Cancer Drug Discovery and Development

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Editor

Insulin-like Growth Factors and Cancer

From Basic Biology to Therapeutics

Humana Press

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ISBN 978-1-4614-0597-9 e-ISBN 978-1-4614-0598-6
DOI 10.1007/978-1-4614-0598-6
Springer New York Dordrecht Heidelberg London

Library of Congress Control Number: 2011935731

Printed on acid-free paper

Humana Press is part of Springer Science+Business Media (www.springer.com)

Preface

The insulin-like growth factor (IGF) system has long been known from cell culture systems to be involved in cancer cell biology. Most varieties of cancer cells express components of the IGF system; ligands, receptors, or IGF-binding proteins (IGFBPs). Furthermore, proliferation and cell survival are affected by manipulations of this system. Only recently has this important relationship become clinically relevant; both from a diagnostic and a therapeutic point of view. In this compilation of chapters by world-authorities on the topic, we have aimed at presenting this concept from the epidemiological, basic biology, and therapeutic aspects.

Epidemiologically, studies have demonstrated that the relative risk for various epithelial cancers, such as prostate, breast, and colon, are associated with circulating IGF-1 levels that are in the upper quartiles of the normal range. Both aging and obesity are associated with increased cancer risk and its relationship with these normal physiological processes maybe explained by varying IGF-1 levels. On the other hand, obesity and Type 2 diabetes are conditions that commonly cause endogenous hyperinsulinemia secondary to the insulin resistance, and the elevated circulating insulin levels have recently been shown to be related to increased cancer risk.

Basic biological studies have given further insights into the connection between cancer and the IGF system. Most cancer cells and indeed tumor samples demonstrate increased expression of the IGF-1 receptor (IGF-1R). The levels of IGF-1Rs are the result, in many cases, of mutations in tumor suppressor gene products, such as p53, WT1, PTEN, and BRAC1/2 genes. These proteins normally inhibit the IGF-1R promoter, but when mutated cause increased gene expression. Activation of the receptor by the ligands, insulin, IGF-1, or IGF-2 results in increased proliferation of the cells, with IGF-2 demonstrating the most powerful mitogenic effects of the three. While the insulin receptor (IR) was generally considered a purely metabolic receptor, studies have identified a mitogenic subtype of the receptor (IR-A) that is also expressed in some common cancers, such as breast cancer. Since insulin and IGF-2 both activate this receptor equally, it may play an important role in the cancer biology.

Inhibition of these effects has become a potentially important therapeutic tool in oncology; from antibodies to the receptor or the ligands to tyrosine kinase inhibitors.

Indeed, many potential drugs have been developed and are being tested in preclinical and phase 1–3 clinical trials.

Thus, the IGF system and cancer is a prime example of translational research, where epidemiology has driven to some degree the basic science, and the basic science is now driving clinical therapeutics. Bringing these concepts and information to the reader has required enormous efforts by the most outstanding investigators in this field and we are all extremely grateful for their devotion and hard work.

New York, NY, USA Derek LeRoith

Contents

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