# Molecular Biochemical Aspects of Cancer

Undurti N. Das

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Undurti N. Das
BioScience Research Centre and Department of Medicine
GVP Medical College and Hospital
Visakhapatnam, India
UND Life Sciences, Battle ground
WA, USA

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*To*

*My wife Lakshmi*

*Friend, philosopher, critic, supporter, and soul*

*and*

*for her understanding of my long hours at work.*

# Preface

Cancer is one of the leading causes of morbidity and mortality in both developing and developed countries. Despite many advances both in our understanding of its molecular biology and development of many newer therapeutics, it continues to be a major health issue. Tumor cells differ from normal cells in many aspects (including gene expressions, metabolism, behavior in terms of proliferation, and ability to metastasize, etc.,) but the role of lipids in cancer has largely been ignored. The cell membrane (including nuclear membrane, mitochondrial membrane, etc.,) lipid composition of tumor cells is different from normal, a fundamental property that has not been paid much attention. Lipids, especially polyunsaturated fatty acids (PUFAs) and their metabolites, both pro- and anti-inflammatory products, seem to play a critical role in the pathobiology of cancer. Tumor cells are deficient in the activity of desaturases that are essential for the formation of long-chain metabolites from dietary essential fatty acids: *cis*-linoleic acid (LA) and α-linolenic acid (ALA). As a result, tumor cells contain low quantities of γ-linolenic acid (GLA, 18: n-6), dihomo-GLA (DGLA, 20:3 n-6), arachidonic acid (AA, 20:4 n-6) formed from LA and eicosapentaenoic acid (EPA, 20:5 n-3), and docosahexaenoic acid (DHA, 22:6 n-3) from ALA that can be referred to as *bioactive lipids (which also include their metabolites)* . As a result, the tumor cell membrane is uniquely different from the normal especially in terms of expression of several receptors on its surface, the way messages are conveyed from the membrane to the DNA and *vice versa*, and its antigenicity including the expression of immune checkpoint proteins/receptors such as PD-1, PD-L1, and CTLA4. These altered properties of tumor cell may render it to escape the immune surveillance system and acquire unique properties in terms of its proliferation ability, metastasis, triggering angiogenesis to survive, and drug-resistance. Studies performed by us and several others showed that tumor cells have low rates of peroxidation and are exquisitely sensitive to the cytotoxic action of lipid peroxides compared to their normal counter parts. Furthermore, some of these *bioactive lipids* protect normal cells from the cytotoxic action of chemicals, chemotherapeutic drugs, cytokines, and radiation. This differential action of *bioactive lipids* on normal and tumor cells (protecting normal cells but produce apoptosis of tumor cells) could be exploited to develop them as potential drugs for cancer. These

*bioactive lipids* seem to regulate the proliferation and action of Treg and Teff cells; cytokines production and action; expression of PD-1, PD-L1, and CTLA4; macrophage function; immune response; and finally as potential mediators of the tumoricidal action of T cells, macrophages, and immune checkpoint inhibitors. They possess antimicrobial properties. These pleiotropic actions of *bioactive lipids* suggest that they are likely to be useful in several diseases. Our recent observation that drug-resistant Hodgkin's lymphoma could be successfully treated by *bioactive lipids* when supplemented with chemotherapeutic drugs with substantial attenuation of side-effects of conventional anti-cancer drugs implies that they have the potential to be exploited as unconventional yet specific and selective anti-cancer molecules. The therapeutic potential of *bioactive lipids* is just being realized and it is only the beginning, and I foresee a bright future for lipid-based drugs for several diseases.

Visakhapatnam, India Undurti N. Das
Battle Ground, WA, USA

# Contents

# About the Author

**Undurti N. Das** is an MD in Internal Medicine from Osmania Medical College, Hyderabad, India; a Fellow of the National Academy of Medical Sciences, India; and Shanti Swaroop Bhatnagar prize awardee. Apart from clinical work, he is researching the role of polyunsaturated fatty acids, cytokines, nitric oxide, free radicals, and anti-oxidants in cancer, inflammation, metabolic syndrome, schizophrenia, autism, and tropical diseases. His current interests include cancer, molecular biological aspects of diabetes mellitus, hypertension, cardiovascular diseases, and metabolic syndrome. Dr Das was formerly scientist at Efamol Research Institute, Kentville, Canada; Professor of Medicine at Nizam's Institute of Medical Sciences, Hyderabad, India; and Research Professor of Surgery and Nutrition at SUNY (State University of New York) Upstate Medical University, Syracuse, USA. At present, he is the Chairman and Research Director of UND Life Sciences LLC, Battle Ground, WA, USA, and Chairman and Professor of Department of Medicine, GVP Hospital and Medical College, Visakhapatnam, India, and serves as a consultant to both Indian and US-based biotech and pharmaceutical companies. Dr Das is the Founding *Editor* of the international journal: *Lipids in Health and Disease* and serves on the editorial board of another 10 international journals. Dr Das has authored more than 500 international publications, written 4 books, and has been awarded 6 US patents. He is now developing lipid-based drugs for cancer, diabetes mellitus, and sepsis.