Receptors and ligands of the TNF superfamily, with the exception of a few members, are transmembrane glycoproteins. They display pleiotropic functions. Several receptors of the family are able to induce apoptosis or cell death. Their cognate ligands are instrumental to immune cells, allowing eradication of unwanted, virally infected or transformed cells. Among these, TRAIL has early on attracted a major interest in oncology, owing to its ability to selectively trigger tumor cell killing while sparing normal cells. TRAIL induces cell death through binding to its two agonist receptors, namely TRAIL-R1 and TRAIL-R2. Its use in the clinic, however, despite clear clinical evidence of antitumoral activity, has remained limited due to a plethora of molecular mechanisms leading to cell resistance as well as to our poor understanding of the biological function and regulation of its receptors. Therapeutic strategies or options to exploit TRAIL or its derivatives in oncology should benefit from a deeper understanding of the signal transduction pathways induced by each TRAIL agonist receptor or beyond. The reader will find in this book chapters describing our current understanding of the molecular mechanisms leading to cell death or tumor cell resistance to TRAIL-induced killing, and beyond to receptors of the TNF family or unrelated receptors, such as Fas/CD95 or TLR3, respectively. Nonapoptotic signaling capabilities of these receptors will also be presented with a special emphasis on Fas/CD95, as increasing body of evidence demonstrates that some of these receptors may also exhibit atypical immune functions and even prometastatic activities. The pleiotropic signaling capabilities of transmembrane receptors and ligands cannot be dissociated from their biochemical context. They are surrounded by lipids and undergo post-translational modifications. We will discuss, in the light of the most recent discoveries, how partitioning, sphingolipids, and glycosylation of TNF receptors or ligands are likely to alter or contribute to their signal transduction capabilities. Last, in silico modeling of these complex systems will be presented, as these simulations are likely to be useful to understand how cellular protein, lipid, or sugar heterogeneities are likely to affect the therapeutic efficacy of TRAIL or TRAIL derivatives.
I would like to thank personally each of the authors for their effort and thoughtful contribution. This timely and comprehensive volume addresses the most advanced knowledge of TNF signaling with a special emphasis on TRAIL. With its strong focus on therapy and innovative concepts, this book will serve as a reference in the field for a wide audience of readers comprising researchers, medical professionals, students, and biotech and pharmaceutical companies.

Dijon, France

Olivier Micheau
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