Signal Transduction in CANCER

Mohamed A. Selmy

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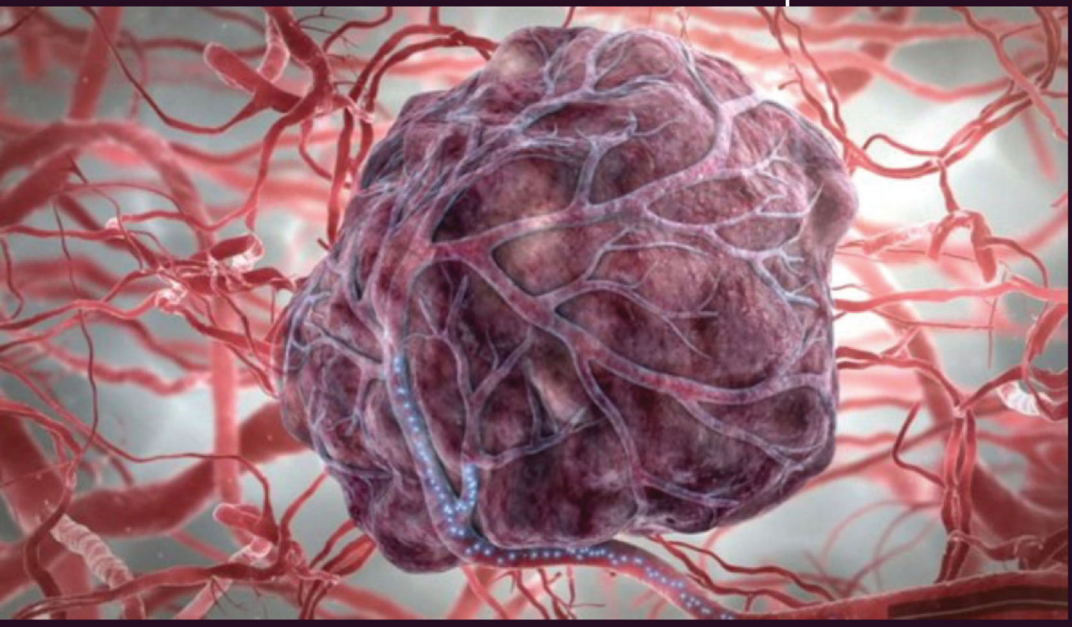

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AIF	Apoptosis-inducing factors
AMPK	AMP-dependent kinase
ANG	Angiopoietins
APAF	Apoptotic peptidase-activating factor
ATRA	All-trans retinoic acid
CARDs	Caspase recruitment domains
CASP3	Caspase 3
CBL	Casitas B-lineage lymphoma
CDK	Cyclin dependent 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.

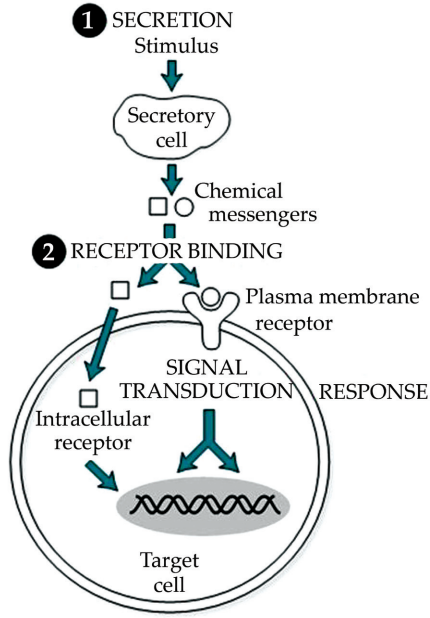

Figure. 1: The mechanism of signaling from the message to the effector (Lehninger, 2004).

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 assorts:
- 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