Biology of Oral Cancer

Key Apoptotic Regulators

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Dedication

We dedicate this work to the late Mr. Shitla Sahai, the son of the soil and great philanthropist, founder trustee of the Cancer Hospital and Research Institute, Gwalior, Madhya Pradesh, India. He realized various socioeconomic problems of the less privileged and the poor man of this region faced in the absence of proper cancer care treatment and vowed to start a cancer hospital in this underdeveloped region. He is the pioneer of the cancer institute started in May 1971, with his limited personal investments and modest resources. The institute now has full facilities of diagnosis and management of the disease under one roof with financial support from the state central government and enjoys the status of regional cancer research and treatment center for cancer treatment and research in India.

Preface

Human civilization has made phenomenal progress during the past couple of centuries. The sequencing of the human genome was a much celebrated event and was believed to be a panacea for all human disease. The availability of wealth of knowledge about molecular events related with any disease can be surely directly or indirectly attributed to the human genome sequencing; however, we have failed to translate this knowledge effectively to alleviate miseries caused by age-old diseases like cancer, stroke, and diabetes. The change in lifestyle and environmental factors have placed humans in a vulnerable position. Cancer is caused by the complex interaction of various internal (genetics) and external (carcinogens, radiation, and smoking) factors, and therefore the key to curing cancer lies in effective identification of these causal factors and their modulation to restore the normal state. The failure of existing treatment modalities for cancer is due to a lack of precise understanding of the interplay of these factors and related molecular events leading to growth and proliferation of cancer cells. Through this book, we have attempted to communicate our understanding about oral cancer, which has consistently ranked among the top 10 causes of cancer-related mortalities worldwide. The incidence and mortality rate for oral cancer is relatively greater in developing and underdeveloped nations than in developed nations, and one of the main reasons is the lack of awareness and medical infrastructure in these countries.

The book has been written as an attempt to spread awareness about cancer-causing factors, along with state-of-the-art medical options available for management and treatment of cancer, and fill the gap between the basic learner and advanced learner who want to learn cancer biology. The informal style of writing has been adopted with a purpose of reaching out to a wider audience whose life is directly or indirectly impacted by various types of cancers, including those of the oral cavity. This book would be indispensable for research/graduate students who want to understand molecular events like the role of apoptosis in causing oral cancer. Our thoughts about cancer have been captured in nine chapters of this book. Each chapter starts with a prologue to the concept, followed by a detailed discussion of the concept, and ends with a vision for the future approach and challenges. The content of every chapter is supported by illustrations for a better understanding of the concept discussed. A large compilation of references has been added at the end of each chapter.

The first two chapters, about cancer in general and oral cancer in particular, were written keeping in mind a broad audience. Chapter 1, "Cancer: A Worldwide Menace," is recommended to all inquisitive readers irrespective of academic or professional background; for instance, it would be resourceful for a lady with a nonscientific background who wants to know about risk factors, detection, and treatment options for various cancers, and thereby take control of her health along with that of others in her family. This chapter is also recommended for graduate students who would like to get an overview of cancer, before diving deep into specific problem areas in cancer research. Chapter 2, "Oral Cancer," throws light on various aspects

of oral cancer, and was written with the intention of providing a detailed appraisal of aspects around the genesis and manifestation of oral cancer.

Programmed cell death or apoptosis plays a very important role in the maintenance of cellular homeostasis. Cancer cells are known to adapt various mechanisms by which they survive and thrive, irrespective of the presence of signals that are responsible for checking the growth of normal cells and maintaining cellular integrity. Evasion of cell death by the apoptotic process is considered one of the most elaborate survival mechanisms present in cancer cells. We dedicated the next six chapters (Chapters 3–8) to explain survival strategies adapted by cancer cells. Chapter 3, "Proliferative and Apoptotic Signaling in Oral Cancer," deals with various factors involved in proliferative and apoptotic regulation in oral cancer. p53 plays a protective role in normal cells and is known to regulate a host of genes/proteins involved in key cellular processes, including apoptosis, cell division, and replication. Chapter 4, "Apoptotic Regulations," explains apoptosis in detail, along with various regulatory modules of the apoptotic pathway. In Chapter 5, "Dynamics of p53 in Oral Cancer," we highlight various roles played by p53, and how its dysregulation is implicated in cancer growth. The therapeutic and diagnostic application of p53 and other molecules from the apoptotic pathway is explained in detail in Chapter 6, "Diagnostic and Therapeutic Potential of Apoptotic Marker." The survivin, a key anti-apoptotic protein, belongs to the IAP family, which is almost exclusively expressed in tumor tissues. The anti-apoptotic role of the survivin protein, and its regulation by various molecules, has been explained in Chapter 7, "Expression and Regulation of Survivin." In Chapter 8, "Therapeutics of Survivin," we discuss various therapeutic approaches designed to control or kill cancer cells by modulation of the survivin protein.

Most of the mortalities due to oral cancer can be attributed to detection of cancer during advanced stages, which essentially reduces the chances of survival by many folds. The effective and accurate detection of oral cancer in its early stage is much desired to reduce mortalities due to it. In the past couple of decades we have witnessed a phenomenal amount of work done in the field of cancer biology. Every individual work has proved as a dot, which taken together have helped us in creating a near-complete picture of cancer at a molecular level. In Chapter 9, "Molecular Diagnosis of Oral Cancer," we have briefly discussed the key molecular events contributing to oral cancer development and molecular techniques that can be used for the effective diagnosis of oral cancer.

We hope that this book will provide a solid foundation to students who wish to pursue research in the area of oral cancer. We have taken utmost care to include all relevant information about concepts discussed in this book; however, there is a chance we might have inadvertently missed some important information, for which we encourage and request all readers to send us their comments and suggestions for improvements in this book.

ABOUT THE BOOK

Cancer has consistently maintained its status as one of the top killers since time immemorial. Developed countries like the United States have observed a decline

in cancer-related death during the past couple of years, which is an encouraging result of dedicated commitment from various stakeholders, including the research community, medical society, support groups, and policy makers. However, cancer statistics from the rest of the world are far from satisfactory, and millions of people are projected to acquire a form of cancer, and more than half of them are expected to die within 5 years from the time of first detection of cancer. According to the latest cancer statistics, oral cancer has become the topmost cause of death in males in Southeast Asia. Oral cancer, like its siblings, is caused by the complex interaction of multiple factors. This book is written with the objective to spread awareness among readers by highlighting factors responsible for causing cancers, including oral cancer. There are various molecular events that lead to the genesis and growth of oral cancer. The oral cavity is one of the most accessible sites of physical examination, which should ideally negate any chance of development of oral carcinogenesis; despite this, there is a large incidence rate of oral cancer, which points to the development of effective techniques for the detection of oral cancer in its nascent stages. This book discusses various detection techniques that leverage molecular events associated with oral carcinogenesis to effectively detect oral cancer. It is written with the hope that it will find its place as a reference book on oral cancer for students, teachers, researchers, and anyone who wants to understand oral cancer.

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1 Cancer
A Worldwide Menace

KEY WORDS

Cancer
Carcinogenesis
Chemotherapy
Metastasis
Oncogenes

1.1 INTRODUCTION

There are more than a hundred different types of cancers. The names for cancers are derived from the organ or type of cell in which it starts; for example, cancer that begins in the colon is called colon cancer; cancer that begins in basal cells of the skin is called basal cell carcinoma. The Greek physician Hippocrates (460–370 B.C.), who is considered the father of medicine, is credited with the origin of the word *cancer*. Hippocrates used the terms *carcinos* and *carcinoma* to describe non-ulcer-forming and ulcer-forming tumors. In Greek, these words refer to a crab, most likely applied to the disease because the finger-like spreading projections from cancer are structurally similar to the shape of a crab. After cardiovascular diseases, cancer is the second biggest cause of human death worldwide. Cardiovascular diseases and cancer together are responsible for over 80% of all deaths in industrialized countries. Global cancer incidence is an ever-increasing trend. Conventional therapies control cancer by acting upon effects (like proliferation, cell growth, etc.) rather than acting on the root cause of carcinogenesis. Because of this, there is no effective cancer therapy available, and cancer-related malignancies and deaths are increasing.

Cancer indiscriminately affects people at all ages, with a propensity toward older people. Cancer occurs predominantly in older people, with three-quarters of cases diagnosed in people aged 60 and over, and more than a third (36%) of cases in people aged 75 and over. Less than 1% of all cases occur in children (0 to 14 years); 1,367 cases of cancer were diagnosed in children in 2007, with a slightly higher incidence in boys than girls. In spite of tremendous progress in the field of research and development, in the area of oncology, cancer is still a major killer across the world. According to recent statistics, cancer accounts for about 23% of the total deaths in the United States (Jamel et al., 2007). The world population is expected to reach 7.5 billion by 2020, and approximately 15 million new cancer cases will be diagnosed, and 12 million cancer patients will die (Brayand and Moller, 2006).