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CKB CLINICAL KNOWLEDGEBASE
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Theme of the Quarter: Tyrosine Kinases

Greetings CKB CORE™ users! We are excited to announce this quarter we are highlighting **Tyrosine Kinase** genes. Of the 50 available genes in CKB CORE™ this next quarter, you will find 25 tyrosine kinase genes.

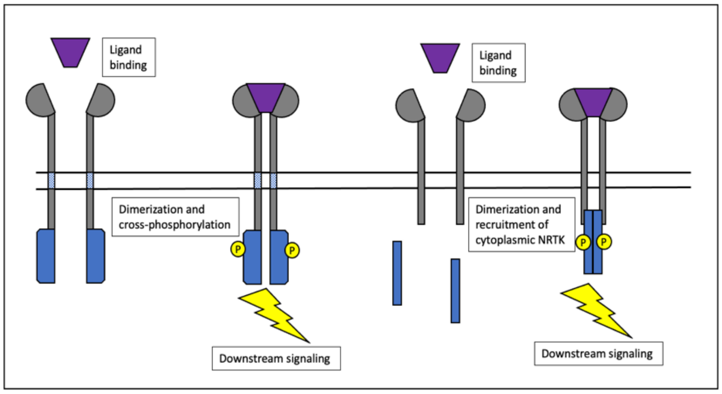
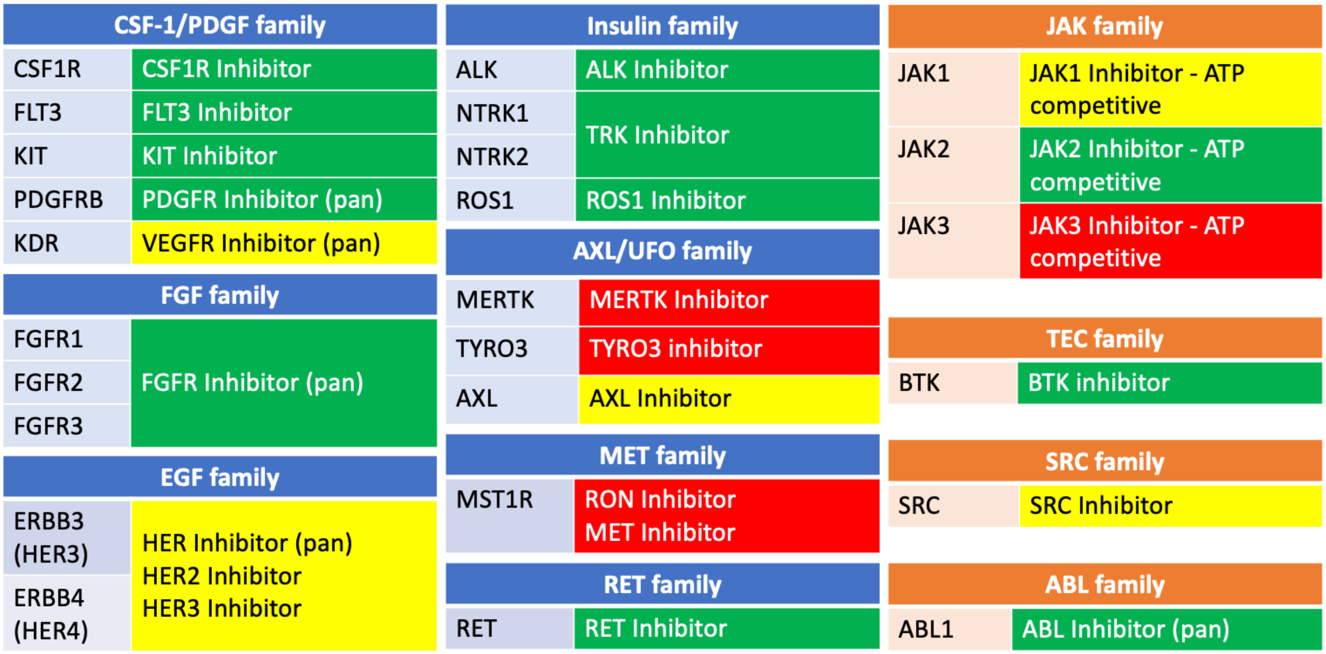


Figure 1: Receptor tyrosine kinase versus cytoplasmic non-receptor tyrosine kinase

Kinases are enzymes that are responsible for transferring a phosphate group to a protein, a process that regulates various fundamental cellular activities including but not limited to proliferation, differentiation, metabolism, survival, and migration.[1] Within the human genome there are approximately 538 different protein kinases and one such group includes the tyrosine kinases, which transfer phosphate groups to tyrosine residues on protein substrates.[2,3] Tyrosine kinases can be separated into two different classes, the transmembrane receptor tyrosine kinases (RTKs) and the cytoplasmic non-receptor tyrosine kinases (non-RTKs) (Fig. 1). RTKs are found on the cell surface and can mediate a cellular response through signaling pathways upon ligand binding in the extracellular domain (Fig. 1). All RTKs are similar in structure and comprised of an extracellular ligand-binding domain and transmembrane domain, and intracellularly, a juxtamembrane domain, tyrosine kinase domain, and carboxyl terminal tail. Some well known examples include VEGFR (KDR), FGFR, EGFR, and PDGFR. Non-RTKs are found in the cytosol of the cell and activate by binding to an RTK that has been activated. Unlike RTKs, non-RTKs lack extracellular and transmembrane domains. Examples of non-RTKs include SRC, ABL, JAK, and FAK.[3] Two common pathways activated through RTKs and non-RTKs include the Ras/MAPK pathway and the PI3K/Akt/mTOR pathway. Often pathway activation can overlap between RTKs and non-RTKs highlighting the significant degree of complexity within these pathways.

Since RTKs and non-RTKs are essential to cellular signaling pathways, their activity is tightly regulated. However, disruption of this activity, largely through genetic mutations or genomic alterations resulting in overexpression or constitutive activation of the protein, can lead to abnormal cellular proliferation, apoptosis, survival, and migration, all hallmarks associated with oncogenesis. As the understanding of the molecular mechanisms underlying the activation of protein kinases in cancer progressed, it became increasingly clear that targeting these proteins would become crucial in the fight against cancer. In 2001, Gleevec (imatinib) became the first tyrosine kinase inhibitor targeting ABL that was FDA approved for the treatment of chronic myeloid leukemia.[4] Soon after, Gleevec (imatinib) became a model for the development of other tyrosine kinase inhibitors, a drug that binds to the ATP binding site of the ABL tyrosine kinase domain and subsequently stabilizing the protein in its "inactive" state.[4] Eventually as more and more protein kinase inhibitors were developed they essentially fell into three different classes. The first class, type I, includes small molecule inhibitors that bind to the active conformation of the protein kinase in the ATP binding pocket. The second class, type II, binds to the inactive conformation of the protein kinase in the ATP pocket, and the third class, type III, is described as a non-ATP competitive inhibitor or allosteric inhibitor.[2] Since the approval of Gleevec (imatinib), there are now over 70 FDA approved drugs targeting kinases.

Clearly, the development of kinase inhibitors has significantly changed the clinical management of cancer. However, even in the early days of chemotherapy, it became evident that cancer cells can develop resistance



CSF-1/PDGF family	
CSF1R	CSF1R Inhibitor
FLT3	FLT3 Inhibitor
KIT	KIT Inhibitor
PDGFRB	PDGFR Inhibitor (pan)
KDR	VEGFR Inhibitor (pan)

FGF family	
FGFR1	FGFR Inhibitor (pan)
FGFR2	
FGFR3	

EGF family	
ERBB3 (HER3)	HER Inhibitor (pan) HER2 Inhibitor HER3 Inhibitor
ERBB4 (HER4)	

Insulin family	
ALK	ALK Inhibitor
NTRK1	TRK Inhibitor
NTRK2	
ROS1	ROS1 Inhibitor

AXL/UFO family	
MERTK	MERTK Inhibitor
TYRO3	TYRO3 inhibitor
AXL	AXL Inhibitor

MET family	
MST1R	RON Inhibitor MET Inhibitor

RET family	
RET	RET Inhibitor

JAK family	
JAK1	JAK1 Inhibitor - ATP competitive
JAK2	JAK2 Inhibitor - ATP competitive
JAK3	JAK3 Inhibitor - ATP competitive

TEC family	
BTK	BTK inhibitor

SRC family	
SRC	SRC Inhibitor

ABL family	
ABL1	ABL Inhibitor (pan)

Figure 2: Tyrosine kinase genes represented in CKB CORE$^{\text{TM}}$ by subfamily (receptor tyrosine kinases in blue and non-receptor tyrosine kinases in orange) with drug classes that include drugs associated with gene relevant therapeutic evidence. Drug classes in green include drugs in NCCN Guidelines and/or are FDA approved. Drug classes in yellow include drugs in clinical trials, and drug classes in red include drugs with clinical and/or preclinical evidence.

mechanisms, thereby undergoing a molecular evolution in order to survive.[4] Not surprisingly, development of resistance to kinase inhibitors quickly ensued hindering their efficacy. Cancer cells acquired secondary resistance mutations as well as other resistance mechanisms including those related to alternative splicing and epigenetic alterations as well as intrinsic mechanisms such as those within the tumor microenvironment.[4] Due to the discovery of various resistant mutations including those in tyrosine kinases such as ABL, several drugs that selectively target these mutations were subsequently developed and termed "next-generation inhibitors".[2]

In this quarterly release, CKB-CORE$^{\text{TM}}$ includes 25 tyrosine kinase specific genes (Fig. 2). The genes include both RTKs and non-RTKs, and in several of the genes you will find high level evidence, including evidence with FDA approved drugs and drugs that are indicated in NCCN guidelines. In addition, some of the genes are associated with drugs that are being investigated in clinical trials and a select few that currently include drugs specific to clinical and/or preclinical evidence (Fig. 2).

Summary

With the 25 tyrosine kinase genes available in CKB CORE$^{\text{TM}}$, users have access to nearly 3,350 gene variants for interpretation, and many lines of preclinical and clinical efficacy evidence to help guide treatment decisions. We hope this updated version of CKB CORE$^{\text{TM}}$ continues to serve as a valuable resource for your variant interpretation needs, and if you have any questions or comments, please feel free to contact us at ckbsupport@jax.org.

Resources

https://www.fda.gov/drugs

References

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2. Bhullar, K, Lagaron, NO, et al. Kinase-targeted cancer therapies: progress, challenges and future directions. Molecular Cancer. 2018; 17(1):48
3. Gocek E, Moulas, A, et al. Non-receptor protein tyrosine kinases signaling pathways in normal and cancer cells. Crit Rev Clin Lab Sci. 2014; 51(3):125-37
4. Rosenzweig, S. Acquired resistance to drugs targeting tyrosine kinases. Adv Cancer Res. 2018; 138:71-98