DOWNLOAD PDF DISORDERS OF THE MONOCYTE MACROPHAGE SYSTEM

Chapter 1 : Central nervous system damage, monocytes and macrophages, and neurological disorders in A

Disorders of the Monocyte Macrophage System Pathophysiological and Clinical Aspects. Editors The Monocyte-Macrophage System In Granulomatous Inflammation.

By the term inflammation we define the response of an organism to noxious endogenous or exogenous stimuli causing tissue injury. Inflammation is a host defence mechanism, which might harm the defending organism. Description The present invention relates to pharmaceutical compositions for the treatment of inflammatory diseases. Endogenous and exogenous noxious agents cause inflammation including infectious diseases. Inflammation is a host defence mechanism, which might eventually harm the defending organism. High levels of these cytokines are seen in severe infectious and various inflammatory disorders. Acute or chronic inflammatory diseases of unknown etiology may be caused by a difficult to isolate infectious agent. One well-known example is the realization that the majority of stomach ulcers are due to infection by the bacterium Helicobacter Pylori. On the other hand, diseases that are usually not associated to inflammation are actually caused by low-grade chronic inflammation. Indeed, arteriosclerosis is a characteristic example. Autoimmune diseases can also cause inflammatory reactions characteristic being the example of the immune complex deposition disease. The pro-inflammatory cytokines IL-1, TNF-alpha, and IL-6, products of stimulated macrophages play a key role in initiating the inflammatory processes. It should be noted that infectious agents might also cause acute or chronic inflammatory diseases of unknown etiology. In the immune system, CRH-R1 receptors have been identified in the spleen and thymus. The recent synthesis of non-peptide receptor antagonists for the CRH-R1 receptor provides a useful tool for a more accurate evaluation of the functional significance of CRH at the tissue level. Interaction Between CRH and Immune Systems CRH affects the immune system directly at the site of an inflammatory reaction, and in an indirect manner via stimulation of cortisol production from the adrenals. CRH is released at the site of the inflammatory response by nerve terminals and epithelial cells directly affecting resident immune cells in the vicinity of inflammation. It should be noted that while the indirect effect of CRH is anti-inflammatory, its direct-paracrine effect is definitely pro-inflammatory. Thus, blockade of its local effect by specific anti-CRH serum, attenuates the inflammatory response in several models of inflammation in vivo. An immune target of CRH is the mast cell. However, in addition to mast cells, many other immune cells exhibits specific CRH binding sites, including mouse splenocytes, human peripheral blood monocytes, lymphocytes, monocytes-macrophages and Th cells. CRH receptors are also present in inflamed synovium and inflamed subcutaneous tissues. The role of CRH has been associated mainly to mast cells, since its administration results in mast-cell degranulation, an effect inhibited by the CRH-R1 receptor antagonist antalarmin. Macrophages are among the initiator cells during an inflammatory response and are the main source of a series of pro-inflammatory cytokines. Activation of macrophages occurs through antigenic signals such as bacterial LPS, which binds on Toll-like Receptor 4 TLR-4 and activates cytokine transcription and secretion by these cells. During both local and systemic inflammation, macrophages are the predominant source of pro-inflammatory cytokines. Indeed, CRH is produced by enterochromaffin cells in human colon while UCN is detectable in both rat stomach and colon. Recently published reports suggest that the CRH family of peptides and their receptors participate in the regulation of GI motility as well as in the GI response to inflammatory processes. Indeed, it is now well established that CRH is present in the colonic mucosa of patients with ulcerative colitis playing a local pro-inflammatory role. In addition, UCN has been identified in macrophages in the lamina propria of human colonic mucosa, participating in the regulation of the local inflammatory response. Indeed, activation of the CRH-R1 receptor results in amplification of colonic propulsive activity whereas activation of the CRH-R2 receptor results in inhibition of gastric emptying rate in,mice and rats. On the other hand, UCN ameliorated the inflammatory response via induction of macrophage apoptosis. Treatment of a RAW We have found that administration of a synthetic CRH-R1 antagonists prior to LPS prolonged survival in a statistically significant

manner. The effect was more evident at the early stages of endotoxin shock. The model of gastritis chosen in this prospective study was that caused by Helicobacter pylori H. Our fresh tissue samples were obtained from gastroscopic biopsies. The design of our study was based on our pilot data showing that the CRH transcript and peptide may not be detectable in normal human gastric mucosa, while UCN may be present and localized to gastric epithelial cells. Our data confirmed our hypothesis indicating that in human stomach UCN is a powerful suppressor of inflammation. Our invention relates to the use of such compounds for the treatment of local and systemic inflammations in humans. Synthetic compounds thus comprise e. In principle any suitable CRH-R1 and CRH-R2 assays known within the art may be used for determining if a candidate synthetic compound is an antagonist or agonist respectively. Assays for biological activity via the CRH-R1 receptor: Assay for biological activity via the CRH-R2 receptor: Urocortin and Urocortin II induce apoptosis on macrophages. This effect is mediated by the CRH-R2 receptor since the specific antagonist sauvagine completely abolishes this effect Tsatsanis et al, submitted. Antalarmin is an example of a synthetic CRH-R1 antagonist. In addition to the active compound s the pharmaceutical compositions may comprise usual exhipients such as diluents, fillers, binders, disintegrants, lubricants, conserving agents, flavourings and colourings. The pharmaceutical compositions may be formulates for any suitable route of administration including oral, parenteral or intraveneous administration. A preferred administration form is injection. The amount of active compound s in the pharmaceutical compositions depends on the actual active compound, the age, weight, and condition of the receiver. It is within the skills of the ordinary practitioner to determine the suitable amounts of a given active compound based on routine experimentations. The amounts to be administered and the frequency and route of administration will depend on the given compound and the actual condition to be treated and will be at the discretion of the attending physician. Inflammatory diseases or disorders to be treated with the pharmaceutical compositions according to the invention includes but are not limited to: If more than one active compound are intended to be used for the treatment of a particular disease, according to the invention, e. In case that a combination of active compounds are formulated in two or more separate pharmaceutical compositions the pharmaceutical compositions may be administrated simultaneously or they may be formulated at different point of times or frequency. The kit may also contain a instruction for the frequency, amount and duration of the administration for the pharmaceutical compositions in the kit. CRH induces expression of all three cytokines and further potentiates the LPS-induced transcriptional activation. Negative control samples are also shown with no reverse transcriptase enzyme noRT , or no DNA template. Immuno-histo-chemical staining for UCN in gastric mucosa from patients with chronic gastritis associated with Helicobacter pylori infection C, D. Human placenta was used as positive control Panels A, B. Positive staining was also observed in the capillaries C and in inflammatory elements scattered of the gastric mucosal stroma S , mostly plasma cells P. In the placental sections, trophoblastic epithelial cells T stained positively for UCN in contrast to the adjacent stroma villii V. Levels of UCN in human gastric mucosa biopsies. Comparison between patients with no gastric inflammation normal and patients diagnosed for gastritis due to Helicobacter pylori infection. Comparison between patients with H. According to pathology findings, the latter was subdivided into responders regression of acute and chronic inflammation and no signs of H. Cells were plated in 25 cm2 flasks one day prior to stimulation. They were kept in our animal facility for at least one week prior to each experiment to allow adjustment and confirmation of their health. Each animal received rodent laboratory chow and water ad libitum. E coli lipopolysaccharide serotype L and Salmonella enteritidis lipopolysaccharide cat. L were purchased from Sigma. Survival of animals was monitored for a period of seven days. The same protocol was used for E. Mice were pre-treated with antalarmin or the diluent 1. The CRH-R1 receptor antagonist Antalarmin alone had no effect in the survival of animals and injection of antalarmin alone was not repeated in the course of the experiments. It should be noted that at 33 cycles all mRNA amplifications were at the exponential phase of amplification as indicated by a standard curve performed for each pair of primers data not shown. Intensity of the bands was quantified using TINAscan software. Primers for actin were: Each experiment was repeated four times. The oligonucleotides were

designed as per the published human sequences for Ucn sense: The size of the amplified product was expected to be bp for Ucn and bp for CRH. Each time point and treatment group was composed of five animals per experiment. Five animals per treatment were used. Quantitative Measurement of Apoptosis Cells were plated in well plates at an initial concentration of 10, cells per well. Cells were washed and analyzed by Flow Cytometry Coulter. Western Blot Analysis Following stimulation cells were harvested and lyzed in The following categories of patients were exclude: Excluded were also patients that were taking any medicine except antacids during the previous month. Following careful exclusion of all the above-mentioned cases, patients that underwent gastroscopy were divided into two groups: The lesions were usually more prominent in gastric antrum. The presence of H. A second gastroscopy was performed two months after eradication treatment, consisting of a double antibiotic day scheme amoxicillin 1 g P. To attain a more representative measurement of immunoreactive urocortin ir-Ucn levels in stomach antrum, samples were collected from antrum lesser and greater curves, front and back wall by endoscopic biopsy forceps. The histological grading of gastritis was based on the Sydney classification and was performed by the same person, not aware of the different groups of patients. The absence of any inflammation was indicated as zero. As normal biopsies, were considered those with absent inflammation and negative for H. Human term placenta was obtained from women undergoing labor at the Obstetrics and Gynecology Department, Heraklion University Hospital.

Chapter 2 : Macrophage - Wikipedia

Gaucher disease is a lipid storage disease characterized by the deposition of glucocerebroside in cells of the macrophage-monocyte system. It was first described by Gaucher in , and the storage of glucocerebroside was first recognized by Epstein in

It has been linked to neurodegenerative disorders as well as primary and metastatic brain tumors. Microglia, the brain-resident immune cells, are emerging as a central player in regulating key pathways in CNS inflammation. Recent insights into neuroinflammation indicate that blood-borne immune cells represent an additional critical cellular component in mediating CNS inflammation. The lack of experimental systems that allow for discrimination between brain-resident and recruited myeloid cells has previously halted functional analysis of microglia and their blood-borne counterparts in brain malignancies. However, recent conceptual and technological advances, such as the generation of lineage tracing models and the identification of cell type-specific markers provide unprecedented opportunities to study the cellular functions of microglia and macrophages by functional interference. In this review, recent developments in evaluating functions of brain-resident and recruited myeloid cells in neurodegenerative disorders and brain cancers will be discussed and unique or shared cellular traits of microglia and macrophages in different CNS disorders will be highlighted. Insight from these studies will shape our understanding of disease- and cell-type-specific effector functions of microglia or macrophages and will open new avenues for therapeutic intervention that target aberrant functions of myeloid cells in CNS pathologies. Introduction The brain has long been regarded as an immunologically privileged site in which the presence of the bloodâ€"brain barrier BBB restricts the entry of blood-borne immune and inflammatory cells to the central nervous system CNS [for review, see Ref. Consequently, key functions in tissue homeostasis and immune defense were attributed to brain-resident cell types, such as microglia or astrocytes 2 , 3. Microglia are regarded as the innate immune cell of the CNS. As part of their routine surveillance, microglia continuously monitor their surrounding with motile protrusions to sense and resolve any disturbance 4. Along with their well-established role as immediate responders to injury and infection 5 , 6 , there has been an increasing appreciation of the importance of microglia for normal CNS development and function, including developmentally regulated neuronal apoptosis, neurogenesis, myelogenesis, and synaptic pruning 7 â€" 9. Given their central role in CNS inflammation, it is not surprising that dysregulation of microglial activation and microglia-induced inflammation is observed in virtually all brain malignancies, including neurodegenerative disorders as well as primary and metastatic brain cancers. Blood-borne immune and inflammatory cells have recently emerged as an important component of the disease-associated microenvironment in the brain and are regarded as critical mediators of progression in neurodegenerative disease and brain cancers. However, the lack of experimental systems that distinguish between recruited and brain-resident myeloid cells has previously halted analysis of cell-type-specific functions in CNS inflammation. The development of new methodologies provides unprecedented opportunities for comprehensive in-depth analyses of the immune landscape of the CNS under steady-state and pathological conditions. Single-cell RNAseq or mass cytometry CyTOF allow for an unbiased view on the immune milieu of the brain parenchyma and adjacent boundaries. In addition to the well-characterized macrophage populations of non-parenchymal areas of the brain 10 , it is increasingly recognized that various immune cell populations including a large diversity of lymphoid and myeloid subpopulations are present in particular in the meninges and the choroid plexus 11 â€" Analysis of parenchymal myeloid cells also revealed high cellular heterogeneity. The existence of distinct myeloid cell phenotypes may reflect functional diversity, different ontological origins, or various cell differentiation states already at steady state The question how environmental cues in different brain malignancies sculpt transcriptional profiles and epigenetic states of microglia and recruited myeloid cell populations during disease progression has recently gained attention. A growing number of studies seek to unravel the heterogeneity of the disease-associated immune landscape to

functionally link different cell states to disease progression. Detailed knowledge of the impact of individual cell populations or activation states across different CNS malignancies is critical for the development of improved therapeutic strategies to target dysfunctional cells without affecting essential physiological or beneficial functions. The aim of this review is to discuss recent insights into the cellular and molecular identity of the heterogeneous population of cerebral myeloid cells in different CNS disorders to highlight common and unique features of the distinct subpopulations in the respective CNS pathologies. However, there was a long-lasting debate on the ontological origin of microglia. An alternative hypothesis proposed that microglia originate from neuro-ectodermal-derived glioblasts This theory was seemingly supported by the findings that donor bone marrow cells failed to contribute to the adult microglia population in either newborn 17 or adult rodents Hickey and Kimura demonstrated that in bone marrow chimera only perivascular microglia derived from the bone marrow The authors used the term perivascular microglia for the cell population that to date is referred to as perivascular macrophages that are located in the Robin-Virchow space. Further evidence that resident microglia are not replaced by cells from the bone marrow was provided by Lassmann et al. The definitive proof for a mesodermal origin of microglia was achieved through a genetic study that showed that mice lacking the crucial transcription factor for myeloid cells, PU. Even after the myeloid origin of microglia was proven, debate about the nature of microglia progenitors remained. Controversy was mainly caused by the fact that there are two major sites of hematopoiesis during embryogenesis: As depicted in Figure 1 , primitive hematopoiesis in mice is initiated in the yolk sac at around E7. Yolk sac-derived primitive macrophages enter the embryo proper after the circulatory system has been established from E8. Population of the fetal brain by primitive macrophages takes place before the onset of monocyte production by the fetal liver and before the establishment of the BBB. In contrast to primitive hematopoiesis, definitive hematopoiesis depends on the transcription factor Myb Around birth, hematopoiesis starts to be restricted to the bone marrow It further remained elusive if under physiological conditions, monocytes contribute to the establishment of the post-natal and adult microglia population. Fate mapping studies using Runx1MerCreMer lineage tracing model, in which exclusively yolk sac-derived progenitors and their progeny are fluorescently labeled following a tamoxifen pulse at E7. It was further demonstrated that microglia develop from erythro-myeloid progenitors EMP in a stepwise PU. The development of microglia and primitive yolk sac macrophages is completely dependent on colony-stimulating factor 1 receptor Csf1r signaling Microglia are absent in Csf1r knock-out mice, while mice lacking functional Csf1 did not show the same severe phenotype 31 , This observation was later explained by the existence of a second ligand for Csf1r, namely IL34 33 that is highly expressed in the brain Microglia represent the only tissue-resident macrophages that are exclusively derived from yolk sac-derived progenitors. By contrast, tissue-resident macrophages in other organs such as Kupffer cells in the liver, alveolar macrophages in the lung, or Langerhans cells in the skin comprise mixed populations and are repopulated by cells originating from the fetal liver during definitive hematopoiesis 27 , In light of recent experimental insight, it became apparent that previous findings that indicated a contribution of blood-borne monocytes to the adult microglia pool were confounded by experimental caveats that conditioned the brain for engraftment of peripheral myeloid cells, such as irradiation or parabiosis bias These findings were further supported by studies using parabiosis in mice without the need for irradiation Moreover, even in the context of inflammation, when monocytes contribute to the inflammatory milieu, blood-borne cells did not integrate into the long-term resident microglia pool The microglia compartment seemed to recover from an internal pool instead. These findings are in line with previous observations demonstrating that peripheral macrophages do not transform and replace microglial cells in EAE models In contrast to these findings, it was shown that under experimental conditions in which the microglial niche is completely vacant in response to microglia depletion strategies, bone marrow-derived cells enter the brain and differentiate into microglia 40 , The authors demonstrated that the repopulating microglia arose exclusively from an internal CNS-resident pool. A contribution of bone marrow-derived cells was only observed in mice that were irradiated and additionally received a bone marrow transfer. Moreover, it was demonstrated that microglia self-renewal is dependent on

IL1 signaling, while reconstitution from bone marrow precursor is IL1 independent. However, until recently the actual turnover rate of microglia in the brain remained elusive. Employing a multicolor fate-mapping model, the microfetti mouse [a microglia-restricted modification of the confetti mouse 44], Tay et al. This study revealed heterogeneous rates of microglia replenishment in different brain regions Following CNS damage, the authors found a shift from a pattern of random self-renewal within the microglial network toward a rapid expansion of selected microglia clones. This finding provides important insight into the question if microglia are recruited from adjacent regions to sites of CNS damage, or if clonal expansion results in microglial accumulation. Results obtained in the Microfetti mouse clearly favor the latter hypothesis. During the recovery phase in which microgliosis is resolved, the restoration of microglial cell density occurred through egress and apoptotic cell death Ontological origin of macrophage subpopulations in the central nervous system CNS. A first wave of myeloid cell development takes place in the yolk sac i between E7. Microglia originate exclusively from yolk sac-derived progenitors, while non-parenchymal CNS macrophages are replenished with fetal liver-derived progenitor cells ii as part of definitive hematopoiesis. Perinatally, hematopoiesis starts to be restricted to the bone marrow iii. Taken together, the field has reached consensus regarding the origin of microglia and the contribution of bone marrow precursors to the microglia pool under steady-state conditions. However, the debate on the functional contribution of yolk sac-derived microglia and blood-borne monocytes in CNS inflammation and their functional interplay is still in its infancy. As discussed in more detail in the following paragraphs, there is evidence that in response to inflammatory conditions associated with, e. However, it remains unclear if the recruited cells persist and become an integral part of the microglial population, or if those cells represent a transient population that vanishes once the inflammatory stimulus is resolved. Another question that still needs to be addressed in more detail is, if yolk sac-derived microglia and bone marrow-derived macrophages BMDM exert redundant or cell type-specific functions in CNS pathologies and if the ontological origin determines responses against therapeutic intervention. Shaping of Cellular Identity by the Tissue Environment To understand the imprinting of disease-associated states on microglia and monocyte-derived macrophage identity in more detail, it is important to first consider the effects of specialized tissue environments on tissue-resident macrophages. It is increasingly recognized that in addition to the ontological origin, environmental factors play a critical role in defining functionality of tissue-resident macrophages and determine the fate and persistence of cells in tissues. Consistent with their diverse locations and functions, tissue-resident macrophages in different organs display distinct gene expression profiles 46 , Several studies have already dissected the genetic and epigenetic imprinting of specific tissue-resident macrophages and identified a range of transcription factors that are essential for cell type restricted gene expression profiles, e. Two recent studies undertook the effort to systematically characterize the genetic and epigenetic imprinting of tissue-resident macrophages in specific organ environments. Both studies used RNA sequencing in combination with chromatin immune-precipitation Chip -Seq 51 and assay for transposase-accessible chromatin ATAC -Seq 52 to identify enhancer regions that are coupled to gene expression and accessible chromatin 53 , The studies by Lavin and Gosselin indicate that tissue-resident macrophages share epigenetic structures and gene expression with other myeloid cell populations. Similarities within the lineage are largely determined by collaborating transcription factors CTFs such as PU. However, each tissue additionally has its unique gene expression profile that is controlled by changes in enhancer landscapes in response to environment-specific signals Figure 2. Interestingly, both studies describe pronounced differences in enhancer landscapes among macrophage subtypes, while promoters are largely shared across different macrophage subpopulations and even between macrophages, monocytes, and neutrophils. It was demonstrated that microglia are most distinct from other tissue-resident macrophages in terms of their genetic landscape This comparison also revealed that macrophage populations that are exposed to similar environmental cues converged to similar expression patterns. For example, Kupffer cells and splenic macrophages were shown to share a cluster of highly expressed genes that are enriched for gene ontology GO annotations, such as heme and porphyrin metabolism, indicating their role in erythrocyte

turnover 48 , Similarly, small and large intestinal macrophages were shown to express genes enriched for GO annotations that reflect exposure to microbiota, such as response to bacteria and antigen processing. A more detailed comparison between microglia and peritoneal macrophages identified tissue-specific signals that determine the epigenetic and genetic imprinting of microglia and peritoneal macrophages. The extent of tissue-specific cues on enhancer landscapes was further proven by transplantation experiments in which peritoneal macrophages were transferred to the lungs. Interestingly, the transferred tissue-resident macrophages lost most of their original tissue marks and acquired a tissue program based on their new host tissue Environmental imprinting of tissue-resident macrophages. Differentiation of precursor cells into specific lineages is determined by binding of lineage-determining transcription factors LDTFs and collaborating transcription factors CTFs to closely spaced recognition patterns on the DNA. Primed enhancers are marked with characteristic histone modifications such as histone lysine 4 monomethylation H3K4me1 or dimethylation H3K4me2. Poised enhancers are defined by the presence of histone H3 lysine 27 trimethylation H3K27me3. Primed or enhancers show low activity due to the lack of enhancer RNA production or the presence of H3K27me3, that has to be removed to induce an active enhancer state upper panel. Tissue-resident macrophage populations are exposed to unique environmental cues that lead to genetic and epigenetic imprinting based on signal-dependent transcription factors SDTF that bind and activate primed or poised enhancers. Environmental imprinting induces cell-type-specific functions of different tissue-resident macrophage populations lower panel. In summary, identification of enhancer landscapes that are imprinted by specific tissue environments together with the notion that environmental cues can override ontological imprinting ultimately leads to the question, how blood-borne monocytes and macrophages are affected by the host tissue upon recruitment to sites of injury, inflammation, neurodegeneration, and neoplastic transformation and also, to which extent, the disease status dominates the imprinting of resident and recruited cell populations. Molecular Identities of Microglia and Macrophages in Brain Malignancy The local tissue environment has been shown to sculpt macrophage transcriptional profiles and epigenetic states under steady state conditions. However, it remained unclear whether an inflammatory tissue environment may affect differently macrophage populations of distinct ontogenies. To answer this question, it is first essential to determine the extent of peripheral recruitment of myeloid cells to the CNS under distinct pathological conditions.

Chapter 3 : Mononuclear phagocyte system - Wikipedia

Disorders of the monocyte/macrophage lineage are quite heterogeneous and include "benign" disorders such as Langerhans-cell histiocytosis, reactive histiocytosis, and the lysosomal storage diseases, as well as monocytic and histiocytic malignant proliferations.

Phagocytosis Macrophages are professional phagocytes and are highly specialized in removal of dying or dead cells and cellular debris. This role is important in chronic inflammation, as the early stages of inflammation are dominated by neutrophils, which are ingested by macrophages if they come of age see CD31 for a description of this process. When a macrophage ingests a pathogen, the pathogen becomes trapped in a phagosome, which then fuses with a lysosome. Within the phagolysosome, enzymes and toxic peroxides digest the pathogen. However, some bacteria, such as Mycobacterium tuberculosis , have become resistant to these methods of digestion. Typhoidal Salmonellae induce their own phagocytosis by host macrophages in vivo, and inhibit digestion by lysosomal action, thereby using macrophages for their own replication and causing macrophage apoptosis. Role in adaptive immunity[edit] This section needs additional citations for verification. Please help improve this article by adding citations to reliable sources. Unsourced material may be challenged and removed. April Learn how and when to remove this template message Macrophages are versatile cells that play many roles. Along with dendritic cells , they are foremost among the cells that present antigens , a crucial role in initiating an immune response. As secretory cells, monocytes and macrophages are vital to the regulation of immune responses and the development of inflammation; they produce a wide array of powerful chemical substances monokines including enzymes, complement proteins, and regulatory factors such as interleukin At the same time, they carry receptors for lymphokines that allow them to be "activated" into single-minded pursuit of microbes and tumour cells. After digesting a pathogen, a macrophage will present the antigen a molecule, most often a protein found on the surface of the pathogen and used by the immune system for identification of the pathogen to the corresponding helper T cell. The presentation is done by integrating it into the cell membrane and displaying it attached to an MHC class II molecule MHCII , indicating to other white blood cells that the macrophage is not a pathogen, despite having antigens on its surface. Eventually, the antigen presentation results in the production of antibodies that attach to the antigens of pathogens, making them easier for macrophages to adhere to with their cell membrane and phagocytose. In some cases, pathogens are very resistant to adhesion by the macrophages. The antigen presentation on the surface of infected macrophages in the context of MHC class II in a lymph node stimulates TH1 type 1 helper T cells to proliferate mainly due to IL secretion from the macrophage. When a B-cell in the lymph node recognizes the same unprocessed surface antigen on the bacterium with its surface bound antibody, the antigen is endocytosed and processed. T cells that express the T cell receptor which recognizes the antigen-MHCII complex with co-stimulatory factors- CD40 and CD40L cause the B-cell to produce antibodies that help opsonisation of the antigen so that the bacteria can be better cleared by phagocytes. Macrophages provide yet another line of defense against tumor cells and somatic cells infected with fungus or parasites. Once a T cell has recognized its particular antigen on the surface of an aberrant cell, the T cell becomes an activated effector cell, producing chemical mediators known as lymphokines that stimulate macrophages into a more aggressive form. Macrophage subtypes[edit] There are several activated forms of macrophages. M1 macrophages have pro-inflammatory, bactericidal, and phagocytic functions. M2 is the phenotype of resident tissue macrophages, and can be further elevated by IL Tumor-associated macrophages are mainly of the M2 phenotype, and seem to actively promote tumor growth. Phenotypes can be predominantly separated into two major categories; M1 and M2. M1 macrophages are activated by four key mediators: These mediator molecules create a pro-inflammatory response that in return produce pro-inflammatory cytokines like Interleukin-6 and TNF. These cytokines are essential in the initial process of wound healing. M2 cells are divided into four major types based on their roles: M2a, M2b, M2c, and M2d. How M2 phenotypes are determined is still up for

discussion but studies have shown that their environment allows them to adjust to whichever phenotype is most appropriate to efficiently heal the wound. If this shift failed to occur, there would be prolonged inflammation. M2 cells are needed for production of collagen at the wound site. They are needed for revascularization and reepithethelisation. It was previously thought that an increase of M2 macrophages may decrease the time it takes for wound closure. However, studies show that rate of wound closure is not affected by an increase in M2 cells. This dysregulation results in insufficient M2 macrophages and its corresponding growth factors that aid in wound repair. At this point, inflammation is not needed and M1 undergoes a switch to M2 anti-inflammatory. The initial wave is a phagocytic population that comes along during periods of increased muscle use that are sufficient to cause muscle membrane lysis and membrane inflammation, which can enter and degrade the contents of injured muscle fibers. These peak between two and four days and remain elevated for several days during the hopeful muscle rebuilding. It is thought that macrophages release soluble substances that influence the proliferation, differentiation, growth, repair, and regeneration of muscle, but at this time the factor that is produced to mediate these effects is unknown. Once they are in the wound site, monocytes mature into macrophages. These factors attract cells involved in the proliferation stage of healing to the area. Role in limb regeneration[edit] Scientists have elucidated that as well as eating up material debris, macrophages are involved in the typical limb regeneration in the salamander. Human iron metabolism As described above, macrophages play a key role in removing dying or dead cells and cellular debris. Erythrocytes have a lifespan on average of days and so are constantly being destroyed by macrophages in the spleen and liver. Macrophages will also engulf macromolecules , and so play a key role in the pharmacokinetics of parenteral irons. The iron that is released from the haemoglobin is either stored internally in ferritin or is released into the circulation via ferroportin. In cases where systemic iron levels are raised, or where inflammation is present, raised levels of hepcidin act on macrophage ferroportin channels, leading to iron remaining within the macrophages. Role in pigment retainment[edit] Until recently[when? In contrast to dendritic juncional melanocytes , which synthesize melanosomes and contain various stages of their development, the melanophages only accumulate phagocytosed melanin in lysosome-like phagosomes. For example, they participate in the formation of granulomas , inflammatory lesions that may be caused by a large number of diseases. Some disorders, mostly rare, of ineffective phagocytosis and macrophage function have been described, for example. Some pathogens subvert this process and instead live inside the macrophage. This provides an environment in which the pathogen is hidden from the immune system and allows it to replicate. Diseases with this type of behaviour include tuberculosis caused by Mycobacterium tuberculosis and leishmaniasis caused by Leishmania species. In order to minimize the possibility of becoming the host of an intracellular bacteria, macrophages have evolved defense mechanisms such as induction of nitric oxide and reactive oxygen intermediates, which are toxic to microbes. Leishmaniasis[edit] Upon phagocytosis by a macrophage, the Leishmania parasite finds itself in a phagocytic vacuole. Under normal circumstances, this phagocytic vacuole would develop into a lysosome and its contents would be digested. Leishmania alter this process and avoid being destroyed; instead, they make a home inside the vacuole. Chikungunya[edit] Infection of macrophages in joints is associated with local inflammation during and after the acute phase of Chikungunya caused by CHIKV or Chikungunya virus. Heart disease[edit] Macrophages are the predominant cells involved in creating the progressive plaque lesions of atherosclerosis. These macrophages function to remove debris, apoptotic cells and to prepare for tissue regeneration. Like T cells , macrophages can be infected with HIV, and even become a reservoir of ongoing virus replication throughout the body. Both circulating monocytes and macrophages serve as a reservoir for the virus. Inflammatory compounds such as tumor necrosis factor TNF -alpha released by the macrophages activate the gene switch nuclear factor-kappa B. Macrophages have been shown to infiltrate a number of tumors. Their number correlates with poor prognosis in certain cancers including cancers of breast, cervix, bladder, brain and prostate. This co-operation involves not only the direct contact of T-cell and macrophage, with antigen presentation, but also includes the secretion of adequate combinations of cytokines, which enhance T-cell antitumor activity. Macrophages can

be protective in different ways: Furthermore, this effect was exaggerated when the mice became obese from a high fat diet. In an obese individual some adipocytes burst and undergo necrotic death, which causes the residential M2 macrophages to switch to M1 phenotype. This is one of the causes of a low-grade systemic chronic inflammatory state associated with obesity. Macrophages and intestinal macrophages have high plasticity causing their phenotype to be altered by their environments. This is a challenge considering the bacteria found in the gut are not recognized as "self" and could be potential targets for phagocytosis by the macrophage. Primarily, intestinal macrophages do not induce inflammatory responses. This change is directly caused by the intestinal macrophages environment. There is no drop off in phagocytosis efficiency as intestinal macrophages are able to effectively phagocytize the bacteria,S. Nor do they express IL-2 and IL-3 growth factor receptors. In a healthy gut, intestinal macrophages limit the inflammatory response in the gut, but in a disease-state, intestinal macrophage numbers and diversity are altered. This leads to inflammation of the gut and disease symptoms of IBD. Intestinal macrophages are critical in maintaining gut homeostasis. The presence of inflammation or pathogen alters this homeostasis, and concurrently alters the intestinal macrophages. Observations were made every 30s over a 2.

Chapter 4 : Disorders of the Monocyte Macrophage System: Pathophysiological and Clinical Aspects

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