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BOOK REVIEW

Design of Caspase Inhibitors as Potential Clinical Agents

(T. O'Brien and S. D. Linton, eds., CRC Press, Taylor & Francis Group, 2009, 299 p., $169.95)

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The book under review is far from being the only work devoted to the development of various means of modulating different components of apoptotic machinery, including killer proteases caspases, as a therapeutic strategy. Nevertheless, never before has such a topic been discussed by the authors directly involved in the pharmaceutical industry. In fact, both editors and over half of contributors of the book represent various pharmaceutical and biotechnology companies, which is decisive for the approaches to the subjects and the practical importance of the volume.

The book comprises 10 chapters and starts with an overview of the caspase proteolytic machine. The pathways involved in propagation of apoptosis (caspase 2, 3, 6, 7, 8, 9, 10) as well as pro-inflammatory cytokine processing (caspase 1, 4, 5) are considered. Several pathways leading to caspase activation such as the mitochondrial pathway, the death receptor pathway, the granzyme B-initiated pathway, and the endoplasmic reticulum and inflammatory-mediated pathways are briefly described. Three different multimeric protein platforms triggering activation of caspase 8/10, 9, and 1 (the death-inducing signaling complex, the apoptosome, and the inflammasome, respectively) are discussed. It is unfortunate that the PIDDosome, another molecular platform for caspase activation, is beyond the scope of the chapter.

The main focus is then directed to the role of caspases in inflammation- (chapter 2) or apoptosis-driven (chapter 3) diseases. In particular, the critical contribution of caspase-1 in pathogenesis of arthritic disorders, hereditary periodic fever syndromes, Crohn's diseases, sepsis, psoriases, contact allergen sensitivity, as well as acute and chronic neurodegenerative disorders is thoroughly explained. A wide variety of human pathologies characterized by excessive apoptosis such as myocardial infarction, atherosclerosis, liver fibrosis, alcoholic and infectious hepatitis, stroke, and Alzheimer's and Parkinson's diseases are also discussed with special emphasis on the beneficial effects of caspase blockade. The next chapter 4 provides valuable insights into the mechanisms of caspase activation, substrate binding, and cleavage. In addition, optimal conditions for inhibiting either caspase activation or its catalytic activity are reviewed.

The authors of chapter 5 discuss in depth current knowledge on design and development of non-peptide small-molecule inhibitors of caspases. One hundred and seventeen caspase-inhibiting compounds are analyzed. As the authors state, the non-peptide caspase inhibitors are likely to be used only for treatment of acute settings due to lack of selectivity (for target cell or tissue type) of those agents. In the following chapter the progress that has been made in the identification of small-molecule inhibitors of inflammatory caspases is considered. Major attention is given to the caspase-1-selective inhibitors that are predominantly peptidomimetics (chapter 6). This chapter also contains a comprehensive table on inflammatory caspase patent filings.

Discovery of >300 caspase inactivators is described in chapter 7, beginning with the reversible peptide aldehydes and ending with the recent reversible and irreversible peptidomimetic inhibitors. The advantages and drawbacks of different approaches to developing agents (both specific and pan inhibitors) for therapeutic blockade of caspases are nicely analyzed. The next chapter 8 revolves around the discovery and characterization of Emricasan (PF-03491390/IDN-6556), a first-in-class apoptotic caspase inhibitor entered into clinical testing. Chapter 9 describes modern strategies to caspase inhibitor design. The recent technologies such as fragment-based screens and inhibition through non-active-site mechanisms are under development today.

Nevertheless, some questions critical for the clinical application of caspase inhibitors arise. (i) It is not known whether other types of cell demise (autophagic cell death, necrosis, etc.) can be activated upon the blockade of apoptosis due to caspase inhibition. (ii) Increasing evidence suggests that some caspases can function in various non-apoptotic cellular processes (survival, proliferation, differentiation, migration, inflammation). Therefore, the adverse effects of caspase inactivation should be taken

into account. (iii) Apoptosis blockade by caspase inhibitors can impair the functional activity of the surviving cells. (iv) Finally, risk of malignant transformation after long-term inhibition of apoptosis might exist. The reader will find the useful discussion of several problems stated above in the final chapter 10. This chapter also provides a competent review of ongoing clinical trials with caspase inhibitors.

To summarize, this new monograph is essential for all persons interested in the involvement of caspase-dependent cell death in human pathologies and caspases as targets in drug discovery.

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