Theme of the Quarter: Tumor Suppressor Genes

Greetings CKB CORE™ users! We are excited to announce this quarter we are highlighting **Tumor Suppressor** genes. Of the 50 available genes in CKB CORE™ this next quarter, you will find 28 tumor suppressor genes (Fig. 1). It was 1971 when Alfred G. Knudson first published his renowned study revealing a class of genes that have the opposite effect of oncogenes.[1] Interested in the genetic mechanisms that lead to retinoblastoma, Knudson concluded that two mutations in the RB1 gene were required to result in retinoblastoma.[1] Following this discovery, it was soon established that tumor suppressor genes are essential in regulating cell growth, thereby acting as the "brakes" in a variety of cell signaling pathways to prevent cell proliferation and subsequent tumor growth. There are two classes of tumor suppressor genes that have been described, the "gatekeeper genes" and the "caretaker genes".[2] The gatekeeper genes include those involved in controlling or inhibiting cell growth while the caretaker genes are involved in maintaining genomic integrity. Consequently, tumor suppressors are involved in a number of cellular processes such as cell-cycle checkpoint responses, detection and repair of DNA damage, protein ubiquitination and degradation, cell specification and differentiation, cell migration, and angiogenesis.[3] As Knudson discovered, tumor suppressor genes typically require biallelic inactivation in order to result in a complete loss of protein function, hence the frequently used term, "two-hit" hypothesis.[1] Most often, a single mutant allele is inherited and the second allele is lost either through a second mutation at the somatic level or gene silencing via epigenetic modifications.

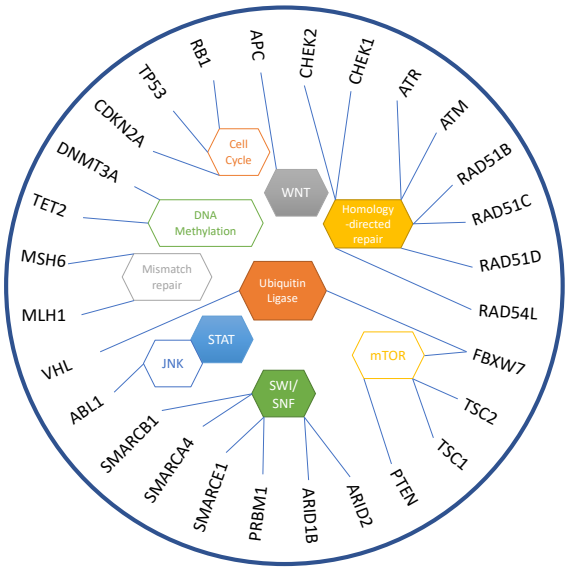

Figure 1: Twenty-eight tumor suppressor genes available in CKB-CORE™ this quarter

One of the most well known tumor suppressor genes, TP53, is mutated in about 50% of human cancers, and plays a role in mediating cellular stress responses via DNA repair, cell-cycle arrest, senescence, and most especially, apoptosis.[4,5] However, there are several other tumor suppressor genes that are frequently mutated resulting in altered signaling of various pathways including the PI3K/Akt/mTOR signaling pathway, cell-cycle control pathway, DNA damage repair pathway, Ras/Raf/MAPK pathway, and the Wnt/β-catenin signaling pathway.[3] While the molecular understanding of tumor suppressor genes and their effect on cancer immensely grew over the years, the challenge that still exists is how to therapeutically target these deficiencies to improve outcomes for patients. Given that tumor suppressor genes result in a loss of protein function, it logically makes sense that it is not as easy to target a tumor suppressor gene compared to a mutated oncogene that results in overactivity of a protein. However, there are a few approaches that have been exploited to "target" tumor suppressor genes. One such approach is to inhibit or shut down the pathway that is activated due to the loss of tumor suppressor gene(s) or take advantage of the vulnerability of cancer cells that have lost tumor suppressor gene(s).[6]

One example of a pathway that is frequently altered in cancer due to loss of a tumor suppressor gene is the PI3K/Akt/mTOR pathway. Four tumor suppressor genes within this pathway that are being highlighted this quarter include PTEN, FBXW7, TSC1, and TSC2. PTEN acts as a direct antagonist of PI3K signaling through catalytic phosphatase activity[7] while FBXW7 targets the enzyme mTOR, resulting in protein ubiquitination and degradation,

and TSC1 and TSC2 are responsible for inhibiting mTOR kinase activity. Therefore, therapies targeting various aspects of the PI3K/Akt/mTOR pathway in the context of loss of function alterations in PTEN, FBXW7, TSC1, or TSC2, could be a potential strategy (Fig. 2).

A second therapeutic approach, centering on the vulnerability of cancer cells, is to induce synthetic lethality. The two other sets of tumor suppressor genes we focus on this quarter are those involved in DNA repair and those within the SWI/SNF complex. Biallelic loss of genes involved in the DNA repair pathway such as RAD51B, RAD51C, RAD51D, RAD54L, CHEK1, and CHEK2 potentially results in a loss of DNA repair but not necessarily a complete loss due to other intact DNA repair mechanisms. Inhibition of genes involved in alternative DNA repair processes such as PARP via PARP inhibitors, including the FDA approved drug Olaparib, may lead to a greater chance of apoptosis (Fig. 2).[8]

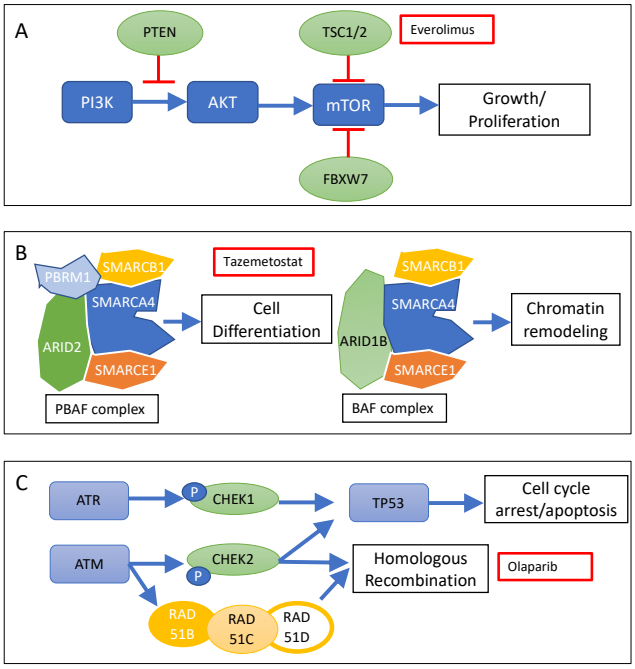

Figure 2: Several CKB-CORE™ genes act in the same pathways or complexes. A) the mTOR pathway B) the SWI/SNF complex C) the DNA repair pathway (red boxes show drugs that may have clinical benefit in the context of these pathways/complexes)

The SWI/SNF complex plays a role in the regulation of genomic architecture and is therefore key to multiple cellular processes including transcription, DNA repair, DNA replication, and chromosomal segregation.[7] The complex consists of several subunits and can exist in a number of compositions. Two of the major complexes in mammals include BAF and PBAF, and genes encoding the subunits within the SWI/SNF complex are frequently mutated in cancer.[9] One such method to "target" these genes is to target the interaction between two subunits such as SMARCA4 and ARID2 (Fig. 2), leading to inactivation of the complex. Currently, there are no biomarker FDA approved drugs for the genes within this complex but there are several investigational therapies either within clinical trials or with preclinical or early stage clinical evidence (Fig. 2).

Summary

In this quarterly release, CKB-CORE™ includes 28 tumor suppressor genes (Fig. 1). The genes include both "gatekeepers" and "caretakers", and users have access to nearly 4,340 gene variants for interpretation, and many lines of preclinical and high level clinical efficacy evidence to help guide treatment decisions. We hope this updated version of CKB CORE™ 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

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