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## Preface

Apoptosis consists of two main signaling pathways distinguished by the origins of the signals. While the interaction of the apoptotic ligands to their respective death receptors (DRs) at the cell surface activates the extrinsic signaling pathway, the intrinsic signaling pathway is provoked by accumulation of DNA damages, oncogene overexpressions, deregulation of mitochondrial functions, reticulum endoplasmic stresses, and/or viral infections. These pathways are interconnected, and both converge on activation of a family of cysteine proteases designated the caspases. The apoptotic role of the mitochondrion is associated with a reduction in its transmembrane potential and the loss of its extracellular membrane integrity, leading to the release of various apoptogenic factors into the cytosol.

DRs (TNFR1, CD95, DR3, DR4, DR5, and DR6) belong to the TNF receptor (TNF-R) superfamily. These type I transmembrane proteins share common features including extracellular amino-terminal cysteine-rich domains (CRDs), and intracellular death domain (DD), which is crucial to implement the apoptotic signal through protein-protein interactions (PPIs). Indeed, TNF-Rs do not possess any enzymatic activity and rely on dynamic PPI formation for signaling. The exhaustive identification of these PPIs provides some insights into the biological roles of these receptors, and protocols described in this book will help researchers to do that.

Because mutations in the DR designated CD95 (Fas or APO-1) or its cognate ligand, CD95L (also known as FasL or CD178) leads to auto-immune disorders such as systemic lupus erythematosus (SLE) and to cancers; and CD95/CD95L pair was initially classified as having a tumor suppressor role. However, recent data emphasize that CD95 can also induce nonapoptotic signaling pathways promoting carcinogenesis and inflammation in chronic inflammatory disorders.

In addition, TNF family members can be processed by metalloproteases and released in bloodstream as soluble ligands. Mainly due to the difference in their stoichiometry, these ligands are able to implement different signaling pathways upon binding to their receptor. CD95L ectodomain can be cleaved close to the plasma membrane by metalloproteases, and then released into the bloodstream as a soluble ligand called cleaved-CD95L (cl-CD95L) to differentiate it from its soluble exosome-bound counterpart. While transmembrane CD95L at the surface of activated lymphocytes and natural killer (NK) cells kills transformed and infected cells, cl-CD95L fails to induce cell death and instead promotes cell migration of cancer cells and immune cells. The biological roles played by cl-CD95L in pathophysiological contexts remain to be elucidated.

In this book, the authors provide original protocols they commonly use to study the apoptotic and nonapoptotic roles of CD95. These methods should help researchers to better understand the biological functions of this cytokine.

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CD95

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