Cell Death and Differentiation (2005) 12, 1152–1153

www.nature.com/cdd

Book Review

Death receptors in cancer therapy

Y Suzuki[1], A Rufini[1] and H Belfield*[,2]

[1] Department of Experimental Medicine and Biochemical Sciences, University of Rome, 'Tor Vergata', Rome, Italy
[2] CDD Rome Editorial Office, University of Rome, 'Tor Vergata', Rome, Italy
* Corresponding author: Dr H Belfield, CDD Rome Editorial Office, University of Rome, Via Montpellier 1, 'Tor Vergata', Rome, Italy.
E-mail: heli.belfield@gmail.com

Cell Death and Differentiation (2005) **12,** 1152–1153. doi:10.1038/sj.cdd.4401681

Cancer Drug Discovery and Development: Death Receptors in Cancer Therapy, edited by Walfik S EI-Deiry. Humana Press, New Jersey, 2005. ISBN 1-58829-172-3

The field of cell death research has been progressing explosively for about 10 years and keywords such as 'Death' Receptor and 'Death' signals have been carried on to various scientific journals covering different fields. It is now well known that cell death plays an important role in biological processes including homeostasis of the immune system, embryonic development, and, as time goes by, it's getting clearer that misfunction of this crucial biological process is involved in the aetiology of a high number of human diseases. It is not surprising then that in 2002 Sydney Brenner, H Robert Horvitz and John E Sulston received the Nobel Prize in medicine for their contribution to further understanding the process of apoptosis. Indeed, one of the mile stones in cancer research has been the understanding that some chemotherapeutic agents act by inducing apoptosis in cancer cells and that tumour resistance to treatment can be due to a failure of these cells to undergo apoptosis. This failure is mediated by different mechanisms involving both the apoptosis-regulating factors and to a lesser extent the proteins of the core apoptotic machinery. A huge number of papers have been published on the subject and it is therefore difficult for researchers outside the field to digest the enormous amount of information on the intrinsic molecular mechanism of cell death through Death Receptors and their possible role in cancer development and therapy.

The book 'Death Receptors in Cancer Therapy' edited by Walfik S EI-Deiry sets out to provide a basic introduction of cell death for the 'beginner' and to give a review of the field for people trying to develop new cancer therapies. It is composed of 21 chapters written by experts in the field of cell death. The first part of the book introduces the mechanisms of apoptosis and cancer resistance, then the reader moves into the chapters elucidating mutations and regulation of death receptors and then finally into chapters specifically dedicated to gene therapy, the role of TRAIL in cancer therapy and the targeting of death receptor inhibitors.

Basic information on death receptors is presented in the first chapter by McDonald III and EI-Deiry. Here the authors, supported by clear schematic figures, provide a clear picture of the mechanism of cell death starting from the historical studies in *Caenorhabditis elegans.* We can then learn how cancer cells can acquire resistance to cell death via dysfunction of the upstream proteins of death signal pathway. Here, McConkey describes inactivation of p53 and activation of AKT as the two most common examples of this event. A more detailed description of p53 and NFkB signalling and their defects can be found in other chapters of the book.

Mutations in other apoptotic genes also contribute to the development and progression of tumours and Lee *et al*. summarise the death receptor mutations found in cancer cells. In addition to mutation in gene encoding apoptotic factors, alterations of their expression also affects the tumour progression; therefore, the book also analyses transcriptional and post-transcriptional regulation of death receptors. Kontny *et al*. explain the promoter structures and transcriptional regulation of some death receptor genes. Although this chapter summarises information about the expression of many factors in the cell death pathway, we feel there is a lack of description of chromatin function on transcriptional regulation, as recent studies show that histone modifications including acetylation and deacetylation also play an important role on transcriptional regulation.

Since TRAIL seems to be the most attractive death ligand in cancer therapy, a large section of the book is dedicated to this molecule and to the regulation of its receptors. TRAIL regulation is complex as it binds to five different receptors such as death receptors DR4 and DR5, decoy receptors DcR1 and DcR2, and osteoprotegerin. DR4 and DR5 are functional TRAIL receptors, while the other receptors do not have a functional death domain, implying that they may act as decoy receptors by competing with DR4 and DR5. What makes this interesting for cancer therapy is that, on the contrary of Fas, TRAIL delivery in anticancer experiments does not result in any deleterious effect on normal cells. Therefore, many oncologists predict that TRAIL has the potential to be developed as an anticancer drug that selectively restricts primary as well as metastatic tumours. However, as described in the book, many cancer cells are resistant to TRAIL, so many investigators hope that combination therapies with TRAIL and chemotherapeutic agents will overcome this problem.

Overall the book is interesting and well written, the major complaint being the 'spreading of information' and the repetition of concepts. In fact, each chapter contains an

introduction, sometimes a very long introduction, for example, Chapter 14 recapitulates the main features of apoptosis discussed in the first chapters and the role of TRAIL in cancer therapy is discussed in more than five different chapters. Despite this, the book provides a good opportunity for a newcomer to the field to understand basic cell death mechanisms becoming friendly with eerie words such as 'Death' Receptors and 'Death' Signals.