Breast Cancer

Major finding: Mutant PIK3CA induces a multipotent transcription program in lineage-committed basal and luminal cells.

Clinical relevance: Mutant PIKC3A–induced multipotency correlates with breast cancer subtypes and clinical outcome.

Impact: PIK3CA-driven plasticity and cell of origin control breast tumor heterogeneity and aggressiveness.

PIK3CA^{H1047R}-MEDIATED MULTIPOTENCY UNDERLIES BREAST TUMOR HETEROGENEITY

Breast cancer is a heterogeneous disease that can be classified into different subtypes including luminal and basal-like cancers. Oncogenic mutations in the *PIK3CA* gene are frequently observed in breast cancer and have been shown to promote tumor heterogeneity in mice. However, the mechanisms underlying mutant PIK3CA–driven heterogeneity and the contribution of cell of origin remain unknown. Using genetically engineered mouse models, Van Keymeulen, Lee, and colleagues showed that expression of oncogenic *PIK3CA*^{H1047R} in basal cells led to luminal adenomyoepithelial tumor formation, whereas *PIK3CA*^{H1047R} expression in luminal cells led to more aggressive and heterogeneous luminal and basal-like tumors. *In vivo* lineage-tracing experiments revealed that expression of *PIK3CA*^{H1047R} in lineage-committed luminal or basal cells gave rise to multipotent clones, suggesting that oncogenic *PIK3CA* promotes lineage plasticity that induces cellular heterogeneity. Gene expression profiling revealed dynamic regulation of specific transcriptional programs according to the cellular origin, which correlated with tumor subtype and clinical outcome in patients. In line with these results, Koren and colleagues found that forced expression of *PIK3CA*^{H1047R} in lineage-restricted murine luminal or basal cells led to dedifferentiation and the expansion of multipotent stem-like cells that co-expressed basal and luminal lineage markers. Moreover, *PIK3CA*^{H1047R}-expressing basal cell–driven and luminal cell–driven tumors were characterized by markers of both lineages. *PIK3CA*^{H1047R} luminal cell–driven tumors were more aggressive and correlated with malignant human basal-like, HER2^{+}, and luminal-B tumors, whereas *PIK3CA*^{H1047R} basal cell–driven tumors were highly heterogeneous but mostly benign, indicating that the cell of origin determines tumor heterogeneity and aggressiveness. Together, these data provide evidence that oncogenic *PIK3CA* drives a multipotent gene transcription program in lineage-committed mammary cells early in tumorigenesis that contributes to intratumor heterogeneity and malignant progression. ■

Van Keymeulen A, Lee MY, Ousset M, Brohée S, Rorive S, Giraddi RR, et al. Reactivation of multipotency by oncogenic PIK3CA induces breast tumour heterogeneity. Nature 2015;525:119–23.

Koren S, Reavie L, do Couto JP, De Silva D, Stadler MB, Roloff T, et al. PIK3CA^{H1047R} *induces multipotency and multi-lineage mammary tumours. Nature 2015;525:114–8.*

Structural Biology

Major finding: HIFα–ARNT heterodimers exhibit distinct domain interactions and small-molecule binding pockets.

Clinical relevance: Cancer-related mutations in *HIF1A* and *HIF2A* map to domain interfaces, pockets, and DNA binding sites.

Impact: The small-molecule binding pockets may enable selective therapeutic targeting of HIF1α and HIF2α.

CRYSTAL STRUCTURES OFFER INSIGHT INTO HIF FUNCTION

Hypoxia-inducible factor α (HIFα) proteins heterodimerize with aryl hydrocarbon receptor nuclear translocator (ARNT, also known as HIF1β) to form active transcription factors that control the molecular response to low oxygen. HIFs regulate genes involved in a variety of adaptive cellular processes, including metabolism, angiogenesis, and erythropoiesis, and dysregulation of HIF signaling has been implicated in tumorigenesis, supporting the development of small-molecule HIF inhibitors. To provide a better understanding of HIF function and drug-binding capabilities, Wu and colleagues solved the crystal structure of the basic helix–loop–helix (bHLH), PAS-A, and PAS-B domains of HIF2α–ARNT heterodimers. This analysis revealed an integrated quarternary architecture distinct from the domain interactions observed in heterodimers of other bHLH–PAS proteins, with asymmetrical interactions between the domains of HIF2α and ARNT proteins and formation of a single DNA-reading head at one end of the heterodimer. Mutagenesis analysis revealed that these domain–domain interactions were required to stabilize the complex. Structural analysis of HIF2α–ARNT bound to synthetic small molecules identified five potential binding pockets within the PAS domains, which may facilitate selective small-molecule binding to either HIF1α or HIF2α. In addition, comparison of the structures of HIFα–ARNT heterodimers in complex with DNA containing the core hypoxia response element highlighted identical interactions of the bHLH domains of HIF1α and HIF2α with DNA and cooperation between the PAS-A domain and the bHLH domains in DNA recognition. Furthermore, cancer-associated mutations in *HIF1A* and *HIF2A* were found to map to pocket regions, domain interfaces, or sites important for DNA binding. Together, these findings demonstrate the unique domain arrangements of HIFα–ARNT heterodimers and suggest that the identified pockets may facilitate therapeutic targeting of HIF1α and HIF2α. ■

Wu D, Potluri N, Lu J, Kim Y, Rastinejad F. Structural integration in hypoxia-inducible factors. Nature 2015;524:303–8.