Kinesins and Cancer

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Editor

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Springer

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ISBN 978-94-017-9731-3 ISBN 978-94-017-9732-0 (eBook)
DOI 10.1007/978-94-017-9732-0

Library of Congress Control Number: 2015932649

Springer Dordrecht Heidelberg New York London

Printed on acid-free paper

Springer Science+Business Media B.V. Dordrecht is part of Springer Science+Business Media (www.springer.com)

Preface

The validation of proteins as disease targets is a notoriously difficult and complex task. In this book, we attempt to validate members of the kinesin superfamily as potential targets for drug development in cancer chemotherapy.

The first chapter sets out the groundwork for subsequent chapters by summarising current knowledge and highlighting common principles and features of the kinesin superfamily, focusing mainly on kinesins involved in mitosis and cytokinesis (mitotic kinesins). The following three chapters illustrate the present status of the most advanced kinesin Eg5 in terms of drug development. Chapter 2 describes the development of highly potent and specific Eg5 inhibitors, a range of which are in clinical development, whereas Chap. 3 details the mechanism of these Eg5-targeting drugs. Chapter 4 summarises the outcome of these inhibitors in multiple phase I and II clinical trials. This chapter also explains some of the reasons why clinical success has so far been only moderate, and in addition provides some intriguing ideas about the lessons to be drawn from these trials for the improvement of future clinical trials on Eg5. In the following eight chapters (Chaps. 5, 6, 7, 8, 9, 10, 11 and 12) experts in the motor field attempt to systematically validate or exclude the remaining 15 human mitotic kinesins as potential targets for cancer chemotherapy. By summarising current knowledge on how mitotic kinesins work, the authors provide a balanced opinion about their usefulness as drug targets, taking into account potential undesired side effects.

Surprisingly, a range of mitotic kinesins seem to represent potential novel targets, making them worthwhile starting points for the development of hits as tool compounds pending further validation. However, previously unknown functions may be discovered or redundant pathways revealed, which may exclude some of the kinesins as potential targets. Will this initial assessment of kinesins as potential targets remain valid in the longer term? Only time will tell.

Kinesins are not the only novel prospective targets of the mitotic spindle. Other non-motor spindle proteins are coming to the fore. Chapter 13, on non-kinesin targets, is an attempt to broaden the search for potential targets of the mitotic spindle.

Finally, the last chapter – on neuronal kinesins – attempts to focus attention on multifunctional kinesins, in particular those that play important roles in mitosis and neuronal development. Work on these kinesins will require careful monitoring to avoid unexpected side effects in the central nervous system, though early results suggest that these worries are unfounded.

These are very exciting times for scientists working in the motor field. By applying cutting-edge methodology, the functions of mitotic kinesins are being elaborated and the mechano-chemistry of these molecular machines revealed in astonishing detail. At the same time kinesins are emerging as medically relevant proteins. They may in the future make the leap from potential to validated targets. Very exciting times lie ahead. I hope that this book will contribute to the initial validation of mitotic kinesins as targets for drug development in cancer chemotherapy.

London, UK
February 2015

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