
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-kappaB, 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 1

The complexity of a mechanistic basis for inflammation-associated carcinogenesis, not infrequently revolving around an intricate amalgamation of multiple biological events occurring at both cellular and molecular levels, stands as a major challenge for clinical and experimental oncology practitioners. The current advancements in deciphering the network of pathway interactions and cross-talks among different cell types at sites of inflammation or infection would be next to impossible without a battery of potent experimental tools evolved and perfected over the recent past. A synopsis of this compilation of contemporary laboratory techniques, with the emphasis placed on carcinogenic events mediated by chronic inflammation and pathogen infection, constitutes a key objective of the first out of two *Inflammation and Cancer* volumes.

Volume 1 of the book, appearing with a subtitle “Experimental Models and Practical Approaches”, is composed of two parts and provides an overview of a spectrum of techniques developed to analyze the outcomes of inflammation-mediated carcinogenesis on the tissue, cellular, and molecular levels while highlighting several diagnostic aspects, such as biomarker discovery and molecular signatures evaluation. This volume as well highlights several techniques aimed at detection and analyses of pathogenic proinflammatory agents, primarily viruses and bacteria. The first part of the volume – entitled “Experimental Approaches to Study Chronic Inflammation-Related Carcinogenesis” – includes methodological chapters covering such aspects of inflammation immunology and cancer biology as a comprehensive description of surgical and molecular techniques for preparation of cancer tissue samples for molecular pattern analyses (“Collection and Preparation of Rodent Tissue Samples for Histopathological and Molecular Studies in Carcinogenesis”), description of both RNA- and protein-based bioassays to determine the cytokine expression (“Cytokine Multiplex Analysis” and “Approaches to Determine Expression of Inflammatory Cytokines”), and evaluation of chronic inflammation-associated biomarkers (“Biomarkers of Cell Proliferation in Carcinomas: Detection of Angiogenesis and Infiltrated Leukocytes” and “YKL-40: A Novel Marker Shared by Chronic Inflammation and Oncogenic Transformation”). Other chapters appearing in this part are devoted to description of bioanalytical tools that afford researchers with capabilities to evaluate the proteolytic environment of inflamed tissues (“Assessment of Local Proteolytic Milieu as a

Factor in Tumor Invasiveness and Metastasis Formation: In Vitro Collagen Degradation and Invasion Assays”), to monitor the chronic inflammation-related angiogenic events as mediators of cancer progression (“Angiogenesis Links Chronic Inflammation with Cancer”), or to study tumor-specific infiltrating immune cells via an elegant technique of their capturing and in vitro clonal expansion (“Selective Immortalization of Tumor-Specific T Cells to Establish Long-Term T-Cell Lines Maintaining Primary Cell Characteristics”). The part is concluded with a review chapter that provides an extensive and amply referenced account on experimental modeling for the most vivid example of cancer-prone inflammation process known as inflammatory bowel disease (“Inflammatory Bowel Disease: A Model of Chronic Inflammation-Induced Cancer”).

The second part of Vol. 1 (entitled “Oncogenic Potential of Inflammation Induced by Viral and Bacterial Infection”) consists of seven chapters that provide a compendium of experimental procedures developed to detect a panel of pathogens linked to the onset of inflammatory events that eventually lead to malignant transformation of infected organs. The list includes one of the most widely acknowledged gastrointestinal cancer-coupled bacterial pathogens *Helicobacter pylori* (“Gastric Carcinogenesis and *Helicobacter pylori* Infection” and “*Helicobacter*-Based Mouse Models of Digestive System Carcinogenesis”), and multiple viral agents such as cervical cancer-associated HPV (“Screening for Molecular Markers of Cervical Papillomavirus Infection: Overview of Methods and Their Clinical Implications” and “Detection and Genotyping Analysis of Human Papillomavirus Isolates from Liquid-Based Cervical Cytology Specimens”), common pathogen in Hodgkin’s lymphomas Epstein–Barr virus (“Screening for Epstein–Barr Virus in Hodgkin’s Lymphoma”), and a hepatitis C virus known to predispose infected liver cells to hepatocellular carcinoma formation (“A Hepatitis C Virus Xenograft Mouse Efficacy Model”). Remaining chapter in this part (“Gene Expression Profiling in Cervical Cancer: Identification of Novel Markers for Disease Diagnosis and Therapy”) exemplifies the application of nucleic acid microarray and bioinformatics techniques to discover novel prognostic markers in HPV-associated cases of cervical cancer.

In summary, the first volume of *Inflammation and Cancer* endows cancer biologists with a collection of contemporary experimental techniques developed to assess the biochemical properties and characteristic gene expression signatures of inflamed tissues, as well as to detect and quantify inflammatory agents of viral and bacterial nature. Additional review style information on modeling the inflammation-associated carcinogenesis in experimental animals supplies a broad reference guide for the investigators intrigued by the current power of in vivo genetic tools in unveiling the molecular networks operating at the numerous anastomoses of inflammation and cancer.

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