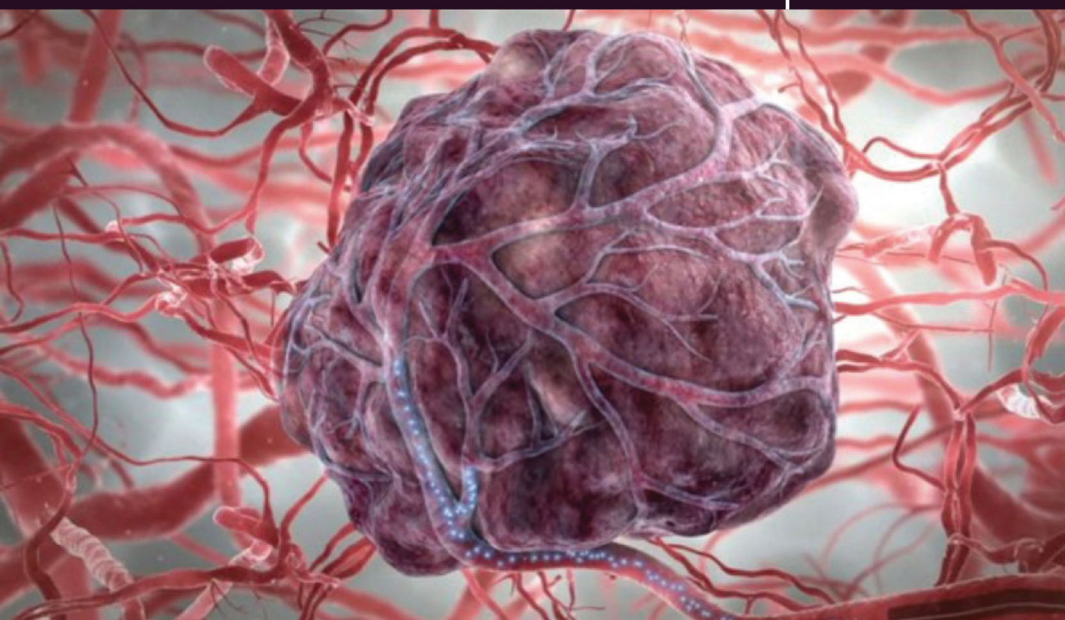


Signal Transduction in **CANCER**

Mohamed A. Selmy

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TABLE OF CONTENTS

<i>List of Figures</i>	<i>xi</i>
<i>List of Tables</i>	<i>xv</i>
<i>List of Abbreviations</i>	<i>xvii</i>
<i>Preface</i>	<i>xix</i>
Introduction: Basics and Tracks of Cell Signaling	xxi
References	xxvii
Chapter 1 Growth Factors and Tyrosine Kinase Receptors	1
1.1. General Characteristics of the GF–TKR Interrelationship	1
1.2. The Paradigmatic Model of the EGF (ERBB) Family	4
1.3. Other Families of GFS and Growth Factor Receptors	10
1.4. Tyrosine Phosphatase Receptors	19
Further Reading	22
Chapter 2 Map Kinase Pathway	25
2.1. From Receptor Stimulation to RAS Activation	25
2.2. Kinase Cascade	28
2.3. Other Signaling Elements	30
2.4. Map Kinase Substrates	32
2.5. Oncogenic Changes	34
2.6. Pharmacological Targeting	36
Further Reading	39
Chapter 3 Phosphatidylinositol 3-Kinase Pathway	41
3.1. From Phosphatidylinositol 3-Kinase to AKT Proteins	41
3.2. AKT Proteins and Their Substrates	43
3.3. mTOR Protein and The TORC Complexes	45
3.4. Oncogenic Alterations	49

	3.5. Pharmacological Targets	50
	Further Reading	52
Chapter 4	G-Protein-Coupled Receptors	55
	4.1. Structure And Mechanism of Action of G-Protein-Coupled Receptors	55
	4.2. Second Messengers of GPCR Activation.....	58
	4.3. Oncogenic Changes And Pharmacological Targeting	62
	Further Reading	65
Chapter 5	TGFβ Pathway.....	67
	5.1. TGF β Family Ligands	67
	5.2. Receptors Activation	69
	5.3. Signal Transduction In The TGF β Pathway	70
	5.4. Oncogenic Changes	72
	5.5. Pharmacological Targeting	73
	Further Reading	75
Chapter 6	Cytokines Pathway	77
	6.1. Cytokines.....	77
	6.2. Cytokine Receptors and JAK Activation.....	78
	6.3. Signal Processing	81
	6.4. Oncogenic Changes	82
	6.5. Pharmacological Targeting	84
	Further Reading	85
Chapter 7	Cell Cycle Control.....	87
	7.1. Cell Cycle Phases	87
	7.2. Effector Proteins of Cell Cycle Regulation	90
	7.3 Control of Cell Cycle Progression	94
	7.4. Oncogenic Changes In Cell Cycle Regulation.....	99
	7.5. Pharmacological Targeting	100
	Further Reading	102
Chapter 8	WNT Pathway	105
	8.1. WNT Ligands and Their Receptors	105
	8.2. WNT- β -Catenin Pathway	106

8.3. 'Non-Canonical' WNT Pathways.....	108
8.4. Oncogenic Changes	109
8.5. Pharmacological Targeting	110
Further Reading	111
Chapter 9 Notch Pathway.....	113
9.1. DSL Ligands.....	113
9.2. Notch Receptors	114
9.3. Notch Receptor Activation And Signal Transduction.....	115
9.4. Oncogenic Changes	116
9.5. Pharmacological Targeting	117
Further Reading	119
Chapter 10 Ion Channel-Coupled Receptors.....	121
10.1. Activation Of Ligand-Gated Ion Channels.....	121
10.2. Purinergic Receptors.....	123
10.3. Ca ²⁺ Signaling.....	123
Further Reading	130
Chapter 11 Apoptosis Process and Regulation	133
11.1. Proteins Implicated In Apoptosis.....	133
11.2. Intrinsic (Mitochondrial) Apoptosis Pathway.....	139
11.3. Extrinsic (Death Receptor) Apoptosis Pathway.....	142
11.4. Oncogenic Alterations Of Apoptosis Pathways	146
11.5. Pharmacological Targets	146
11.6. Dependence Receptors.....	147
Further Reading	150
Chapter 12 Hedgehog Pathway	153
12.1. Hedgehog Ligands.....	153
12.2. Patched Receptors and Their Activation.....	154
12.3. HHG Signal Transmission	156
12.4. Oncogenic Changes	157
12.5. Pharmacological Targeting.....	157
Further Reading	159

Chapter 13	Integrins.....	161
	13.1. Integrins And Integrin Ligands.....	161
	13.2. Signaling Pathways Starting From Integrins.....	165
	13.3. Oncogenic Changes	167
	13.4. Pharmacological Targeting	168
	Further Reading	171
Chapter 14	Semaphorins.....	173
	14.1. Semaphorins And Semaphorin Receptors.....	173
	14.2. Semaphorin-Induced Signal Transmission	176
	14.3. Oncogenic Changes and Pharmacological Targeting.....	177
	Further Reading	179
Chapter 15	Nuclear Receptor Pathways	181
	15.1. Structure And Function of Nuclear Receptors.....	181
	15.2. Steroid Hormones Receptors.....	185
	15.3. Thyroid Hormones Receptors	188
	15.4. Vitamin D Receptors	188
	15.5. Retinoic Acid Receptors.....	190
	15.6. Peroxisome Proliferator-Activated Receptors	191
	15.7. Xenobiotics Receptors	192
	Further Reading	194
Chapter 16	Signaling By Oxygen And Nitric Oxide	197
	16.1. Hypoxia.....	197
	16.2. Oxidative Stress	201
	16.3. Nitric Oxide	202
	16.4. Guanylyl Cyclase Receptors	204
	Further Reading	205
	Index.....	207

LIST OF FIGURES

Figure 1. The mechanism of signaling from the message to the effector.

Figure 2. Hallmarks of Cancer

Figure 3. The tyrosine kinase receptors family.

Figure 4. EGF family growth factors.

Figure 5. Growth factors of the ERBB family.

Figure 6. EGFR dimerization; in the absence of ligand, and in the presence of a ligand.

Figure 7. EGFR autophosphorylation. (a) Before receptor activation. (b) receptor activation.

Figure 8. The interaction between growth factors and their cognate receptors.

Figure 9. The tyrosine phosphatase receptors family.

Figure 10. Post-translational modifications of RAS proteins.

Figure 11. Effectors of the RAS proteins.

Figure 12. MAP kinase pathways.

Figure 13. Kinases organization and scaffold proteins.

Figure 14. The different modules of kinase cascades.

Figure 15. Activation of PI3 kinase by different ways.

Figure 16. Catalytic activities of PI3 kinase and PTEN.

Figure 17. PI3 kinase pathway after activation by a TKR.

Figure 18. mTOR protein and the TORC complexes.

Figure 19. Activation of the mTOR protein.

Figure 20. Downstream signaling of mTOR

Figure 21. Activation and function of large heterotrimeric G-proteins.

Figure 22. Formation of second messengers.

Figure 23. PKC-activating and PKC-activated pathways.

Figure 24. Small G-protein activation downstream GPCR signaling.

Figure 25. The TGF β dimer.

Figure 26. TGF β reception complex.

Figure 27. TGF β signaling pathway.

Figure 28. Structure of SMAD proteins.

Figure 29. Signal reception complexes of the main type I cytokines.

Figure 30. Cytokine receptor activation via the JAK kinases.

Figure 31. Structure of the JAK and STAT proteins.

Figure 32. The JAK–STAT signaling pathway.

Figure 33. Schematic representation of mitosis.

Figure 34. Cyclin–CDK complexes and their intervention during the cell cycle.

Figure 35. Control exerted on cell cycle.

Figure 36. G1 \rightarrow S transition: phosphorylation of RB proteins.

Figure 37. G2 \rightarrow M transition: activation of the cyclin B–CDK1 complex.

Figure 38. Two aspects of mitosis: metaphase and anaphase.

Figure 39. Cell cycle checkpoints and control of DNA integrity.

Figure 40. Intercellular junctions involving E-cadherin.

Figure 41. The Wnt– β -catenin pathway.

Figure 42. Non-canonical Wnt pathways.

Figure 43. DSL ligands.

Figure 44. NOTCH receptors.

Figure 45. Notch signaling pathway.

Figure 46. Organization of ion channel-coupled receptors.

Figure 47. Ca²⁺ Signaling

Figure 48. Intracellular Ca²⁺ channels and their ligands.

Figure 49. Caspase structure and activation.

Figure 50. Caspase proteolytic cascade.

Figure 51. BCL2 family proteins.

Figure 52. IAP family proteins.

Figure 53. Cell death receptors, ligands and adapter proteins.

Figure 54. Formation and activation of the apoptosome.

Figure 55. Intrinsic (mitochondrial) apoptosis pathway.

Figure 56. Extrinsic (death receptors) apoptosis pathway.

Figure 57. Signaling pathways activated by death receptors and other TNFRSF members.

Figure 58. Dependence receptors.

Figure 59. Hedgehog (HH) protein biogenesis and release.

Figure 60. PTCH receptor information transduction to SMO proteins.

Figure 61. The Hedgehog signaling pathway.

Figure 62. Integrin assembly from their α and β subunits.

Figure 63. Integrin structure and conformation of α and β chains.

Figure 64. Integrin-activated signaling pathways.

Figure 65. Structure of semaphorins, plexins and neuropilins.

Figure 66. Semaphorin 3A signaling pathway.

Figure 67. Structure of the main ligands of some nuclear receptors.

Figure 68. Structure of nuclear receptors.

Figure 69. Transcription activation by nuclear receptors.

Figure 70. Hypoxia signaling.

LIST OF TABLES

- Table 1.** Tyrosine Kinase Inhibitors
- Table 2.** Semaphorins and semaphorin receptors.
- Table 3.** Main nuclear receptors and their ligands

LIST OF ABBREVIATIONS

AIF	Apoptosis-inducing factors
AMPK	AMP-dependent kinase
ANG	Angiopoietins
APAF	Apoptotic peptidase-activating factor
ATRA	All-trans retinoic acid
CARDs	Caspase recruitment domains
CASP3	Caspase 3
CBL	Casitas B-lineage lymphoma
CDK	Cyclin dependent kinase
cGMP	cyclic guanosine monophosphate
DAG	Diacylglycerol
DLL	Delta-like ligands
ECM	Extracellular matrix
EGF	Epidermal growth factor
EMT	Epithelial-to-mesenchymal transition
ERK	Extracellular signal-regulated kinases
FGF	Fibroblastic Growth Factors
FLT	FMS-like tyrosine kinase
GAP	GTPase- activating protein
GEF	GDP–GTP exchange factor
GIST	Gastrointestinal stromal tumors
GPCR	G-Protein-Coupled Receptors
HDAC	Histone deacetylase
HGF	Hepatocyte Growth Factor
HIF	Hypoxia-inducible factor
HSP	Heat shock protein

IGF	Insulin-Like Growth Factors
IL	Interleukin
IRS	Insulin receptor substrates
LKB1	Liver kinase B1
MCSF	Macrophage colony-stimulating factor
MMPs	Matrix metalloproteinases
mTOR	mechanistic target of rapamycin
NO	Nitric Oxide
NPP	Natriuretic peptides
PDGF	Platelet-Derived Growth Factors
PI3K	Phosphatidylinositol 3-kinases
PIP	Phosphatidylinositol 4,5-bisphosphate
PLC	Phospholipase C
PTB	Phosphotyrosine-binding domains
ROS	Reactive Oxygen Species
SH2	SRC homology domains 2
TACE	TNF-alpha-converting enzyme
TGF α	Transforming growth factor α
TSC	Tuberous sclerosis complex
VEGF	Vascular Endothelial Growth Factor
VHL	von Hippel–Lindau

PREFACE

There is a fundamental necessity for oncologists to identify cell–cell signaling pathways, to comprehend their interactions, their role in cell proliferation, motility, survival and their contribution in cancer. The clinical oncology practice has turned to be dependent upon the awareness of cancer biology. The understanding of the pathways and their downstream signals would restrain the toxic and expensive treatments to half of the patients suffering from certain metastatic cancers.

This book aims at illustrating the signaling pathways to readers involved in the oncology practice. The key cell signaling pathways are presented in independent chapters, each of them illustrating a “signaling system” characterized by the intimate pairing of a receptor type and its related ligands. Despite the complexity of these pathways, I have tried to make it palatable and simple as possible as I can. In order to provide a complete understanding, the general mechanisms governing DNA repair, gene regulation, epigenetics and protein expression have been illustrated, together with the changes of these mechanisms that share in the process of oncogenesis. As the crosstalks and interactions between signaling pathways are so diverse and crucial, a note was given at the each chapter illustrating the interaction among pathways. In addition, each chapter was tailed by a short review of the oncogenic changes of the pathway studied and by a short appraisal of the pharmacological targets that may be put in concern for therapeutic agents. The references, provided at the end of each chapter, were limited to selected updated reviews about the topic of the chapter. In its final format, this book represents an informative summary of many books covering the topic of oncological cell signaling; especially the book “Textbook of Cell Signalling in Cancer” by Jacques Robert which we shadowed its format. I have tried to give a useful summary of these books for a quicker and focused revision.

There are numerous options for the revision of cell signaling in oncology. One can start from the demonstration of the players that interfere in all pathways: ligands, ligands, protein kinases, transcription factors and small G-proteins and define their numerous roles. Another way is to provide a “horizontal”

combination level: plasma membrane, cytoplasm, mitochondria and nucleus. It is also possible, as illustrated here in this book, to shape a “vertical” level of interaction, presenting each pathway by the type of receptor complicated and illustrating the available linked data: ligands, receptor activation, the information transduction and execution of effectors.

In relation, despite the density and the numerous connectivity of signaling pathways, there are homogenous receptor clusters, able to deduce the signals brought by ligands belonging to certain families: this book is framed around this ligand–receptor alignment. This way permits a more simplified illustration of signaling modules but it may retain some difficulties at the level of the “shared final pathways” of cell signaling, it would have been conceivable to write special chapters on final transcription factors, but it would be beyond the scope of this book.

I hope that this book will realize its goal in yielding the necessary information regarding the oncological signaling pathways in cancer. Hopefully, these summary notes will keep the reader safe in the jungle of the pathways, yet giving him a concise review of structures, mechanisms and therapeutic targeting of these pathways.

INTRODUCTION: BASICS AND TRACKS OF CELL SIGNALING

Cell communication is vital for multicellular organisms: cells must inevitably give-and-take the information compulsory for organizing their activities. The main lines of cell communication are generally universal: signaling molecules are released by a known cell and identified by another one, which in turn stimulates a transduction pathway, allowing an effector system capable of achieving the matching tasks. The attainment of this information transmission necessitates from the source cell the encrypting of the communication message in a way that could be appropriately understood, and from the cell in receipt of the message to the agreeing decoding structures (Fig. 1). The diversity of signal transduction systems is extensive, at the level of both signal reception and task implementation. Nevertheless, it is definitely probable to recognize general outlines and shared structures of organization.

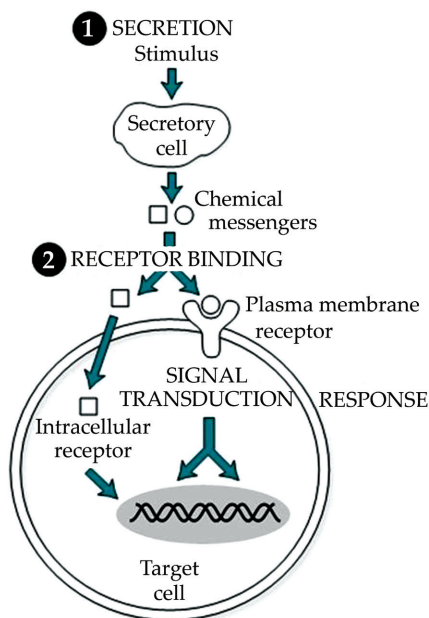


Figure. 1: The mechanism of signaling from the message to the effector (Lehninger, 2004).

At the level of signal response, the mechanisms are generally reliant on the chemical structure of the messengers:

- Hydrophilic messengers (proteins, peptides, amino acids and derivatives) cannot go in the cells as they cannot simply cross the membranes; a membrane receptor is a prerequisite to attain and comprehend the message and to transmit the information afterwards.
- Lipophilic messengers (steroids, fatty acids and derivatives) and the simple compounds (oxygen, nitric oxide) are capable of diffusing inside cell membranes and to affect directly their corresponding intracellular targets, in the cytoplasm or the nucleus.
- Ionic compounds (Na^+ , K^+ , Cl^- and Ca^{2+}) are capable of induction of opening or closing of membrane channels permitting the production of transmembrane currents which are employed for the transmission of nervous impulses but are also accountable for numerous intracellular actions. The transmission of the signals

attained by the receptors trails many different processes but the general mechanisms are not plentiful, the main mechanisms are:

- Enrollment of adapter proteins capable of interacting with other proteins and inducing conformational changes, and subsequently protein activity.
- The phosphorylation and dephosphorylation cascades, stimulated by kinases and phosphatases, which adjust the protein three-dimensional structures.
- The activation of small G-protein, through exchange and hydrolysis processes of guanyl nucleotides, which also stimulate alterations in the conformation of protein.
- Production of second intracellular messengers, which transmit the information, carried to the membrane by the extracellular first messengers.
- In addition, the effectors are also various, but again it is conceivable to group them together in a few assort:
- Transcriptional factors which order target genes transcription; these are the most classical effectors and the most frequently employed downstream the signal transduction pathways.
- Translational regulators executing on protein synthesis, which are directly integrated in certain signaling pathways.
- Proteins of the cytoskeleton or the extracellular matrix, which regulate the cellular adhesion, motility and migration.
- Ionic channels involved especially (but not exclusively) in synaptic transmission.

The cell, consequently, has a ‘toolbox’ from which it can draw the sufficient tools to comprehend the information established and perform the given orders.

On the other hand, cell signaling may also work at highly flexible distances: the first signaling system that has been recognized is the endocrine system, in which the endocrine gland secretes hormones targeting distant cells and organs. The molecules produced in a certain cell could be delivered to the neighboring cells, which is termed ‘paracrine’ signaling; also the term ‘juxtacrine’ is given for the signal transmitted between jointed cells; and ultimately the term ‘autocrine’ is established when the molecules, after transiting in the extracellular space, execute their effect on the same cell. In addition to the intercellular signaling, an intracellular signaling