ARSENIY E. YUZHALIN AND ANTON G. KUTIKHIN

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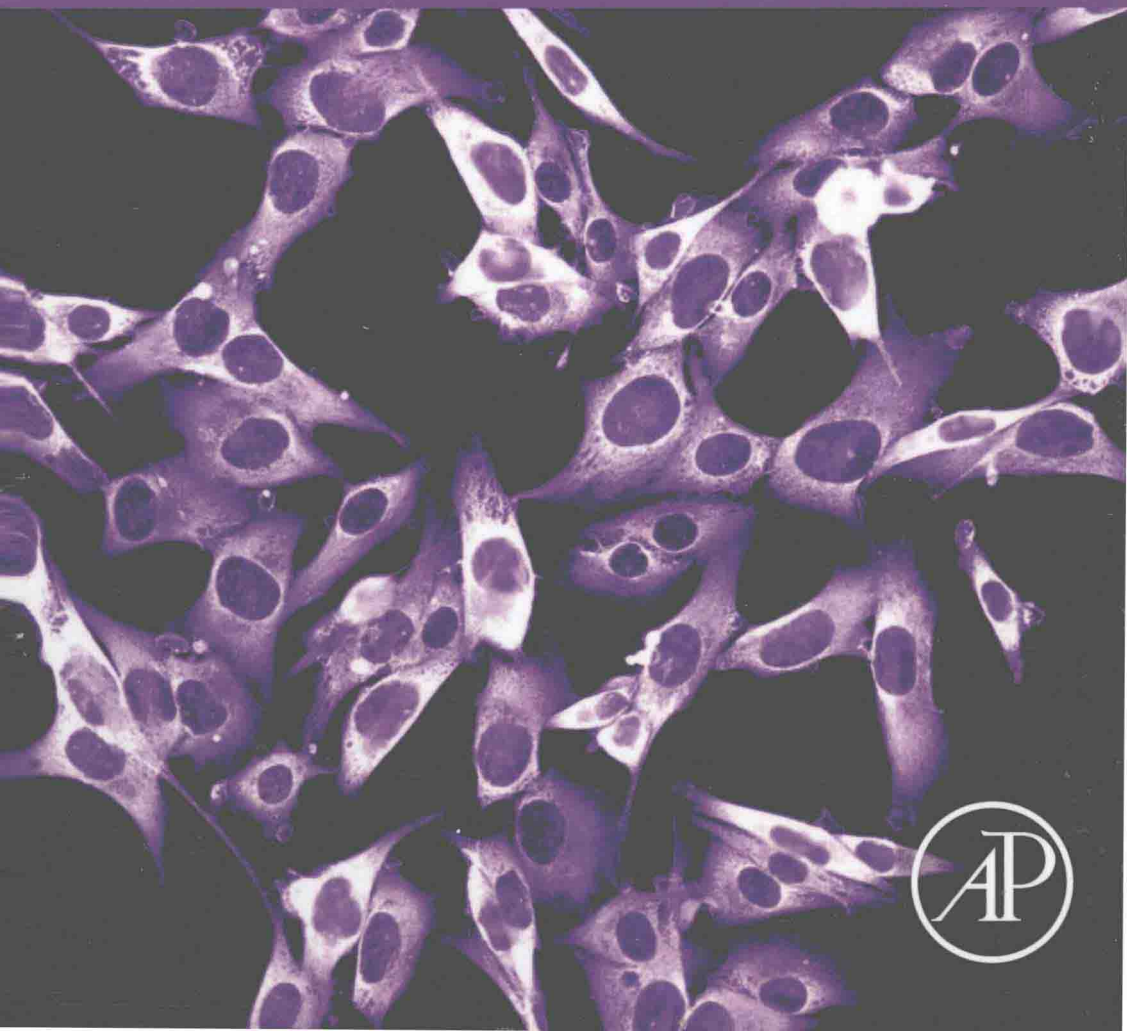
Their Heterogeneous Role



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Their Heterogeneous Role

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INTERLEUKINS IN CANCER BIOLOGY

DEDICATION

For my brother.

—Arseniy E. Yuzhalin, Oxford, 2014

PREFACE

Long standing data implicate interleukins as major mediators of innate and adaptive immune response. Their functions are incredibly diverse: promoting differentiation, proliferation, and maturation of immune cells, facilitating communication between them, regulating the expression of numerous genes, controlling transcription factors, and finally, governing the inflammatory process and secretion of antibodies. Interleukins provide coordinated interactions between white blood cells, thereby granting proper and effective immune response against numerous diseases, including cancer. There is a huge amount of evidence indicating that interleukins play a key role in the battle of the organism against cancer cells. Sometimes their role is ambiguous, showing both tumor-promoting and anticancer effects. On the one hand, interleukins markedly stimulate immune cells to recognize and eliminate cancer cells; on the other hand, they may also cause prolonged inflammation, angiogenesis, formation of prometastatic niche, and immune escape of tumors. Almost 40 representatives of interleukins have been discovered to date, not including multiple isoforms, receptors, and accessory proteins. Such diversity often creates confusion in the clear understanding of the functioning of interleukins as a unified network of cellular mediators capable of performing various biological effects depending on current state of the organism. Moreover, the amount of published information on this issue is extremely large, which significantly hampers the understanding of the topic. Current monograph was written with the aim to clearly sort all interleukins on their role in cancer and bring clarity to this problem. We herein summarize and discuss existing facts on the impact of all known interleukins in occurrence, development, and progression of cancer.

This book focuses on interleukins and cancer nothing more, nothing less. Using this book, the reader will find comprehensive and exhaustive information on a particular molecule in one place. We tried to make the content understandable and clear. Multiple illustrations are aimed to help to realize and remember the most important moments, and attention to subtle details is maintained in spite of the breadth of the topic. In addition, at the end of each paragraph, we offer the most promising targets for future research, which may help the investigators to develop the experimental

design. Despite the fact that we try to present the material relatively simply, it is expected that the readers already have a basic knowledge in the fields of oncology, molecular biology and immunology. This book will be interesting and helpful to a wide audience, particularly biologists, immunologists, oncologists, molecular biologists, cellular biologists, pathologists, general practitioners, and other health care professionals engaged in cancer research. Interleukins on Cancer Biology: Their Heterogenous Role is advisable for graduate students of biomedical faculties studying the appropriate course and their lecturers as well.

CONTENTS

CHAPTER 1

Introduction: Basic Concepts

Nothing has such power to broaden the mind as the ability to investigate systematically and truly all that comes under thy observation in life.

Marcus Aurelius, Roman emperor (121–180 AC)

1.1 A BRIEF OVERVIEW OF CANCER PHENOMENON

1.1.1 What is Cancer?

Cancer is a disease that has always been a part of the human life. References to cancer have been found in numerous early sources, some of which are thousands of years old. The most ancient descriptions of tumors and cancer treatment methods are the ancient Egyptian papyruses dated roughly to 1600 BC (Bozzone, 2009). From this source, we know that the Egyptians used cauterizing ointments containing arsenic for the treatment of superficial tumors. Similar descriptions were found in the manuscripts of ancient India, which described surgical removal of tumors and the use of arsenic ointments (Bozzone, 2009). The term "cancer" itself was introduced by Hippocrates, who described and investigated various tumors, including those of breast, stomach, skin, cervix, rectum, and throat (Figure 1.1). Hippocrates noticed that all the cancers have a visual similarity to a crab (Greek, *karkinos*) because of characteristic outgrowths aimed in opposite directions. Regarding the treatment of cancer, Hippocrates proposed the surgical removal of available tumors followed by treatment of postoperative wounds with ointments containing either plant poisons or arsenic, which were supposed to kill the remaining cancer cells. In cases of internal tumors, Hippocrates suggested to give up any kind of treatment, because he believed that the consequences of such a complex operation will kill the patient faster than the tumor itself.

Nowadays, we understand cancer as a pathological condition of the body where cells grow and reproduce in an uncontrollable manner. Alternatively, cancer is referred to as a large group of diseases characterized by disorganized and unregulated cell division. To date, more than 200 different cancers are known. Importantly, almost every cell of an organism may give rise to cancer; therefore, cancer is rather regarded as a disease of a cell than a disease

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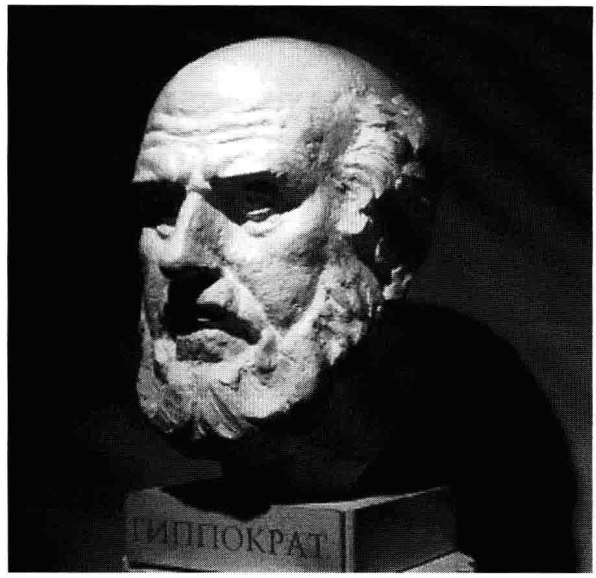

Figure 1.1 Hippocrates of Cos (460–370 BC) was an ancient Greek physician and philosopher.

of an organ. Cancer cells grow and form tumors, which are classified according to their clinical and morphological features in two main groups, namely, benign and malignant tumors. Benign tumors are characterized by a slow expansive growth, the absence of metastases, and no overall effect on the body; thus, they are regarded as noncancerous. Instead, malignant tumors are highly cancerous, which means they have several typical features, such as rapid progression, tendency to infiltration, high metastatic potential, and frequency of recurrence. In everyday practice, the term "cancer" is commonly used as a synonym for malignant tumor, and it should also be mentioned that in our book we will consider malignant tumors only. The overall effect of malignant tumors is often manifested by significant weight loss, various metabolic disturbances, skin changes, fatigue, fever, pain, and, ultimately, development of cachexia. Other general symptoms and signs may also include bleeding, indigestion, and emergence of unusual thickenings or lumps.

1.1.2 Cancer Statistics

Cancer is one of the most hazardous public health problems nowadays. According to the data of International Agency for Research on Cancer, more than 12.4 millions of new cancer cases, 7.6 millions of cancer-caused

deaths, and 28 millions of cancer survivors were registered in 2008 worldwide (Jemal et al., 2010, 2011; Siegel et al., 2012). About half of cancer cases and two-thirds of cancer deaths occur in low- and middle-income countries (Jemal et al., 2010, 2011; El-Basmy et al., 2012; Kutikhin et al., 2012a; Zhivotovskiy et al., 2012; Baade et al., 2013; Krishnan et al., 2013; Krishna Rao et al., 2013; Moore, 2013; Pandey and Chandravati, 2013; Perez-Santos and Anaya-Ruiz, 2013; Zhang, 2013). Despite this scary statistics, annual death rates have been decreasing gradually since 1990 in men and since 1991 in women (Jemal et al., 2011). This progress is largely as a result of intensive development of modern preventative measures against cancer, the efficacy of which is growing every year. Obviously, prevention of a disease is much easier than its treatment, and so the problem of cancer prevention is one of the most basic issues when combating the burden of the disease.

1.1.3 Carcinogenesis and Cancer Risk

Carcinogenesis is a sophisticated multistep process of initiation, development, and progression of cancer. The key feature of this process is that it leads to a fundamental reorganization of the normal cells of the body. The occurrence of cancer is associated with an impaired proliferation and differentiation of cells due to genetic alterations. One of the most common genetic alterations is a mutation. In order to provoke cancer, the mutation must occur in a specific gene, called proto-oncogene. The proto-oncogenes are a class of genes that encode proteins and enzymes involved in the regulation of cell cycle, as well as cell differentiation, and proliferation. The proto-oncogenes are often engaged in multiple signal transduction pathways of mitosis regulation; hence, their proper functioning is extremely important for the normal cell development and homeostasis. It is important to underline that the proto-oncogenes are entirely normal genes, but occasionally they may initiate cancer development due to acquisition of genetic alterations within their structure. A single error in the proto-oncogene converts it to the oncogene, which is able to give rise to the malignant transformation (Weinberg, 2007). The oncogene is characterized as a proto-oncogene expressed at inappropriate (i.e., significantly high) levels. As a consequence, excessively high expression of the oncogene leads to an increase in protein expression and stability of its mRNA. This, in turn, alters numerous metabolic processes within a cell and ultimately results in cancer development. Currently, oncogenes are regarded as a broad class of genes that includes numerous transcription factors, receptor or cytoplasmic tyrosine kinases, mitogens, growth factors, and GTPases (Weinberg and Robert, 2007).

Apart from carcinogenesis itself, other important points we should mention are cancer risk factors and individual cancer susceptibility. A risk factor is a chance that a person will have a disease or recurrence. Some do not get cancer. Some do, and we have nothing to do with that. Why do not we all develop this disease? What is the lifetime risk for getting cancer or dying from cancer? These questions have been investigated for decades as hundreds and thousands of epidemiological studies were performed. Large-scale investigations of cancer incidence and mortality revealed that the risk of getting this disease is largely due to the possession of specific risk factors. In other words, this means any risky behavior that might provoke massive damage to genome, thereby initiating malignant transformation. So far, a huge number of factors determining the likelihood of acquiring cancer throughout life have been established. Most of them include lifestyle factors, such as excessive alcohol consumption, tobacco smoking, overweight and obesity, and lack of physical activity, and unhealthy diet (Weinberg and Robert, 2007). The above-mentioned factors are common for all malignancies; however, some types of cancer have their own risk factors. For example, prolonged exposure to UV rays and getting multiple sunburns greatly increase skin cancer risk (de Gruijl, 1999; Dummer and Maier, 2002; Rigel, 2002). The other case in the point is that long-term estrogen therapy is associated with an increased risk of breast cancer in postmenopausal women (Lumachi et al., 2011; Rozenberg et al., 2013; Williams and Lin, 2013). According to recent research, even blood group is to be considered as a risk factor for certain cancers (Xie et al., 2010; Khalili et al., 2011; Yuzhalin and Kutikhin, 2012a; Liumbruno and Franchini, 2013).

Of course, possessing a particular risk factor does not mean that a person will definitely get a disease. On the other hand, not having any risk factors does not guarantee total absence of cancer throughout life. But one thing is certain—the accumulation of risk factors is directly proportional to the probability of the occurrence of the disease.

The good thing about lifestyle factors is that they can be easily avoided, i.e., can be controlled. We can give up with pernicious habits and lead a healthy life to live without illnesses. It is estimated that up to 40% of cancers could be prevented by lifestyle changes. However, we are unfortunately not able to change our genetic predisposition to cancer. Due to differences in our genomes, some individuals are especially prone to malignant transformation and at first glance there is nothing we can do about it. However, it is well known that early defined, most of the cancers have a good cure rate. Therefore, early prevention and diagnosis based on genetic counseling are

the most basic issues when combating the burden of the disease (Yuzhalin and Kutikhin, 2012b). The Human Genome Project has laid the groundwork for the understanding of the roles of genes and their inherited variations (especially single nucleotide polymorphisms) in the etiopathogenesis of cancer (Sachidanandam et al., 2001; Tsigris et al., 2007; Yuzhalin, 2011; Yuzhalin and Kutikhin, 2012c,d,e; Kutikhin and Yuzhalin, 2012a,b,c; Kutikhin et al., 2014). Importantly, some examples of personalized cancer management are applicable even today. For instance, testing for mutations involved in the development of familial breast and ovarian cancer prompts individualized prophylactic therapy including mastectomy and oophorectomy (Wang et al., 2012).

Yet another uncontrollable risk factor for cancer is age. Moreover, growing older is the biggest risk factor for developing tumors. It is well known that cancer is primarily a disease of older people, and incidence rates increase with age for most malignancies. During the twentieth century, a dramatic increase in average life expectancy has been observed; therefore, even 100 years ago the problem of cancer was not as acute as it is today. Longer lifespan is essentially associated with a higher number of accumulated mutations within the genome, which in turn increases the share of mutations within the proto-oncogenes. Much research is being performed to investigate mediators that are supposed to connect cancer and aging. For example, tumor suppressor protein p53 has a considerable influence on both general aging and cancer development; currently, multiple therapeutic approaches are being developed to ameliorate or delay aging and simultaneously prevent tumor formation (reviewed by Hasty and Christy, 2013).

1.1.4 General Mechanisms of Carcinogenesis

It is important to note that carcinogenic mutations as well as all other mutations are caused by a wide range of substances called *carcinogens*. All known mechanisms of human tumorigenesis may be divided into three main groups, namely, physical, chemical, and biological. So far, many important features of carcinogenesis are not well understood and therefore we here give only a brief insight on the existing knowledge about carcinogens and their types.

- *Physical carcinogens* are extremely variable in their nature and sources. The term "physical carcinogen" includes the following agents: ionizing radiation (all types, including X-rays, γ rays, neutrons, radon gas, and UV light), leather dust, talc, coal soot, wood dust, asbestos, erionite, and other natural and man-made mineral fibers and respirable dusts (Maltoni et al., 2000).

Plenty of experiments on mice models demonstrated that dusts and fibers cause cancer when inhaled for a long time. It was also revealed that intratissue implantations of hard and soft metallic or synthetic materials in the form of films, disks, squares, and foams are associated with cancer development as well (Maltoni et al., 1980; Maltoni and Sinibaldi, 1982). In addition, numerous nonfibrous particulate materials, such as crystalline silica and metallic nickel, are also regarded as carcinogens (Hueper, 1955). The mechanisms of physical carcinogenesis are well studied. Physical carcinogens are believed to have a nonspecific irritative effect on cells, which significantly violates various metabolic processes and leads to an excessive DNA damage, which results in cancer development. Generally, physical carcinogens require many years of exposure after getting inside the body to develop cancer. It has been long discovered that lung cancer is fairly frequent among industrial workers who are exposed to prolonged inhalation of asbestos, talc, or coal soot (Falk and Jurgelski, 1979; Wild, 2006; Lenters et al., 2011). With regard to radiation, it is well known that UV rays directly damage cell DNA and therefore are responsible for most cases of skin cancer. Regular use of tanning lamps and prolonged indoor tanning have long been established as important risk factors for skin cancer (Narayanan et al., 2010). The list of the most common physical carcinogens is represented in Table 1.1.

- *Chemical carcinogenesis* is characterized by the modification of the molecular structure of the DNA by various chemical compounds. Importantly, chemical carcinogens are responsible for about 80–90% of all human cancers. The most evident example of chemical carcinogenesis is the association between smoking and lung cancer (Risser, 1996). Virtually all the chemical carcinogens are ubiquitous, i.e., they can be found in the general environment, like prepared food, tobacco smoke, engine exhausts, paints, alcoholic beverages, etc. Some of the chemical carcinogens are regarded as occupational carcinogens, i.e., they can be found in specific work locations only. Importantly, many chemical substances are not carcinogenic themselves, but they convert to the carcinogenic products within the body; therefore, they are termed procarcinogens. It is interesting to note that cancer may also be initiated by the metabolism of endogenous chemicals as well. For example, products of lipid peroxidation and estrogens are known to produce DNA adducts as well as excessive DNA damage (Chung et al., 1996; Bolton et al., 1998). Table 1.2 includes the list of the most dangerous chemical carcinogens.