PERIODICUM BIOLOGORUM
VOL. 116, No 4, 335–336, 2014

UDC 57:61
CODEN PDBIAD
ISSN 0031-5362

Introduction

SONJA LEVANAT[1]
DAMIR VRBANEC[2,3]

[1]Laboratory for Hereditary Cancer
Division of Molecular Medicine
Ruđer Bošković Institute, Zagreb, Croatia
E-mail: sonja.levanat@irb.hr

[2]Department of Medical Oncology,
University Hospital Center Zagreb, Croatia

[3]University of Zagreb, School of Medicine, Croatia

This issue of PB is entirely dedicated to cancer. Decades ago, cancer was clonal disease initiated from a single cell, but since then vast heterogeneity within and across tumor types has been discovered. We now know that any single tumor sample is unique and may contain more than a hundred different mutations.

Huge body of factual knowledge has been accumulating through basic research in fast advancing fields of genetics, cellular biology and immunology, accompanied by a virtual maze of working hypotheses and tentative explanations of underlying mechanisms. On a higher conceptual level, quest for organizing principles that may provide logical framework for understanding the remarkable diversity of neoplastic diseases has been attempting to match the inflow of research data. Among such frameworks, perhaps the widest recognition has been achieved by the evolving proposition of cancer hallmarks, defined as the abilities of cancer to sustain proliferative signaling, evade growth suppressors, resist cell death, enable replicative immortality, induce angiogenesis, activate invasion and metastasis etc.

It remains to be seen whether and how this diverse and proliferative research may be aided by the high level conceptual frameworks in the ambitious task of understanding and defeating cancer. In the meantime, however, quite a few among numerous poorly correlated facets of experimental investigation have already made notable progress towards clinical applications.

Rapidly growing numbers of potential therapeutic targets are identified almost daily, involving various signaling pathways or separate genes and proteins, within tumors or in their microenvironment. While most of them are still tentative, yet to be investigated on models, some have made it to clinical trials and few to actual cancer therapy.

Until more complete conceptual understanding of malignant processes, which may shed more light on important unanswered questions related to immune response, drug resistance and other cancer features interfering with therapy, oncology will continue to explore potential therapeutic targets revealed through versatile experimental research of particular cancer properties.

This issue of PB addresses very different aspects of the vast „sum of knowledge“ constituting present-day oncology, reflecting versatile interests of the contributors as well as the notorious fact that cancer is not just one disease but comprises variety of integrated damages in whole organism. Various aspects of cancer-related research, presented in this issue through original scientific articles and reviews, are briefly depicted below.

Some contributions address closely related themes of cancer research, but occasionally from a very different perspective. For example, one of the contributions integrates the classic understandings of the mechanistic role of obesity in cancer, implying obesity-related carcinogenic processes, whereas another one suggests a beneficial role of brown fat to humans.

On the other hand, the study of cancer-related hypoxia is an example of a stand-alone theme, although hypoxic regions are common characteristic of majority of solid neoplasms, resulting from discordance between high metabolic needs of rapid growing malignant tissues and oxygen supply through structurally and functionally impaired microvasculature. Activation of hypoxia signaling pathways stimulates neoangiogenesis, induces transcription of tumor promoting genes leading to increased tumor cell proliferation and metastatic potential.

Two contributions address related aspects of cancer immunology. Tumor microenvironment, not only tumor cells and not only stroma but also other cells, such as infiltrated lymphocytes, contribute to malignancy. Chronic inflammation increases risk of cancer, and inflammatory microenvironment, including action of different cells like macrophages and activated T lymphocytes, is involved in the immune response against tumor, and in respect to tumor type could have different outcomes. Recent positive results with the relatively novel immunotherapeutic anti-cancer strategies such as adoptive T cell transfer, engineered T cells with chimeric antigen receptors, therapeutic anti-cancer vaccine and checkpoint blockade inhibitors, do indicate that patient's immune system can be effectively used against autologous tumor cells. Interactions between the immune system and the malignancy are complex but the results are promising and are undergoing active clinical testing.

Finally, most contributions in this issue are concerned with proliferative signaling, some addressing the role of signaling pathways on a rather general level, whereas others are limited to a particular tumor context.

Misregulation of molecular signaling pathways that control fundamental cellular processes such as cell growth, cell division and cell death has been directly associated with a variety of cancer diseases. Aberrant activation of particular pathway or pathways, involving receptor tyrosine kinases, frequently occurs during cancer initiation and progression, and these tumorigenic cascades may cooperate through multiple signaling cross-talks in the malignant transformation of cells, treatment resistance and disease relapse. For example, in thyroid cancer genetics, alterations exert oncogenic potential through Mitogen-activated protein kinase (MAP kinase) pathway where BRAF mutation is the most common genetic alteration.

On the other hand, targets against VEGF, VEGFR and mTOR continue to play a crucial role in the management of metastatic renal cell cancer, although complete response is extremely rare, probably because resistance in tumor cells develops frequently and adverse effects of therapy are not unusual finding.

Importance of steroid receptors in some tumors is well known. In case of prostate carcinoma androgen receptors are a major signaling pathway for survival. But activation of enzyme machinery or *de novo* production of androgen within the cells is a two way road. For breast cancer both the estrogen and progesterone receptor status are markers for prognosis as well as a guide for adjuvant therapy.

In spite of a broad variety of cancer-related themes in this PB issue, the contributions generally tend to incorporate one common consideration – therapeutic potential of the cancer research described. Clinical relevance of basic research has become almost mandatory ingredient in recent research strategies.

Although we are still quite far from truly personalized and efficient therapies for various cancers, this accelerating quest for potential therapeutic targets across the entire basic research domain has greatly expanded creative interactions with clinical practice.