recurrence in patients with cancer
-- depletion of this regulatory immunosuppressive cell population overcomes this effect

Lymphocyte cell adhesion
- Selectins, Integrins are used as a tether to migrate into tissues
- Intra-cellular Adhesion Molecule 1 [ICAM-1]….Vacular Adhesion Molecule [VCAM-1]
    --- inducible cell surface glycoproteins
- interleukin-1beta causes VCAM-1 production
- gamma interferon causes ICAM-1 production
- abnormal sequestration [inability to migrate] of lymphocytes is a cause of auto-immune disease
- redox imbalances affect cell adhesion molecule production
    --- oxidants stimulate adhesion molecule production
    --- anti-oxidants inhibit adhesion molecule production
    --- mechanism by which Vit C, Vit E, etc can inhibit platelet aggregation
    --- bioflavanoids inhibit gamma interferon induced T cell adhesion
- exercise stimulates integrin production
    --- degree of production affected by duration and intensity
- exercise causes increased adhesion of granulocytes to endothelial cells
- exercise decreases selectin in peripheral blood lymphocytes, increases in monocytes

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Cytokines
- Cytokines are stimulated by endotoxins, viruses, parasites, and other cytokines.
- Cytokines are small peptides that are immuno-modulators
- 3 main ones elevated post exercise = TNF, IL-1, and IL-6

IL-1
- is the agent linking the immune and central nervous systems.
- It stimulates production of nerve growth factor, induces fever, and elevates body temperature
- IL-1 is primarily a peripheral mediator of immunological responses to infection.
- It's mRNA has been found in neurons and glia cells of the CNS.
- has overlapping functions with TNF
- activates macrophages
- increases leukocyte adhesion
- IL-1 alpha, and IL-1 beta
- IL-1 alpha and beta are increased by UV light……causes production of IL-6……causes production of matrix metalloproteinase-1, and collagenase…….these may lead to loss of interstitial collagen that occurs with photo-aging of skin

IL-2

IL-2 indirectly stimulates TNF production.
Stimulates Lymphokine-activated killer (LAK) activity
--- a glycoprotein that influences central nervous system activity
--- mesocorticolimbic system has emerged as a major central target of IL-2.
--- significantly influences dopamine turnover or release in these brain regions
--- is associated with pathological abnormalities in humans (i.e. schizophrenia, movement disorders, cognitive abnormalities) that are mediated by alterations of mesolimbic activity
--- cognitive deficits and schizophrenic-like behavior are displayed in cancer and AIDS patients receiving IL-2 immunotherapeutically
--- IL-2 promotes survival of hippocampal cells
--- IL-2 modulates the excitability of VTA neurons via NMDA receptor/channel

IL-4
- enhances production of Fibroblast Growth Factor

IL-6
- inhibits release of IL-1 and TNF-alpha, thus contributing to termination of inflammation.
- catecholimines increase IL-6, thus decreasing immune function
--- pro-inflammatory cytokine.
--- plays a role in hematopoiesis
--- enhances T cell activation and B cell immunoglobulin synthesis
--- In nervous tissue, it is involved in early vasculogenesis;
--- important in the activation of astrocytes and microglia, as well as in microglial proliferation, with subsequent gliosis
--- has both neuroprotective and neurotrophic functions
--- Once activated, IL-6 leads to cytokine production and further proliferation ¯ activated microglia (CD11 b/Mac-1+) can also act as antigen presenting cells
--- involved in angiogenesis, re-vascularization, and healing in vivo
- major growth factor for connective tissues
- stimulates collagen production
- produced by fibroblasts
- mechanical loading is a stimulus for IL-6 production
- small level increase in IL-6 seen following intense, prolonged exercise
- IL-6 may down regulate growth factors in muscle leading to muscle atrophy
- small level increase in IL-6 seen in elderly
- small level increase in IL-6 seen in disease
- in brain IL-6 can interfere with growth hormone--IFG-1 axis

IL-10
- produced by T-cells, B-cells, macrophages
- inhibitor of cytokine synthesis
- suppresses T-cell proliferation and IL-2 production
- causes apoptosis of macrophages
- stress induced adrenaline production causes inhibition of NO production in macrophages, which increases IL-10, which causes a decrease in TNF-alpha
--- OX40 ligand (OX40L) completely inhibited the generation of IL-10-producing CD4+ T cells
--- induced by the immunosuppressive drugs dexamethasone and vitamin D3
--- IL-10 receptors
    - IL-10 R1 [specific to IL-10]
    - IL-10 R2 [can receive many cytokines]
- IL-10 receptor genes
    - IL-10 RA = R1 protein
    - IL-10 RB = R2 protein
    - Mutation in IL-10 RB gene causes production of IL-10 R2 proteins that don't work
    - can't turn off inflammation
-- Lactococus lactis produces IL-10 in the intestines
    - may be mechanism by which probiotic supplementation may help in celiac disease

IL-12
- neutrophils and macrophages produce IL-12
- bacteria ae inducers of IL-12 production
- IL-12 stimulates production of gamma-Interferon by T-cells and Natural killer cells
- IL-12 enhances Natural killer cell cytotoxicity
- inhibition of IL-12 causes suppression of Nk cell activity and lymphocyte proliferation
- activates macrophages at tumor sites……can be injected for cancer cell destruction
-- Interleukin-12 (IL-12) has the ability to inhibit keratinocyte apoptosis induced by ultraviolet-B (UVB) irradiation
-- keratinocytes are induced by IL-12 to repair their damaged DNA. "
-- cyclobutane pyrimidine dimers (CPDs) the major type of DNA lesion induced by UVB)…..stopped by IL-12

IL-15
- increases gamma interferon by NK cells
- chemo attractant for T-lymphocytes
-- IL-15-driven NK cells mediate anti-tumor immunity
-- CIS, a member of the suppressor of cytokine signaling family, suppresses the response to IL-15
-- CIS-deficient mice are more resistant to cancer metastasis

IL-17
-- involved in the inflammatory cascade in several immune-mediated and inflammatory diseases
psoriasis, psoriatic arthritis, and ankylosing spondylitis.
-- 5 members of the interleukin-17 family.....interleukin 17A has the most inflammatory effect

IL-31
- produced by T-cells [T helper type 2 cells]
- binds to receptors…IL-31 receptor A, and oncostatin M receptor
- receptors are increased in diseased tissue
- over production IL-31 by T-cells in skin may cause dermatitis and epithelial problems

Granulocyte Colony-Stimulating Factor [G-CSF]
- growth factor, stimulates proliferation of progenitor cells
- improves neutrophil function
- modulates immune cell inflammatory functions…reduces ability to produce pro-inflammatory cytokines
- activates STAT-3 transcription factor

Interferon

-- interferon beta 1a…..affects Tcells……down regulates survivin, causing apoptosis

Tumor Necrosis Factor

soluble TNF Receptor Type 1 = sTNFRT1
sTNFRT1 is shed from the cancer cell surface by proteolytic cleavage…it retains the ability to bind TNF with high affinity, which antagonizes binding to TNF cell surface receptors.
- sTNFRT1 is significantly elevated in cancer patients…high levels correlate with poorer treatment outcomes

TNF directly induces apoptosis
Vascular endothelial cells are induced to apoptosis by TNF, destroying the circulatory network that serves the tumor, thus contributing to tumor cell death.
TNF produced by Lymphokine-activated killer (LAK) and cytotoxic T-Lymphocytes
IL-2 indirectly stimulates TNF production.
Apoptosis can be triggered by TNF-alpha
- activates the transcription factor called NF-kB, which supresses Myo-D [Myo-D is required for muscle function and repair]
- TNF and gamma interferon work in conjunction to reduce Myo-D production…….results in muscle wasting

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Vitamin D & Immune System Cells

--- Vitamin D metabolized in the liver to produce 25(OH)D……calcidiol
--- calcidiol is the main form of circulating vitamin D.
--- calcidiol concentration in the blood provides a good assessment of a person's vitamin D level
--- calcidiol is converted [in the kidneys] to an active hormone, 1,25(OH)2D……calcitriol
--- The main role of calcitriol, is to regulate the amount of calcium and phosphorous in circulation. When calcium levels are low the body

activates the parathyroid gland, which produces PTH (parathyroid hormone). This hormone starts vitamin D hormone production and helps to remove calcium from the bones to be used in more important functions.
--- immune cells carry a receptor for the active hormone of vitamin D….. calcitriol
--- calcitriol causes the production of calcium channels in cells lining the small intestine, so that calcium may be absorbed
--- Cortisol caused a reduction in the number of receptors for 1,25-(OH)2D3 in parathyroid cells. This decrease was accompanied by abolition of the response to 1,25-(OH)2D3. It is proposed that this phenomenon may, in part, explain the reduction in calcium absorption which occurs in man after chronic glucocorticoid treatment.
--- Potent antagonism by glucocorticoids of vitamin D action on specific gene expression has been demonstrated.
--- Adrenalectomy caused an increase in 1,25-(OH)2D3 receptors

Immune-regulating actions for vitamin D hormone

----- Suppresses antibody production by B cells and the proliferation of T cells in the thymus
----- Upregulates cytokines TGF-beta and IL-4 [These act as suppressants of inflammatory T cells]
----- Inhibits production of pro-inflammatory cytokines such as IL-1, IL-2, TNF and IFN gamma
----- Inhibits the production of NO (nitric oxide) by immune cells [NO has been identified as one of the most destructive products of the immune system and is an important factor in demyelination]
----- Exerts immunomodulating effects in the CNS by inducing a profound downregulation of antigen expression by both infiltrating and resident antigen presenting cells (e.g. macrophages)

- zinc deficiency results in…….

--- thymic atrophy
--- decreased thymic hormone activity
--- decreased NK cell activity
--- decreased IL-2 production in cancer, elderly, dialysis patients, etc
--- decreased gamma interferon production
--- increased TNF-alpha production in chron's, rheumatoid arthritis, etc

Glutamine

Glutatmine is an amino acid serving several functions --- nitrogen precursor for synthesis of nucleotides, fuel for gut mucosal cells, and fuel for immune cells (lymphocytes, macrophages, and natural killer cells). Glutamine is primarily produced by muscle. Muscle is the major organ of glutamine release into circulation. Small amounts are produced by lungs, brain, and liver. The majority is stored in muscle, and this represents 60% of the total amino acid pool within muscle. Type I muscle fibers contain 3 times more than type II. Muscle is capable of increasing glutamine synthesis and release in response to increased demand by other tissues. Glucocorticoids increase glutamine release from muscle, increase glutamine synthase activity and mRNA, decreases muscle glutamine stores, and increases glutamine transporter activity in muscle. Muscle uses glutamine synthase to combine glutamate with ammonia to synthesize glutamine. The kidney uses glutaminase to breakdown the glutamine into glutamate and ammonia. Glutamate dehydrogenase breaks down glutamate further into alpha-ketoglutarate. Oxidation of glutamine carbons by kidney yields bicarbonate. Chronic Fatigue Syndrome suffers have decreased glutamine levels. Glutamine is a precursor for GABA and glutamate.
ammonia produced is normally bound to glutamate by the action of glutamine synthatase, thus muscle releases large amounts of glutamine , and only small amounts of ammonia.
Glutamate taken up from the circulation only contributes a small proportion of the glutamate required for glutamine synthesis.
Endurance exercise leads to large decrease of muscle glutamine concentration
In a glycogen depleted state, large reliance on branch chain amino acids (BCAA) for krebs cycle ATP production could drain the krebs cycle BCAA aminotransferase reaction in which 2-oxoglutarate is used as an amino group acceptor, and thus lead to a reduced flux in the krebs cycle and a reduced ability to oxidize blood glucose and fatty acids. This may be a mechanism by which glycogen depletion leads to reduction in performance.
The combination of prior carbo loading and carbo intake during exercise can prevent the activation of the BC complex

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Lymph system

- lymphatic sinuses of draining lymph nodes
  --- soluble lymph-borne antigens enter reticular conduits
  --- lymphocytes transmigrate to the parenchyma
  --- regulates parenchymal entry of lymphocytes and soluble antigens
- prototypic endothelial protein of blood vessels
  --- synthesized in the sinus-lining lymphatic endothelial cells covering the distal conduits
- filtering function of lymphatic sinus endothelium.....dependent on diaphragms formed fibrils in transendothelial channels

Auto-immunity

- Fas - FasL system is essential in immune cells self-tolerance. A defect in the system is major etiology factor for autoimmune disease
-- apoptosis selectively eliminates autoreactive T-cells from the central nervous system
-- an increased autoreactive T-cell population may temporarily overwhelm the central nervous system's protective mechanism
-- altered/impaired function of T-suppressor cells
-- zinc deficiency leads to disorder of T helper cells, and decrease in cytokines IL-2, INTF-gama, TNF-alpha,
-- impairment of leukocyte inhibitory factor
-- T cells that develop immune responses to "self-proteins" are killed or inactivated by one of many "self-tolerance" pathways. Defects in these pathways result in a proliferation of anti-self T cells....autoimmune disease.
- these diseases are marked by increased sympathetic activity....are are associated with dysregulation by autonomic nervous system
- suppressor T-cells may fail to function properly to inactivate other T-cells
- Genes for MHC could be messed up, thus Immune cells would fail to recognize cells as "self" and would attack.
- in hypertensive people....have increased sympathetic tone....the severity of the disease is increased
- arthritis does not present in the joints of a paralyzed limb.....no nerve, no arthritis
- patients have a deminished pain threshold....and have a reduced capacity to deal with stressful situations
- Immune cells have beta adrenergic receptors on their cell surface. Activation of the receptors leads to production of cAMP which is an inhibitory signal for immune system cells. They also downregulate IL2, and decrease it's production. The immune system of subjects with active rhematoid arthritis cannot be controled efficiently by the autonomic nervous system.
- adult patients with rheumatoid arthritis have immune cells with lower than normal beta adrenergic receptors.
- low cAMP can also be due to high activity of cAMP degrading enzyme (CNP-ase).
- mediated by prostaglandins
- prostaglandins are produced by an upregulated cyclooxygenase-2
- IL-1 is produced by a number of different cells in the affected joints (macrophages, synovial fibroblasts, endothelial cells)
- may be due to inflammatory (delayed-type hypersensitivity, DTH)
- DTH responses are dependent on CD4 lymphocyte helper cells and macrophages. Both are in inflammed synovium.
- the macrophages function both as the cell types causing the tissue damage, and when activated, as cells capable of presenting antigen to recruit more T cells.
- there is an increased level of norepinephrine in patients with juvenile rheumatoid athritis
- loss of peripheral tolerance is often driven by innate nucleic-acid sensors
    ——- leads to the activation of autoreactive lymphocytes
- transcription factor….STAT-3 negatively regulates inflammatory response
- 80% of kids that develop atopic dermatitis also develop asthma or allergic rhinitis
- suppressive function and number of regulatory T cells (Treg cells) is reduced in autoimmune disease
- As disease severity increases, Treg cell proliferation progressively decreases and is associated with impaired IL-2 release and IL-2 receptor and mTOR signaling.
- Antigen-driven activation in an inflammatory environment results in downregulation of Foxp3 transcription in Treg cells
- Loss of the transcription factor Foxp3 in Treg cells has been noted in various inflammatory conditions
- stability of antigen-specific Treg cells might be important for the course and control of autoimmunity
- IL-2 stabilizes Foxp3 expression in Treg cells

Asthma

- mediated by T helper cells [Th2]
- Vitamin C, E, intakes are low in asthmatics
- Vitamin C, E levels in lungs of asthmatics is between low…to…non-measurable

Allergic reactions -- IgE attaches to mast cells and basophils , binds w/allergen, triggers release of mediators.
Asthma/allergic reactions -- IgE production and inflammation regulated by T lymphocytes that produce cytokines. 100ug of selenium per day reduced asthma symptoms, by way of lowering oxidant stress from inflammatory response. Asthmatics have depleted glutathione levels from each episode which go uncompensated by intake of exogenous antioxidants and precursors for endogenous antioxidant systems. Thus future episodes are easily precipitated due to decreased immune competence. Asthmatics have lower selenium levels in blood. Where selenium intake is low, asthmatic prevelance is high.

- asthmatics have increased psychopathology and negative emotions than non-asthmatics.
- stress is a common trigger of bronchoconstriction
- stress induced bronchoconstriction occurs in asthmatics bu no non-asthmatics
- lung tissue receives parasympathetic activity via the vagal nerve.
- possible cause of acquired allergies is superantigen induced T-cell downregulation
- decreased symptoms come with decreased leukocytes that have low affinity receptors for IgE
- stimulation of IgE responses by antigens [CD4's produce IgE]
    -- IgE sensitizes mast cells

-- degranulation of mast cells

-- release of vasoactive and bronchoconstritive amines and leucotriens

-- attract inflammatory cells [esinophils, macrophages]

- IL-10…..anti-inflammatory cytokine, inhibits the synthesis of pro-inflammatory cytokines…patients with asthma have decreased production in alveolar macrophages and peripheral blood immune cells
- people with asthma have decreased IL-10 production
- CD4 lymphocytes are involved in the pathogenesis of asthma
- ROS increases inflammation by oxidative damage of lung airway cells…….thus antioxidants can decrease asthma symptoms
- respiratory tract antioxidant capacity is altered in mild, stable asthma
- airway epithelial cells have decreased antioxidant levels during an asthma attack
- eosinophils product IL-5, may cause the late stage asthmatic response affecting inflammation, T-cells can be involved also

-- T-bet, a transcription factor that activates IFN- [small gamma, Greek] in T-helper-1 cells (Th-1)
-- people with asthma have less T-bet in their lungs
-- Prostaglandins are produced during allergic reactions.
  --prostaglandin E receptor EP3
  --Mice lacking EP3 developed allergic inflammation that was much more pronounced than that in wild-type mice
  --Conversely, an EP3-selective agonist suppressed the inflammation.

- IL-4 causes mitochondrial dysfunction in allergic asthma
- vitamin E reduces IL-4
- deficiency of anti-oxidant defenses, characteristic of asthma
- childhood asthma…..a state of fat soluble vitamin deficiency

Arthritis

- B cells are attracted by lipid peroxidation products on self-proteins…this can destroy their tolerance to "self" proteins
- synovial fluid has many T cells [CD4 lymphocytes] and macrophates
- may be a IL-10 problem
- IL-10…..anti-inflammatory cytokine, inhibits the synthesis of pro-inflammatory cytokines
- people with arthritis have decreased IL-10 production
- Rheumatoid arthritis…..T-cell attack on synovial membranes in joints
- 1 in 6 Americans have some form of arthritis
- 2 most common forms = osteo-arthtritis……rheumatoid arthritis

- Inflammation in the joint caused primarily by TNF-alpha (tumor necrosis factor). When this is suppressed, inflammation and symptoms go away eventhough there are several inflammatory substances. Antioxidants can regulate cytokine production by way of NFKB, an oxidative stress sensitive transcription factor that modulates production of several cytokines (IL-1,IL-8, TNF).

Is the most common form of arthritis. Pathological changes of osteoarthritis are seen as the result of active processes, many of which may be reparative rather than destructive.

- correlations = age, female, obescity, joint trauma, women after menopause
- increased bone expression of matrix metalloproteinase enzymes
- changes in subchondral bone occur before cartilage changes are detected.
- apoptosis of chondrocytes

- The articular cartilage and subchondral bone are both involved.
- The major structural protein is collagen type II
- since elimination of lymphocytes depends on apoptosis, all autoimmune disorders can be viewed as primary deficiencies of apoptosis
- Arthritis may be a dysfunction of soluble TNF Receptor Type 1
- TNF in arthritis joints may decrease blood flow to cells of joints by apoptosis of synovial vascular cells.
- Foxp3+ regulatory T (Treg) cells maintain self-tolerance
- inflammatory environment in autoimmune arthritis induces conversion of a subset of Foxp3+ T cells into interleukin-17-producing cells that contribute to pathogenesis
- subset of Treg cells can lose Foxp3 expression and convert into TH17 cells
- these cells are osteoclastogenic and exacerbate arthritis
- Loss of the transcription factor Foxp3 in Treg cells has been noted in various inflammatory conditions

Rheumatoid Arthritis

— there is a metabolic reprogramming in rheumatoid arthritis T cells, from glycolysis to fat utilization
  —-— rewiring of cellular metabolism alters the rheumatoid arthritis T cells
  ——- makes them tissue invasive
  ——- this directly promoting disease-inducing effector functions

Osteo-arthritis

- B cells acquire a proteoglycan [aggrecan] from cartilage
- aggrecsan presented as an antigen
- damage to cells cause antigen production, B cell presents the antigen, attracts CD 4 cells

Multiple Sclerosis

-- Treg cell proliferation is reduced in subjects with relapsing-remitting multiple sclerosis.

Colitis

- may be due to ischemia of the intestines……irritable bowel syndrome

Pain & Immune Cells

analgesia
-- can be mediated by opioid receptors in immune cells
-- activation of leukocyte opioid receptors leads to the secretion of opioid peptides
----- Met-enkephalin
----- β-endorphin
----- dynorphin A
-- act at local neuronal receptors to relieve pain

"In this 16-year longitudinal study of 105 healthy elderly men, we analyzed one aspect of immunosenescence--a decline in the absolute number of peripheral blood lymphocytes--with particular reference to its relationship with subsequent mortality."

"It was found that there was **a significantly lower absolute lymphocyte count (1432 +/- 55/mm3; mean +/- SEM) within three years of death** when compared with five years (1719 +/- 89/mm3) or 10 years (1715 +/- 98/mm3) before death."

B.S.Bender, et
Absolute peripheral blood lymphocyte count and subsequent mortality of elderly men. The Baltimore Longitudinal Study of Aging. Journal Of The American Geriatric Society....Volume 34 #9....page 649 - 654