# Cancer Biology

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## How Science Works

Second Edition

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# Preface

This book begins with sobering news: *approximately one in two individuals in high-income countries will receive a cancer diagnosis during their lifetime*, meaning a malignant tumor will be detected in their body. Yet there is encouraging news as well: *fewer than half of all cancer patients die from the disease, and every second cancer-related death is preventable*. Cancer is not a single disease but a heterogeneous group of disorders that can arise in virtually any organ. What they all share is uncontrolled cellular growth.

Every newly diagnosed malignant tumor in adulthood reflects an individual history of *two or more decades of tumorigenesis*. Cancer is traditionally viewed as a disease of the genome, driven by accumulated DNA point mutations, as well as chromosomal translocations, deletions, and amplifications. Tumorigenesis also involves profound alterations in cellular identity, responsiveness to internal and external signals, and major shifts in the transcriptome. These changes are rooted in *epigenomic dysregulation*. In fact, most cancers harbor mutations and alterations not only in their genomes but also in their epigenomes.

Cells in our body have the capacity to grow when needed: during wound healing or in the continuous renewal of blood, skin, and intestinal tissues. Because malignant transformation is typically slow, *cancer is largely an age-related disease*, one that seems inevitable as we grow older. Yet tumorigenesis depends on numerous environmental influences, including the ability of the immune system to detect and eliminate cancer cells. Many environmental factors that either promote or protect against cancer lie within our own control: *avoiding smoking, choosing a healthy diet, and staying physically active* are key examples. Thus, *cancer prevention through lifestyle choices* remains the most powerful strategy for reducing cancer risk.

Understanding cancer requires insight into ourselves, both in detail and within a broader context. Basic biology explains the cellular mechanisms of growth, differentiation, and cell death that make life possible. Every human being represents an intricate interplay of hundreds of cell types, each forming specialized tissues and organs. These processes must be precisely coordinated during embryonic development and maintained throughout adult life to preserve homeostasis. Studying the cellular and molecular foundations of these processes is deeply fascinating, yet also demanding. Much of what we know about normal biology has arisen from investigating what happens when these mechanisms go awry in disease.

Accordingly, this book not only describes the *fundamental mechanisms underlying cancer* but also aims to offer a more holistic perspective placing molecular insights into the wider context of the personal and societal implications of lifestyle choices.

The content of this book is linked to the lecture course "*Cancer Biology*," taught by one of us (C. Carlberg) at the University of Eastern Finland in Kuopio since 2005, alongside related courses in *Molecular Medicine and Genetics*, *Molecular Immunology*, and *Nutrigenomics*. The biological concepts introduced here are complemented by clinical insights drawn from daily oncology practice, contributed by one of us (E. Velleuer). This book also relates to the books *Gene Regulation and Epigenetics: How Science Works* (ISBN 978-3-031-68729-7), *Aging: How Science Works* (ISBN 978-3-031-61256-5), *Molecular Immunology: How Science Works* (ISBN 978-3-031-04024-5), and *Nutrigenomics: How Science Works* (ISBN 978-3-031-85880-2), which may interest readers seeking more detailed information.

Chapters 1, 2, and 3 provide a general overview of cancer. Chapters 4, 5, 6, 7, and 8 examine the molecular basis of the disease, Chaps. 9, 10, and 11 discuss its cellular aspects, and Chaps. 12 and 13 present the principles of effective cancer therapy. By integrating fundamental biological mechanisms with clinical examples, we aim to make this book not only informative but also personally engaging. A glossary in the appendix defines key specialized terms; gene and protein name abbreviations are explained in the abbreviations list.

We hope readers will enjoy this visually rich book and become as enthusiastic as we are about understanding life, and its malfunctioning counterpart, cancer biology.

Kuopio, Finland — Carsten Carlberg
Düsseldorf, Germany — Eunike Velleuer
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# Acknowledgments

The authors dedicate this book to all those affected by cancer whom we have known personally. Some have survived and continue to enrich the world with their presence. Others are no longer with us, yet they remain unforgettable and forever cherished.

**Competing Interests** The authors have no competing interests to declare that are relevant to the content of this manuscript.

# Contents

# Abbreviations

| | |
|---|---|
| 3C | Chromosome conformation capture |
| 3D | Three-dimensional |
| 5hmC | 5-Hydroxymethylcytosine |
| 5hmU | 5-Hydroxyuracil |
| 5mC | 5-Methylcytosine |
| β-hCG | Beta–human chorionic gonadotropin |
| A | Adenine |
| ABL1 | ABL proto-oncogene 1, non-receptor tyrosine kinase |
| AFP | α-fetoprotein |
| AI | Artificial intelligence |
| AIDS | Acquired immune deficiency syndrome |
| AKT | Akt murine thymoma viral oncogene homolog |
| ALK | Anaplastic lymphoma kinase |
| ALL | Acute lymphoid leukemia |
| ALOX12 | Arachidonate 12-lipoxygenase |
| AML | Acute myeloid leukemia |
| AMPK | AMP-activated protein kinase |
| AP1 | Activating protein 1 |
| APAF | Apoptotic peptidase activating factor |
| APC | APC regulator of WNT signaling pathway |
| APL | Acute promyelocytic leukemia |
| APOBEC | Apolipoprotein B mRNA editing catalytic subunit |
| AR | Androgen receptor |
| ARID | AT-rich interaction domain |
| ARTR | Atypical teratoid/rhabdoid tumor |
| ASC | Apoptosis-associated speck-like protein containing a CARD |
| ASNS | Asparagine synthetase (glutamine-hydrolyzing) |
| ATAC-seq | Assay for transposase-accessible chromatin using sequencing |
| ATM | ATM serine/threonine kinase |
| ATR | ATR serine/threonine kinase |
| ATRX | ATRX chromatin remodeler |
| BCL2 | BCL2 apoptosis regulator |
| BCR | B cell receptor |
| BER | Base excision repair |

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|---|---|
| BH3 | BCL2 homology 3 domain |
| BID | BH3 interacting domain death agonist |
| bp | Base pair |
| BRAF | B-Raf proto-oncogene, serine/threonine kinase |
| BRCA | BRCA DNA repair-associated |
| BRD | Bromodomain containing |
| BRIP1 | BRCA1 interacting protein C-terminal helicase 1 |
| C | Cytosine |
| CAR | Chimeric antigen receptor |
| CASP | Caspase |
| CCL | Chemokine (C-C motif) ligand |
| CCN | Cyclin |
| CCR | C-C chemokine receptor |
| CD | Cluster of differentiation |
| CDH | Cadherin |
| CDK | Cyclin-dependent kinase |
| CDKI | Cyclin-dependent kinase inhibitor |
| CDR | Complementarity-determining region |
| CEBPA | CCAAT enhancer binding protein alpha |
| cGAS | Cyclic GMP–AMP synthase |
| CHEK | Checkpoint kinase |
| ChIP-seq | Chromatin immunoprecipitation sequencing |
| CIITA | Class II major histocompatibility complex transactivator |
| CIMP | CpG island methylator phenotype |
| CIN | Cervical intraepithelial neoplasia |
| CIS/TIS | Carcinoma in situ |
| CLEC12A | C-type lectin domain family 12 member A |
| CLL | Chronic lymphoid leukemia |
| CML | Chronic myeloid leukemia |
| CMMRD | Constitutional mismatch repair deficiency |
| CNS | Central nervous system |
| CNV | Copy number variation |
| COVID-19 | Coronavirus disease 2019 |
| CREBBP | CREB-binding protein, also called KAT3A |
| CRP | C-reactive protein |
| CSF | Cerebrospinal fluid |
| CSNK2A | Casein kinase 2 alpha |
| CT | Computed tomography |
| CTCF | CCCTC binding factor |
| ctDNA | Circulating tumor DNA |
| CTLA4 | Cytotoxic T-lymphocyte-associated protein 4 |
| CXCL | Chemokine (C-X-C motif) ligand |
| CYP | Cytochrome P450 |
| DAMP | Damage-associated molecular pattern |
| DAXX | Death domain-associated protein |

| | |
|---|---|
| DBD | DNA-binding domain |
| DCIS | Ductal carcinoma in situ |
| DDR | DNA damage response |
| DFS | Disease-free survival |
| DLBCL | Diffuse large B cell lymphoma |
| DNMT | DNA methyltransferase |
| DOT1L | DOT1 like histone lysine methyltransferase |
| E2F | E2 promoter-binding factor |
| EBV | Epstein-Barr virus |
| ECM | Extracellular matrix |
| EFS | Event-free survival |
| EGF | Epidermal growth factor |
| EGFR | Epidermal growth factor receptor |
| EHMT | Euchromatic histone lysine methyltransferase |
| EMA | European Medicines Agency |
| EMT | Epithelial-mesenchymal transition |
| ENCODE | Encyclopedia of DNA elements |
| EP300 | E1A binding protein p300, also called KAT3B |
| EPN | Ependymoma |
| ERBB2 | Erb-B2 receptor tyrosine kinase 2, also called HER2 |
| ERCC3 | ERCC excision repair 3, TFIIH core complex helicase subunit |
| eRNA | Enhancer RNA |
| ES | Embryonic stem |
| ESCAT | ESMO Scale for Clinical Actionability of molecular Targets |
| ESR1 | Estrogen receptor |
| ETMR | Embryonal tumor with multilayer rosettes |
| EZH | Enhancer of zeste homolog |
| FACS | Fluorescence-activated cell sorting |
| FAD | Flavin adenine dinucleotide |
| FBXO32 | F-box protein 32 |
| Fc | Fragment crystallizable |
| FDA | US Food & Drug Administration |
| FGF | Fibroblast growth factor |
| FGFR | Fibroblast growth factor receptor |
| FLT | Fms-related receptor tyrosine kinase |
| FOS | Fos proto-oncogene, AP1 transcription factor subunit |
| FOXO | Forkhead box O |
| G | Guanine |
| G-CSF | Granulocyte colony-stimulating factor |
| GART | Phosphoribosylglycinamide formyltransferase |
| GBM | Glioblastoma |
| GD2 | Disialoganglioside 2 |
| GDF | Growth differentiation factor |
| GDP | Guanosine diphosphate |
| GH | Growth hormone |

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|---|---|
| GLS | Glutaminase |
| GM-CSF | Granulocyte–macrophage colony-stimulating factor |
| GTEx | Genotype–Tissue Expression |
| GTP | Guanosine triphosphate |
| GVHD | Graft-versus-host disease |
| GWAS | Genome-wide association study |
| HAT | Histone acetyltransferase |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HDAC | Histone deacetylase |
| HGF | Hepatocyte growth factor |
| Hi-C | High-throughput chromosome capture |
| HIF1A | Hypoxia inducible factor 1 subunit alpha |
| HIV | Human immunodeficiency virus |
| HLA | Human leukocyte antigen |
| HP1 | Heterochromatin protein 1, official name CBX5 |
| HPV | Human papilloma virus |
| HR | Homologous recombination |
| HSP | Heat shock protein |
| ICAM | Intercellular adhesion molecule |
| ICGC | International Cancer Genome Consortium |
| IDH | Isocitrate dehydrogenase |
| IDO | Indoleamine 2,3-dioxygenase |
| Ig | Immunoglobulin |
| IGF | Insulin-like growth factor |
| IGFBP3 | Insulin-like growth factor binding protein 3 |
| IGH | Immunoglobulin heavy locus |
| IL | Interleukin |
| IL3RA | Interleukin 3 receptor subunit alpha |
| IL6R | IL6 receptor |
| ILC | Innate lymphoid cell |
| indel | Short insertion or deletion |
| INFγ | Interferon γ |
| iPS | Induced pluripotent stem |
| ITAM | Immunoreceptor tyrosine-based activation motif |
| JAK | Janus kinase |
| JUN | Jun proto-oncogene, AP1 transcription factor subunit |
| kb | Kilo base pairs (1000 bp) |
| KDM | Lysine demethylase |
| KDR | Kinase insert domain receptor, also called VEGFR2 |
| KIT | KIT proto-oncogene, receptor tyrosine kinase |
| KLF | Krüppel-like factor |
| KMT | Lysine methyltransferase |
| KRAS | Kirsten RAt Sarcoma viral oncogene homolog |
| LAD | Lamin-associated domain |

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|---|---|
| LDHA | Lactate dehydrogenase A |
| LIN28A | Lin-28 homolog A |
| LINE | Long interspersed element |
| lncRNA | Long ncRNA |
| LOCK | Large organized chromatin K9-modification |
| LSD1 | Lysine specific demethylase 1, also called KDM1A |
| LTR | Long terminal repeat |
| MAF | Minor allele frequency |
| MAPK | Mitogen-activated protein kinase |
| MAX | MYC-associated factor X |
| MB | Medulloblastoma |
| Mb | Mega base pairs (1,000,000 bp) |
| MBD | Methyl-DNA binding domain |
| MBP | Methyl-binding proteins |
| MDM2 | MDM2 proto-oncogene, E3 ubiquitin protein ligase |
| MDSC | Myeloid-derived suppressor cell |
| MECP2 | Methyl-CpG binding protein 2 |
| MET | Mesenchymal-epithelial transition |
| MGMT | O-6-methylguanine-DNA methyltransferase |
| MHC | Major histocompatibility complex |
| miRNA | Micro RNA |
| MIS-C | Multisystem inflammatory syndrome in children |
| MLH | MutL homolog |
| MMP | Matrix metalloproteinase |
| MMR | Mismatch repair |
| MNT | MAX network transcriptional repressor |
| NPV | Negative predictive value |
| MRI | Magnetic resonance imaging |
| MS | Myeloid sarcoma |
| MSI | Microsatellite instability |
| MSS | Microsatellite stable |
| mTOR | Mechanistic target of rapamycin |
| mTORC1 | mTOR complex 1 |
| MYC | MYC proto-oncogene, BHLH transcription factor |
| NAD | Nicotinamide adenine dinucleotide |
| NADPH | Nicotinamide adenine dinucleotide phosphate |
| NANOG | Nanog homeobox |
| NBN | Nibrin |
| ncRNA | Non-coding RNA |
| NER | Nucleotide excision repair |
| NFκB | Nuclear factor κB |
| NGS | Next-generation sequencing |
| NHEJ | Non-homologous end-joining |
| NK | Natural killer |
| NLR | NOD-like receptor |

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|---|---|
| NLS | Nuclear localization sequence |
| NO | Nitric oxide |
| NOTCH | Neurogenic locus notch homolog protein |
| NPM | Nucleophosmin |
| NSCLC | Non-small-cell lung cancer |
| NSD | Nuclear receptor binding SET domain protein |
| OCT | Octamer-binding transcription factor |
| OS | Overall survival |
| PALB2 | Partner and localizer of BRCA2 |
| PAMP | Pathogen-associated molecular pattern |
| PARP | Poly(ADP-ribose) polymerase |
| PCAWG | PanCancer Analysis of Whole Genomes |
| PD-L1 | Programmed cell death 1 ligand 1, also called CD274 |
| PD1 | Programmed cell death 1, also called PDCD1 |
| PDGF | Platelet-derived growth factor |
| PDGFRA | Platelet-derived growth factor receptor α |
| PET | Positron emission tomography |
| PGE | Prostaglandin E |
| PI3K | Phosphoinositide 3-kinase |
| PICS | PTEN loss-induced cellular senescence |
| PIK3CA | Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha |
| PIN | Prostatic intraepithelial neoplasia |
| PIP3 | Phosphatidylinositol-3,4,5-triphosphate |
| PML | PML nuclear body scaffold |
| Pol II | RNA polymerase II |
| PRKDC | Protein kinase, DNA-activated, catalytic subunit |
| PSA | Prostate-specific antigen |
| PTEN | Phosphatase and tensin homolog |
| PTGS2 | Prostaglandin-endoperoxide synthase 2, also called COX2 |
| PTHrP | Parathyroid hormone-related protein |
| qPCR | Quantitative PCR |
| RAD51 | RecA-like amiloride-binding protein DNA repair protein 51 |
| RAF1 | Raf-1 proto-oncogene, serine/threonine kinase |
| RARA | Retinoic acid receptor alpha |
| RAS | Rat sarcoma |
| RB1 | RB transcriptional corepressor 1 |
| RECQL4 | RecQ like helicase 4 |
| RNA-seq | RNA sequencing |
| RSV | Rous sarcoma virus |
| RT-PCR | Real-time PCR |
| RTK | Receptor tyrosine kinase |
| SAGA | Spt–Ada–Gcn5 acetyltransferase |
| SAM | S-adenosyl-L-methionine |
| SARS-CoV 2 | Severe acute respiratory syndrome coronavirus 2 |

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|---|---|
| scFv | Single-chain variable fragment |
| SERPINE | Serpin peptidase inhibitor, clade E |
| SETD | SET domain containing |
| SETDB | SET domain bifurcated histone lysine methyltransferase |
| SINE | Short interspersed element |
| SIRPα | Signal regulatory protein alpha |
| SIRT | Sirtuin |
| SLAMF | SLAM family |
| SLC | Solute carrier family |
| SMAD | SMAD family member |
| SMARC | SWI/SNF-related matrix-associated actin-dependent regulators of chromatin |
| SNAI | Snail family transcriptional repressor |
| snoRNA | Small nucleolar RNA |
| SNP | Single nucleotide polymorphism |
| SNV | Single nucleotide variant |
| SOX2 | SRY-box 2 |
| SP1 | Specificity protein 1 |
| SRC | SRC proto-oncogene, non-receptor tyrosine kinase |
| STAB | Stabilin |
| STAT | Signal transducer and activator of transcription |
| STING | Stimulator of interferon genes |
| SUV39H1 | Suppressor of variegation 3-9 homolog 1, also called KMT1A |
| SV40 | Simian virus 40 |
| SWI/SNF | Switching/sucrose non-fermenting |
| T | Thymine |
| TAD | Topologically associating domain |
| TAM | Tumor-associated macrophage |
| TCGA | The Cancer Genome Atlas |
| TCR | T cell receptor |
| TERT | Telomerase reverse transcriptase |
| TET | Ten-eleven translocation |
| TGFβ | Transforming growth factor β |
| $T_H$ | T helper |
| THBS | Thrombospondin |
| TLR | Toll-like receptor |
| TNF | Tumor necrosis factor |
| TNFRSF | TNF receptor superfamily member |
| TP53 | Tumor protein p53 |
| $T_{reg}$ | T regulatory |
| TRIM | Tripartite motif containing |
| TSS | Transcription start site |
| TWIST | Twist family BHLH transcription factor |
| U | Uracil |
| UGDH | UDP-glucose 6-dehydrogenase |

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|---|---|
| UICC | Union for International Cancer Control |
| VCAM | Vascular cell adhesion molecule |
| VEGF | Vascular endothelial growth factor |
| VHL | Von Hippel-Lindau tumor suppressor |
| WAT | White adipose tissue |
| WHO | World Health Organization |
| WNT | Wingless-type MMTV integration site family member |
| ZAP70 | Zeta-chain–associated protein kinase 70 |
| ZEB | Zinc finger E-box binding homeobox |