Original Article Angiogenic And Innate Immune Responses

Clearance of apoptotic cells is essential for proper development, homeostasis and termination of immune responses in multicellular organisms. Thus, cellular and molecular players taking part in the sequential events of this process are of great interest. Research in the last 20 years has indicated that specific ligands and receptors take part in the attraction of immune cells toward apoptotic targets and in the interactions between apoptotic cells and professional as well as non-professional phagocytes that engulf them. Moreover, phagocytosis of apoptotic cells (efferocytosis) leads to significant phenotypic changes in the engulfing cells suggesting that it is a major fate-determining event for phagocytes. Particularly, efferocytosis has an important impact on the inflammation-resolution axis as well as embryonic development and tissue morphogenesis. Deficiencies in these processes can result in health threats, such as autoimmunity, atherosclerosis, bone loss, obesity, infertility, neurodegeneration, fibrosis and cancer. This eBook brings together 24 original research and review manuscripts that cover various aspects of apoptotic cell removal during normal development and homeostasis as well as in tumorigenesis and regenerative processes following injury.

The group of pattern recognition receptors (PRRs) includes families of Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), and AIM-2-like receptors (ALRs). Conceptually, receptors constituting these families are united by two general features. Firstly, they directly recognize common antigen determinants of virtually all classes of pathogens (so-called pathogen-associated molecular patterns, or simply PAMPs) and initiate immune response against them via specific intracellular signaling pathways. Secondly, they recognize endogenous ligands (since they are usually released during cell stress, they are called damage-associated molecular patterns, DAMPs), and, hence, PRR-mediated immune response can be activated without an influence of infectious agents. So, pattern recognition receptors play the key role performing the innate and adaptive immune response. In addition, many PRRs have a number of other vital functions apart from participation in immune response realization. The fundamental character and diversity of PRR functions have led to amazingly rapid research in this field. Such investigations are very promising for medicine as immune system plays a key role in vast majority if not all human diseases, and the process of discovering the new aspects of the immune system functioning is rapidly ongoing. The role of Toll-like receptors in cancer was analyzed in certain reviews but the data are still scattered. This collection of reviews systematizes the key information in the field.

Once viewed solely as fat storage cells, adipocytes and their adipokines have now

been proven to be central for human health. Understanding that overweight and obesity may increase the risk for various diseases requires detailed characterization of adipokine function. Weight gain, weight regain, and fasting affect adipocyte health and accordingly their secretome. Different adipose tissue deposits exist and they vary in cellular composition and function. The evidence is strong of a role of adipokines in cancer, reproductive function, neurological diseases, cardiovascular diseases ,and rheumatoid arthritis. Adipokines are considered useful biomarkers for adipose tissue and metabolic health, and may be used as diagnostic tools in rheumatoid arthritis, cancer, or sepsis. This book contains 10 original articles and 9 review articles focusing on these bioactive peptides. Several articles deal with chemerin, an adipokine discovered more than 20 years ago. Data so far have resulted in promising insights related to its biological function. We are only beginning to understand the multiple roles of chemerin, the mechanisms regulating its activity, and the signaling pathways used by this chemokine. Adipokine receptor agonists and antagonists may result in the formulation of novel drugs and ultimately may lead to new therapeutic targets to be used in clinical practice.

Angiogenesis, the formation of new blood vessels, is fundamental for physiological processes such as embryonic and postnatal development, wound repair, and reproductive functions. Angiogenesis plays a major role in tumor growth and in several autoimmune and allergic disorders. Lymphangiogenesis, the formation of new

lymphatic vessels, is also important for tumor growth, the formation of metastasis, and chronic inflammatory diseases. Judah Folkman, a pioneer in the study of angiogenesis, first proposed that macrophages and mast cells could be a relevant source of angiogenic factors. Since then, much effort has gone into the elucidation of the role of immune cells in the modulation of angiogenesis and lymphangiogenesis. There is now compelling evidence that several components of the innate and adaptive immune system are implicated in inflammatory and neoplastic angiogenesis and lymphangiogenesis. Articles in this volume deal with the emerging, intriguing possibility that immune cells are both a source and a target of angiogenic and lymphangiogenic factors. Therefore, cells of the immune system might play a role in inflammatory and neoplastic angiogenesis/lymphangiogenesis through the expression of several angiogenic factors and their receptors and co-receptors. The important new findings in this volume will be of special interest to vascular biologists, basic and clinical immunologists, oncologists and to specialists in allergic and immune disorders.

Over recent years, native pentameric C-reactive protein (pCRP) and its biologically active dissociated form, monomer monomeric CRP (mCRP) have assumed an important role in disease development and pathophysiology. In this series, we have highlighted the thoughts and research of the most eminent scientists in the field of CRP research. This eBook is a collection of original articles and reviews on the subject, creating an archive of current knowledge and understanding. This Research Topic

provides new findings of the role of CRP in the fields of neuroscience, cardiovascular disease, inflammation, and macular degeneration as well as defined links to stages in pathological disease progression. These articles explain the mechanisms and pathways through which the dissociated mCRP interacts with a variety of cells, and provide possible prognostic implications and new methods for analysis. Over the coming years, the importance and fascination of the active role of CRP in health and disease is set to rise, and we hope this collection will serve as a valuable reference for these future investigations.

The Mononuclear Phagocyte System (MPS) of vertebrates is composed of monocytes, macrophages and dendritic cells. Together, they form part of the first line of immune defense against a variety of pathogens (bacteria, fungi, parasites and viruses), and thus play an important role in maintaining organism homeostasis. The mode of transmission, type of replication and mechanism of disease-causing differ significantly for each pathogen, eliciting a unique immune response in the host. Within this context, the MPS acts as both the sentinel and tailor of the immune system. As sentinels, MPS cells are found in blood and within tissues throughout the body to patrol against pathogenic insult. The strategy to detect 'microbial non-self' relies on MPS to recognize conserved microbial products known as 'pathogen-associated molecular pattern' (PAMPs). PAMPs recognition represents a checkpoint in the response to pathogens and relies on conserved 'pattern recognition receptors' (PRRs). Upon PRR engagement, MPS mount a cell-autonomous attack that includes the internalization and compartmentalization of intracellular pathogens into toxic compartments that promote

destruction. In parallel, MPS cells launch an inflammatory response composed of a cellular arm and soluble factors to control extracellular pathogens. In cases when innate immunity fails to eliminate the invading microbe, MPS serves as a tailor to generate adaptive immunity for pathogen eradication and generation of "memory" cells, thus ensuring enhanced protection against re-infection. Indeed, MPS cell functions comprise the capture, process, migration and delivery of antigenic information to lymphoid organs, where type-1 immunity is tailored against intracellular microbes and type-2 immunity against extracellular pathogens. However, this potent adaptive immunity is also a double-edge sword that can cause aberrant inflammatory disorders, like autoimmunity or chronic inflammation. For this reason, MPS also tailors tolerance immunity against unwanted inflammation. Successful clearance of the microbe results in its destruction and proper collection of debris, resolution of inflammation and tissue healing for which MPS is essential. Reciprocally, as part of the evolutionary process taking place in all organisms, microbes evolved strategies to circumvent the actions bestowed by MPS cells. Multiple pathogens modulate the differentiation, maturation and activation programs of the MPS, as an efficient strategy to avoid a dedicated immune response. Among the most common evasion strategies are the subversion of phagocytosis, inhibition of PRR-mediated immunity, resistance to intracellular killing by reactive oxygen and nitrogen species, restriction of phagosome maturation, modulation of cellular metabolism and nutrient acquisition, regulation of cell death and autophagy, and modulation of pro-inflammatory responses and hijacking of tolerance mechanisms, among others. The tenet of this eBook is that a better understanding of MPS in infection will yield insights for development of therapeutics to enhance antimicrobial processes or dampen detrimental inflammation for the host's benefit.

We believe that contributions to this topic will serve as a platform for discussion and debate about relevant issues and themes in this field. Our aim is to bring expert junior and senior scientists to address recent progress, highlight critical knowledge gaps, foment scientific exchange, and establish conceptual frameworks for future MPS investigation in the context of infectious disease.

Angiogenesis, Lymphangiogenesis and Clinical ImplicationsKarger Medical and Scientific Publishers

We acknowledge the initiation and support of this Research Topic by the International Union of Immunological Societies (IUIS). We hereby state publicly that the IUIS has had no editorial input in articles included in this Research Topic, thus ensuring that all aspects of this Research Topic are evaluated objectively, unbiased by any specific policy or opinion of the IUIS.

Stroke remains one of the most devastating diseases in industrialized countries. Recanalization of the occluded arterial vessel using thrombolysis is the only causal therapy available. However, thrombolysis is limited due to severe side effects and a limited time window. As such, only a minority of patients receives this kind of therapy, showing a need for new and innovative treatment strategies. Although neuroprotective drugs have been shown to be beneficial in a variety of experimental stroke models, they ultimately failed in clinical trials. Consequently, recent scientific focus has been put on modulation of post-ischemic neuroregeneration, either via stimulation of endogenous neurogenesis or via application of exogenous stem cells or progenitor cells. Neurogenesis persists within the adult brain of both rodents and primates. As such, neural progenitor cells (NPCs) are found within distinct niches like the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone of the

dentate gyrus. Cerebral ischemia stimulates these astrocyte-like progenitor cells, upon which NPCs proliferate and migrate towards the site of lesion. There, NPCs partly differentiate into mature neurons, without significantly being integrated into the residing neural network. Rather, the majority of new-born cells dies within the first weeks post-stroke, leaving post-ischemic neurogenesis a phenomenon of unknown biological significance. Since NPCs do not replace lost brain tissue, beneficial effects observed in some studies after either stimulated or protected neurogenesis are generally contributed to indirect effects of these new-born cells. The precise identification of appropriated cellular mediators, however, is still elusive. How do these mediators work? Are they soluble factors or maybe even vesicular structures emanating from NPCs? What are the cues that guide NPCs towards the ischemic lesion site? How can post-ischemic neurogenesis be stimulated? How can the poor survival of NPCs be increased? In order to support post-ischemic neurogenesis, a variety of research groups have focused on application of exogenous stem/progenitor cells from various tissue sources. Among these, cultivated NPCs from the SVZ and mesenchymal stem cells (MSCs) from the bone marrow are frequently administered after induction of stroke. Although neuroprotection after delivery of stem/progenitor cells has been shown in various experimental stroke models, transplanted cells are usually not integrated in the neural network. Again, the vast amount of grafted cells dies or does not reach its target despite profound neuroprotection, also suggesting indirect paracrine effects as the cause of neuroprotection. Yet, the factors being responsible for these observations are under debate and still have to be addressed. Is there any “optimal” cell type for transplantation? How can the resistance of grafted cells against a non-favorable extracellular milieu be increased? What are the molecules that are vital for interaction between

grafted cells and endogenous NPCs? The present research topic seeks to answer - at least in part - some of the aforementioned questions. Although the research topic predominantly focuses on experimental studies (and reviews alike), a current outlook towards clinical relevance is given as well.

The Research Topic is organized in the framework of the project BIORECAR (grant number: 772168; http://www.biorecar.polito.it/index.html)

Macrophages have unique and diverse functions necessary for survival. And, in humans (and other species), they are the most abundant leukocytes in tissues. The Innate functions of macrophages that are best known are their unusual ability to either “Kill” or “Repair”. Since killing is a destructive process and repair is a constructive process, it was stupefying how one cell could exhibit these 2 polar – opposite functions. However, in the late 1980’s, it was shown that macrophages have a unique ability to enzymatically metabolize Arginine to Nitric Oxide (NO, a gaseous non – specific killer molecule) or to Ornithine (a precursor of polyamines and collagen for repair). The dual Arginine metabolic capacity of macrophages provided a functional explanation for their ability to kill or repair. Macrophages predominantly producing NO are called M1 and those producing Ornithine are called M2. M1 and M2 – dominant responses occur in lower vertebrates, and in T cell deficient vertebrates being directly driven by Damage

and Pathogen Associated Molecular Patterns (DAMP and PAMP). Thus, M1 and M2 are Innate responses that protect the host without Adaptive Immunity. In turn, M1/M2 is supplanting previous models in which T cells were necessary to “activate” or “alternatively activate” macrophages (the Th1/Th2 paradigm). M1 and M2 macrophages were named such because of the additional key findings that these macrophages stimulate Th1 and Th2 – like responses, respectively. So, in addition to their unique ability to kill or repair, macrophages also govern Adaptive Immunity. All of the foregoing would be less important if M1 or M2 – dominant responses were not observed in disease. But, they are. The best example to date is the predominance of M2 macrophages in human tumors where they act like wound repair macrophages and actively promote growth. More generally, humans have become M2 – dominant because sanitation, antibiotics and vaccines have lessened M1 responses. And, M2 dominance seems the cause of ever - increasing allergies in developed countries. Obesity represents a new and different circumstance. Surfeit energy (e.g., lipoproteins) causes monocytes to become M1 dominant in the vessel walls causing plaques. Because M1 or M2 dominant responses are clearly causative in many modern diseases, there is great potential in developing the means to selectively stimulate (or inhibit) either M1 or M2 responses to kill or repair, or to stimulate Th1 or Th2

responses, depending on the circumstance. The contributions here are meant to describe diseases of M1 or M2 dominance, and promising new methodologies to modulate the fungible metabolic machinery of macrophages for better health. Long-lasting T cell immunity is delivered by an array of individual T lymphocytes expressing clonally distributed and highly specific antigen receptors recognizing an almost infinite number of antigens that might enter in contact with the host. Following antigen-specific priming in lymphnodes, naïve CD4 and CD8 T lymphocytes proliferate generating clones of effector cells that migrate to peripheral tissues and deliver unique antigen-specific effector functions. Moreover, a proportion of these effector lymphocytes survive as memory T cells that can be rapidly mobilized upon new exposure to the same antigen, even years after their primary induction. Innate immune cells play crucial roles in the induction and maintenance of this efficient protection system. Following the seminal discovery of Steinman and Cohen in 1974 describing a rare cell type capable of initiating antigen-specific responses in lymphnodes, Dendritic Cells (DC) have taken up the stage for several decades as professional Antigen Presenting Cells (APC). Although DC possess all attributes to prime naïve T lymphocytes, other immune cell subsets become crucial accessory cells during secondary and even primary activation. For instance, Monocytes (Mo) are rapidly

recruited to inflammatory sites and have recently been recognized as capable of shaping T cell immunity, either directly through Ag presentation, or indirectly through the secretion of soluble factors. In addition, upon sensing of T cell-derived cytokines, Mo differentiate into functionally different APC types that further impact on the quality and persistence of memory T cell responses in peripheral tissues. Other innate immune cells, including Myeloid Derived Suppressor Cells, Granulocytes and iNKT lymphocytes, are known to modulate T cell activation by interacting with and modifying the function of professional APC. Notably, innate immune cell determinants also account for the tissue-specific regulation of T cell immunity. Hence, the newly discovered family of Innate Lymphoid Cells, has been recognized to shape CD4+ T cell responses at mucosal surfaces. Although the actions of innate immune cells fulfills the need of initiating and maintaining protective T cell responses, the excessive presence or activity of individual determinants may be detrimental to the host, because it could promote tissue destruction as in autoimmunity and allergy, or conversely, prevent the induction of immune responses against malignant tissues, and even modulate the response to therapeutic agents. Thus, understanding how defined innate immune cell subsets control T cell immunity is of fundamental relevance to understand human health, and of practical relevance for preventing and curing

human diseases. In this research topic, we intend to provide an excellent platform for the collection of manuscripts addressing in depth how diverse innate immune cell subsets impact on T cell responses through molecularly defined pathways and evaluating the rational translation of basic research into clinical applications.

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The non-classical HLA class I molecule HLA-G is different from classical HLA class I molecules because of the low polymorphism in the coding region, the fact that HLA-G primary transcript is alternatively spliced in seven isoforms, and the inhibitory action on immune cells. Although HLA-G is low polymorphic, variants in both promoter and 3' un-translated region (UTR) of HLA-G locus regulate its expression. In healthy conditions, a basal level of HLA-G gene transcription is observed in most cells and tissues; however, translation into HLA-G protein is restricted to trophoblasts in the placenta, where it participates in promoting tolerance at the fetal-maternal interface. HLA-G is also expressed by thymic epitelial, cornea, mesenchymal stem cells, nail matrix, pancreatic beta cells, erythroid, and endothelial precursors. HLA-G can be neo-expressed in adult tissues in pathological conditions, and its expression has been documented

autoimmune disorders, viral infections, and cancer. In the latter setting de novo HLA-G expression is associated with the capability of tumor cells to evade the immune control. In the last decade it has become evident that HLA-G expression on T cells and antigenpresenting cells confers to these cells tolerogenic properties. This Research Topic focused on i) summarizing updated clinical and immunological evidences that HLA-G expression is associate with beneficial or detrimental tolerance, ii) gathering new insights into the mechanisms governing the expression of HLA-G in healthy and pathological conditions, such as pre-eclampsia, and iii) examining the mechanisms underlying HLA-G mediated tolerance.

The comprehensive guide to the current understanding of galectins and their promising potential in drug design This is the first book focusing on galectins. It was inspired by topics discussed at the symposium "Galectins: Structures, Functions, and Therapeutic Targets" that was a part of the 234th American Chemical Society meeting in 2007. To help chemists, biochemists, and others understand the challenges inherent in the study of galectins and build on recent advances in the field, the editors have compiled articles from leading experts on galectins and their biomedical applications. Galectins includes: * An overview of early galectin research * An explanation of the nature of galectins * A discussion

of the structure and functions of galectins, their ligand specificity and molecular mechanisms of action, and the localization of galectins in the cell * An exploration of the roles galectins play in tumor growth and cancer, fibrosis, inflammation, and immunity * A discussion of the effect of galectins on cell migration, angiogenesis, and chemoresistance * An introduction to new approaches to designing galectin inhibitors This is the premier reference on galectins for organic, medicinal, carbohydrate, and pharmaceutical chemists, biochemists, molecular and cell biologists, pharmacologists, cancer researchers, and graduate-level students in these disciplines, as well as clinicians and drug developers.

This book was prepared as extension of author's accidental discoveries on experimental models of acute and chronic ocular inflammatory diseases that were established at the University of Pennsylvania in 1980's. Analyses of original data suggest a series of first evidence for direct link between inflammation and developmental phases of immune dysfunction in multistep tumorigenesis and angiogenesis. The only evidence presented on initial events for interactions and synergies between activated host and recruiting cells toward tumorigenesis. Effective immunity was defined as balance between two highly regulated and biologically opposing arms, Yin and Yang of acute inflammation, an amazingly precise signal communications between immune and non-immune systems requiring differential

bioenergetics. Unresolved inflammation is a common denominator mapping aging process and induction of ‘mild’, ‘moderate’ or ‘severe’ immune disorders including cancers. Our knowledge of the fascinating biology of immunity in health or chronic diseases is fragmentary, chaotic and confusing, particularly for cancer science. Lack of progress in curing majority of chronic diseases or cancer is primarily due to the fact that scientists work on isolated molecules/cells or topics that are funded and promoted by decision makers in medical/cancer establishment. Despite existence of over 25 million articles on cancer-related topics, cancer biology and cure remain mysteries to be solved. After a century of cancer research, the failure rates of therapies for solid tumors are 90% (+/-5). Current reductionist views on cancer science are irresponsible, shut-gun approaches and create chaos. Outcomes are loss of millions of precious lives and economic drain to society. Very little is known about initial events that disturb effective immunity whose function is to monitor and arrest growth of cancerous cells or defend against other external or internal hazardous agents that threaten body’s survival. The author demonstrates the serious need for systematic understanding of how immune disruptors and aging process would alter effective immunity. Outcomes of proposed orderly studies are expected to provide logical foundations for cost-effective strategies to promote immunity toward a healthier society. The policy makers and medical/cancer establishment are urged to return to the common sense that our Forefathers used to serve the public.

In the past, neutrophils were often reduced to their ability to release preformed mediators and kill pathogens. The present volume of Chemical Immunology and Allergy, however, offers a very broad and timely view by highlighting the versatile functions of neutrophils in inflammatory, immune and antitumoral responses. Leading investigators uncover novel aspects of neutrophils, such as their capacity to control gene expression at the transcriptional level, or respond to proinflammatory cytokines, cytokine receptor chains (gc) and endogenous anti-inflammatory lipid mediators. Further points under discussion are neutrophils presenting antigens, activating T cells, participating in chemokine networking, and producing IL-12 and other cytokines during infectious diseases. Among the most original findings presented in this publication figure the observations that neutrophils cause increased vascular permeability during acute inflammation, regulate directly the angiogenic process, and influence tumor development. A final article offers a detailed description of the molecular processes affecting neutrophil cell death and survival. Unique in its field, this valuable volume is recommended reading not only for immunologists and pathologists, but also for cell biologists, hematologists and immunobiologists.

Transcription depends on an ordered sequence of events, starting with (i) setting of the enhancer and chromatin environment, (ii) assembly of DNA binding and general transcription factors, (iii) initiation, elongation, processing of mRNA and termination, followed by (iv) creation of epigenetic marks and memory formation. Highlighting the

importance of these activities, more than 10% total genes are dedicated to regulating transcriptional mechanisms. This area of research is highly active and new insights are continuously being added to our knowledge. Cells of the immune system have unique features of gene regulation to support diverse tasks required for innate and adaptive immunity. Innate immunity involves the recognition of external infectious and noxious agents as well as internal cancer cell components, and the elimination of these agents by non-specific mechanisms. Adaptive immunity involves gene rearrangement to achieve highly specific T and B cell responses, imparting the capability of self and non-self discrimination. This requires transcription and epigenetic regulation. Adaptive immunity also employs epigenetic memory, enabling recapitulation of prior transcription. Recent advances in nuclear architecture, chromatin structure, and transcriptional regulation have provided new insights into immune responses. The increased understanding of these molecular mechanisms is now affording opportunities to improve therapeutic strategies for various diseases.

We acknowledge the initiation and support of this Research Topic by the International Union of Immunological Societies (IUIS). We hereby state publicly that the IUIS has had no editorial input in articles included in this Research Topic, thus ensuring that all aspects of this Research Topic are evaluated objectively, unbiased by any specific policy or opinion of the IUIS. Part of the APCs for articles in this collection were financed by the Fondazione Beppe e Nuccy Angiolini ONLUS. Publisher’s note: In this

2nd edition, acknowledgment for the Fondazione Beppe e Nuccy Angiolini ONLUS has been added.

Angiogenesis is the physiological process where new blood vessels grow from existing ones, in order to replenish tissues suffering from inadequate blood supply. Perhaps the most studied angiogenic process occurs in solid tumors whose growing mass and expanding cells create a constant demand for additional supply of oxygen and nutrients for survival. However, other physiological and clinical conditions, such as wound healing, ischemic events, autoimmune and age-related diseases also involve angiogenesis. Angiogenesis is a well-structured process that begins when oxygen and nutrients are depleted, leading to the release of chemokines and growth factors that attract immune cells, particularly macrophages and endothelial cells to the site. Macrophages that are recruited to the site, as well as tissue cells and endothelial cells, secrete pro-angiogenic mediators that affect endothelial cells and promote angiogenesis. These mediators include growth factors such as vascular endothelial cell growth factor (VEGF), matrix metalloproteinases (MMPs), as well as low levels of mediators that are usually seen as pro-inflammatory but are pro-angiogenic when secreted in low levels (e.g. nitric oxide (NO) and TNFa). Thus, macrophages play a major role in angiogenesis. Macrophages exhibit high plasticity and are capable of shifting between different activation modes and functions according to their changing microenvironment. Small differences in the composition of activating factors (e.g. TLR

ligands such as LPS, anti-inflammatory cytokines, ECM molecules) in the microenvironment may differently activate macrophages to yield classically activated macrophages (or M1 macrophages) that can kill pathogen and tumor cells, alternatively activated macrophages (or M2 macrophages) that secrete antiinflammatory cytokines, resolution macrophages (rM?) that are involved in the resolution of inflammation, or regulatory macrophages (e.g. Myeloid-Derived Suppressor Cells - MDSCs) that control the function of other immune cells. In fact, macrophages may be activated in a spectrum of subsets that may differently contribute to angiogenesis, and in particular non-classically activated macrophages such as tumor-associated macrophages (TAMs) and Tie2-expressing monocytes (TEMs) can secrete high amounts of pro-angiogenic factors (e.g. VEGF, MMPs) or low levels of pro-inflammatory mediators (e.g. NO or TNFa) resulting in pro-angiogenic effects. Although the importance of macrophages as major contributors and regulators of the angiogenic process is well documented, less is known about the interactions between macrophages and other cell types (e.g. tumor cells, normal epithelial cells, endothelial cells) that regulate angiogenesis. We still have only limited understanding which proteins or complexes mediate these interactions and whether they require cell-cell contact (e.g. through integrins) or soluble factors (e.g. the EGF-CSF-1 loop), which signaling pathways are triggered in each of the two corresponding cell types, and how this leads to secretion of pro- or antiangiogenic factors in the microenvironment. The regulation of such interactions and through them

of angiogenesis, whether through post-translational modifications of proteins or via the involvement of microRNA, is still unclear. The goal of this Research Topic is to highlight these interactions and their regulation in the context of both physiological and pathological conditions.

The main scope of this topic is to give an update on pharmacologic and non-pharmacologic approaches to enhance uptake and penetration of cancer drugs into tumors. Inadequate accumulation of drugs in tumors has emerged over the last decade as one of the main problems underlying therapeutic failure and drug resistance in the treatment of cancer. Insufficient drug uptake and penetration is causally related to the abnormal tumor architecture. Thus, poor vascularization, increased resistance to blood flow and impaired blood supply represent a first obstacle to the delivery of antitumor drugs to tumor tissue. Decreased or even inverted transvascular pressure gradients compromise convective delivery of drugs. Eventually, an abnormal extracellular matrix offers increased frictional resistance to tumor drug penetration. Abnormal tumor architecture also changes the biology of tumor cells, which contributes to drug resistance through several different mechanisms. The variability in vessel location and structure can make many areas of the tumor hypoxic, which causes the tumor cells to become quiescent and thereby resistant to many antitumor drugs. In addition, the abnormally long distance of part of the tumor cell population from blood vessels provides a challenge to delivering cancer drugs to these cells. We have recently

proposed additional mechanisms of tumor drug resistance, which are also related to abnormal tumor architecture. First, increased interstitial fluid pressure can by itself induce drug resistance through the induction of resistance-promoting paracrine factors. Second, the interaction of drug molecules with vessel- proximal tumor cell layers may also induce the release of these factors, which can spread throughout the cancer, and induce drug resistance in tumor cells distant from blood vessels. As can be seen, abnormal tumor architecture, inadequate drug accumulation and tumor drug resistance are tightly linked phenomena, suggesting the need to normalize the tumor architecture, including blood vessels, and/or increase the accumulation of cancer drugs in tumors in order to increase therapeutic effects. Indeed, several classes of drugs (that we refer to as promoter drugs) have been described, that promote tumor uptake and penetration of antitumor drugs, including those that are vasoactive, modify the barrier function of tumor vessels, debulk tumor cells, and overcome intercellular and stromal barriers. In addition, also non-pharmacologic approaches have been described that enhance tumor accumulation of effector drugs (e.g. convection-enhanced delivery, hyperthermia, etc.). Some drugs that have already received regulatory approval (e.g. the anti-VEGF antibody bevacizumab) exert antitumor effects at least in part through normalization of the tumor vasculature and enhancement of the accumulation of effector drugs. Other drugs, acting through different mechanisms of action, are now in clinical development (e.g. NGR-TNF in phase II/III studies) and others are about to enter clinical

investigation (e.g. JO-1).

How can we slow the signs of aging? Although aging is a natural process for all living things, doing so without dramatic alterations of health and well-being is an important aim in health care. Understanding this gradual but continuous process is fundamental in order to avoid, or at least improve, aging associated illnesses and conditions. The reviews and studies compiled here address various aspects of the relationship between systemic and central changes during the aging process, with hormonal signals as the important liaison.

This selection of articles from the Encyclopedia of the Eye provides a comprehensive overview of immunological features, diseases and inflammation of the eye and its support structures and organs. Rather than taking an immunological focus that is strictly suitable for clinicians, the volume offers a considerable basic science background and addresses a broad range of topics - the immune system of the eye, its various disorders, mechanisms of inflammation of the eye and visual system, treatment, wound healing mechanisms, stem cells, and more. The first single volume to integrate comparative studies into a comprehensive resource on the neuroscience of ocular immunology Chapters are carefully selected from the Encyclopedia of the Eye by the world's leading vision researchers The best researchers in the field provide their conclusions in the context of the latest experimental results

Since the invention of nanomedicine decades ago, considerable progresses have been

made, especially with cancer as a target. Nanoparticles have been proven to be powerful imaging tools or potent agents for cancer diagnosis, treatment and prevention. Active research spread from fundamental research to clinical investigations. This topic intends to cover several important aspects in this field including nanocarrier development, gene delivery, intrinsically active nanoparticles, tumor microenvironment, immunology, and toxicity.

This book is a printed edition of the Special Issue "AR Signaling in Human Malignancies: Prostate Cancer and Beyond" that was published in Cancers