
Preface

The evolving paradigm, suggesting the existence of an intricate link connecting inflammatory processes with oncogenesis, finds its roots all the way back into the nineteenth century. Rudolf Virchow, one of the most prominent German physicians of his time, was the first to uncover almost 150 years ago the presence of white blood cells in tumor specimens. This observation led Virchow to suggest – largely intuitively – that carcinogenesis could occur at sites of chronic inflammation, and that a set of secreted factors produced by inflamed tissues supports neoplastic growth while helping the tumor to escape the immune system surveillance by inducing a state of so-called immunosuppression concurrently inhibiting natural elimination of malignant cells via the process currently known as apoptosis.

Today, clinical oncology data strongly support Virchow's intuition by acknowledging one out of seven newly diagnosed malignancies worldwide to result from infection and chronic inflammation. To no surprise, recognition of this astounding rate of cancer incidence caused by inflammatory processes robustly correlates with an increasing attention within both academic research environment and the biomedical industry circles towards closer evaluation of the infection–inflammation–cancer axis on a molecular level, as well as on the level of search for novel markers allowing, once targeted, to selectively restrain the oncogenic drift triggered by inflammation. The last two decades of the past millennium marked by a breathtaking evolution of molecular methods in biology – including complete sequencing of genomes in key species, nascency of proteomics and DNA microarray technologies, development of comprehensive toolkits for pathway analyses, as well as rapid maturation of chromosome engineering and gene targeting methodologies – consolidated the theoretical foundation of inflammation-associated carcinogenesis. An impressive body of evidence has been collected to develop the molecular groundwork for infection-mediated tumorigenesis with the role of reactive oxygen species, free radicals, inflammatory cytokines, such as TNF α and lymphotoxins, but also angiogenic factors secreted by an inflamed tissue to assist in its healing process, gradually becoming well recognized. Furthermore, signaling pathways known previously to primarily play either developmental or tissue homeostasis roles have now been demonstrated to critically influence the oncogenic outcome of inflammation; examples include NF- κ B, prostaglandin/cyclooxygenase-2, and p53 pathways, the DNA repair machinery, and a family of the Toll-like receptor proteins. Intriguingly for both infection experts and oncologists, the systemic inflammation appeared to influence cancer progression during each of three stages in tumor lifetime: initiation/promotion, expansion, and invasive metastatic growth. Different mechanisms associated with the inflammation onset and its resolution have been demonstrated to play pleiotropic, yet distinct, roles at different phases of tumorigenesis.

As the number of scientific reports directly addressing the issue of inflammation-mediated tumorigenesis surpassed a notable 2,000 mark in the last year only, the value of review-type publications summarizing the findings at the cancer–inflammation boundary became almost impossible to overestimate. And yet, highest quality of the theoretical framework delivered by numerous reviews in the field provides little, if at all, room to

deduce the collinear scaffold of methodological procedures developed and validated in a variety of labs to practice the “molecular oncology of inflammation” either at the lab bench level or in the clinical diagnostics. There is a clear need to conceptualize, systematize, and standardize the existing arsenal of analytical tools developed by both oncologists and immunology experts to bring the wealth of experimental techniques under a common denominator toolkit equally valuable for biomedical researchers in academia, R&D scientists in the industry, and clinical oncologists in hospital labs.

In this light, the publication of *Inflammation and Cancer* is well timed to say the least. Although facing a challenging task of in a way shooting at a moving target because of the contemporary pace of practical arsenal development in the field, it is my sincere intention to not only collect a plethora of current methods under a single cover, but rather deliver a systematic guide to techniques addressing various aspects of experimental cancer biology selectively focusing on inflammation-mediated tumorigenesis and leaving an ample room for improvisations on a per-case basis. Apart from an unquestionable relevance of the fundamental experimental principles for a long future to come, the current collection of experimental approaches is almost certainly destined to live through the continuous waves of revisions and amendments. In my view, the significance of this book is also in setting “square zero” requirements for techniques still in the development pipeline or just added to the application pool and awaiting experimental substantiation.

The *Inflammation and Cancer* set is subdivided into four topics each consisting of chapters discussing a specific methodology with extensive citation list and reference guide for laboratory troubleshooting. Each chapter provides an introductory paragraph reviewing the relevant theoretical foundations. The following topics will be covered in the actual order as they appear in the book: *Vol. 1*, (I) Experimental Approaches to Study Chronic Inflammation-Related Carcinogenesis; (II) Oncogenic Potential of Inflammation Induced by Viral and Bacterial Infections; *Vol. 2*, (I) Crossroads of Inflammation and Cancer: Molecular Aspects; and (II) Molecular and Cellular Approaches to Diagnostics and Drug Target Discovery in Inflammation-Related Oncogenesis. It was my strong objective to maximize the page/information quality ratio of the book, but also to seek a balanced presenting of experimental procedures vs. background theoretical material.

In its present format with the scope and style of covered material, the book shall find a wide-ranging appeal among the diverse audience of scientific professionals practicing experimental oncology, immunology, cell biology, genetics, and pharmacology in both academic research and industrial R&D laboratories. Medical practitioners and clinical laboratory personnel, as well as students learning the experimental aspects of molecular medicine, will equally find helpful the roster of laboratory procedures discussed in the book. My further hope extends to a notion that the methodological arsenal discussed in its pages will in fact beget the perception of its incompleteness and stimulate further efforts in expanding the battery of experimental approaches, focusing among others on implementation of cell-based and in vivo preclinical models, to address the biology – and ultimately the therapeutic aspects – of inflammation-related tumorigenesis. On another note, fostering the rigorous scientific interactions among basic and clinical researchers aimed at further molecular demarcation of the elaborate pathways leading from inflammation to tumor formation is both the primary purpose of the book and a key metrics of its success.

Undoubtedly, this project will be next to impossible without the exceptional work of all contributing authors. It is understandably difficult to tailor – and then re-tailor again – the chapter style to reflect the editor’s strategy and big-picture vision for the entire

volume, and I am very much obliged for each piece of experimental wisdom shared with the reader audience, as well as for the praiseworthy commitment of every contributing author to bear with the editor through the entire duration of the work.

On a final note, every single day we were working on this book, over 15,000 lives have been claimed worldwide due to cancer-related deaths. Current estimates give us reasons to believe that about 2,200 fatalities are actually caused by the inflammation-related oncogenesis. It is this frustrating statistic that stipulates a powerful dedication to succeed in the demanding quest of disseminating the novel diagnostic tools and therapies targeting the adverse clinical facets of inflammatory processes. My hope is that copies of these current volumes will find themselves rapidly tunneled from a library bookcase to lab benches of investigators and clinicians alike who enthusiastically seek a means to stand up against the clinical challenges reflected in the above numbers.

Volume 2

An in-depth pathway analysis has been proven instrumental on multiple occasions to construct and navigate through detailed molecular charts for a variety of processes starting from gametogenesis and early embryonic development through the cell senescence and death, not excluding onset and resolution of inflammation and oncogenic transformation. The second volume of the book, appearing under the title “Molecular Analysis and Pathways”, is thus logically devoted to an extensive description of experimental strategies aimed at investigating the molecular cross-talks among components of cell signaling chains and their ramifications for diagnostic development and drug target discovery.

Part I of this volume (Crossroads of Inflammation and Cancer: Molecular Aspects) places in a spotlight several pathways proven critical for translating inflammatory outcomes into malignant cell transformation. Among those are NF- κ B signaling (chapters by Goh et al., Blander, and Yang et al.) and one of the free radical turnover pathway (nitric oxide signaling, chapter by Hiraku and Kawanishi and review chapter by Yang et al.). Two other chapters discuss methodological aspects of monitoring the inflammatory-related molecular footprints on the genomic DNA level and account on techniques of detecting the chronic inflammation-directed genomic instability and aberrant DNA methylation signatures (chapters by Yan et al. and Suzuki et al., correspondingly). Chapter by Nunez et al. addresses the experimental basis applicable to study a recently uncovered link between inflammation and carcinogenesis mediated by insulin and IGF pathways. Lastly, Van Laere’s et al. chapter provides an in-depth description of a whole transcriptome analysis technique known as cDNA microarray hybridization and illustrates its power in the context of identification of the molecular signatures featured by inflammatory breast tumor tissue.

Part II of the book (Molecular and Cellular Approaches to Diagnostics and Drug Target Discovery in Inflammation-Related Oncogenesis) aims at introducing the reader into the realm of translational research and discusses the techniques instrumental at the interface of basic laboratory experimentation processes and clinically oriented studies. In juxtaposition with the eventual goal of every carcinogenesis-centric investigation – to develop and implement novel, more efficient antitumor therapeutic strategies – the structure of the *Inflammation and Cancer* final part steers an academic researcher, a preclinical scientist, and a molecular pathology clinician alike through a compendium of techniques

devoted to application of inflammatory pathways information and dynamic properties of inflammation-associated cells for both diagnostic purposes and prediction of therapeutic entry points. Starting from experimental description of cell-based assays designed to quantify the inflammatory status in biologic fluids based solely on cell signaling readouts (chapter by Kozlov), **Part II** proceeds with tools for analytical assessment of multiple “druggable” pathways operating on the inflammation–cancer axis and providing promising gateways for pharmacological intervention. Two chapters underscore a pivotal role of NF- κ B signaling (chapters by Mauro et al. and Madge and May) as a key molecular trigger of inflammation-assisted tumorigenesis and equally as a therapeutic target. Among other pathways that present significant clinical interest and deserved coverage in **Part II** are JNK/Jun (chapter by Kaminska), STAT (chapter by Adach et al.), FAK (chapter by Mon et al.), and PPAR (chapters by Wu and Liou and Ritzenthaler et al.) signaling as well as the molecular machinery regulating posttranslational histone modifications (chapter by Glauben and Siegmund). Chapter by Thomson and Udalova provides a representative sample of current techniques in clinical detection for a variety of inflammatory mediators, in particular cytokines, chapter by Hagemann and Lawrence describes assays applicable to analyze responsiveness of innate immunity components to malignant cells, and chapter by Smirnov exemplifies a collection of experimental imaging procedures summoned to follow the course of pathology while presenting cancer biologists with a cell-based therapeutic modality. Finally, chapter by Lee et al. illustrates the experimental principles of phage display methodology in application to identification of tumor-specific molecular determinants, and chapter by Alosi and McFadden presents the novel approach to interfere with inflammation-associated tumorigenesis employing the YY peptide.

Serguei V. Kozlov
Frederick, MD
July 2008

Inflammation and Cancer

Methods and Protocols: Volume 2, Molecular Analysis
and Pathways

Kozlov, S.V. (Ed.)

2009, XVI, 408 p. 51 illus., Hardcover

ISBN: 978-1-60327-529-3

A product of Humana Press