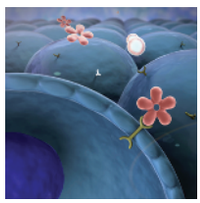
Signaling

Major finding: Heparin binds directly to the N-terminal region of the ALK extracellular domain.

Concept: Heparin-induced ALK activation is dependent on heparin chain length and sulfation pattern.

Impact: Targeting the N-terminal region to block glycosaminoglycan binding may be an effective way to inhibit ALK.

HEPARIN IS AN ACTIVATING ALK LIGAND



ALK is considered an orphan receptor tyrosine kinase (RTK) because it has no known ligand. The heparin-binding molecules pleiotropin (PTN) and midkine (MK) were initially reported to be ALK ligands, but these findings have not been confirmed. Murray and colleagues observed that although mixtures of heparin and PTN or MK stimulated ALK autophosphorylation, heparin alone was sufficient to activate ALK, suggesting that heparin, which can bind and activate (when acting together with a growth factor) other RTKs such as FGFRs, is an ALK ligand. Indeed, heparin bound with high affinity and specificity to the full-length ALK extracellular domain (ECD) *in vitro* but not to an ALK truncation mutant lacking the N-terminal region (NTR) of the ECD. Heparin chain length correlated with affinity for ALK and the degree of ALK oligomerization *in vitro*, and stimulation of neuroblastoma cells with heparin with various chain lengths revealed that only heparin molecules with more than 15 disaccharide units were capable of inducing ALK autophosphorylation. Given that heparin is an experimental substitute for physiologic glycosaminoglycan ligands distinguished by various sulfation patterns that can affect receptor binding and activation, the authors evaluated the effect of different heparin and glycosaminoglycan sulfation patterns on ALK activation and found that only heparin with N- and O-linked sulfate groups or glycosaminoglycans with sulfation patterns similar to heparin could activate ALK. Consistent with these results, an antibody that competitively blocked heparin binding to the ALK NTR potently inhibited heparin-induced ALK autophosphorylation and downstream activation of AKT and ERK in neuroblastoma cells. The identification of heparin as an activating ALK ligand or co-ligand thus not only provides insight into ALK biology but also suggests that targeting glycosaminoglycan binding by the ALK NTR may be an effective strategy to inhibit ALK signaling. ■

Murray PB, Lax I, Reshetnyak A, Ligon GF, Lillquist JS, Natoli EJ Jr, et al. Heparin is an activating ligand of the orphan receptor tyrosine kinase ALK. Sci Signal 2015;8:ra6.

Mutations

Major finding: Mutation of both DNA replication error repair pathways is associated with ultra-hypermutated cancer.

Mechanism: Somatic POLε/δ mutations increase the mutation rate in patients with inherited biallelic MMR deficiency.

Impact: Ablation of replication repair is a mechanism to induce rapid mutagenesis and cancer initiation.

COMPLETE LOSS OF REPLICATION REPAIR DRIVES ULTRA-HYPERMUTATED CANCERS

Mutations that occur during DNA replication are repaired by DNA polymerase proofreading and mismatch repair (MMR), and failure of each of these repair pathways results in the persistence of mutations that can lead to cancer. Sporadic cancers contain various mutations in DNA repair pathways and accumulate multiple types of mutations over many years, whereas inherited DNA-repair deficiencies result in early-onset cancers and allow for the study of secondary pathways that drive carcinogenesis. Shlien and colleagues sequenced tumor samples from children with inherited biallelic mismatch repair deficiency (bMMRD) and found that all malignant bMMRD brain tumors analyzed harbored a much higher number of point mutations (249 mutations/Mb) relative to other pediatric cancers (0.61 mutations/Mb). These "ultra-hypermutated cancers" were unique in that the mutations were evenly distributed across the genome, lacked copy-number alterations, and were microsatellite stable. In contrast, non-neoplastic samples from bMMRD patients did not exhibit excessive mutations, suggesting that ultra-hypermutation requires secondary mutations. Indeed, ultra-hypermutated cancers acquired somatic mutations in genes encoding the DNA proofreading polymerases ε (*POLE*) or δ (*POLD1*), which were not present in nonmalignant tissue or non–ultra-hypermutated bMMRD cancers. *POLE* and *POLD1* mutations affected conserved residues, resulting in impaired intrinsic proofreading activity, loss of replication fidelity, and a substantial increase (230-fold) in exonic mutation load compared with that of bMMRD tumors. bMMRD/polymerase-mutant cancers were characterized by distinct mutational signatures that occurred early in tumorigenesis and were also present in sporadic cancers with somatic MMR and *POLE* mutations. In addition, serial analysis of tumor samples indicated that bMMRD/polymerase-mutant cancers simultaneously accumulated sufficient driver mutations in less than 6 months and continuously mutated until reaching a threshold. These studies suggest a novel mechanism of carcinogenesis in which complete loss of DNA replication repair leads to massive accumulation of point mutations and rapid cancer initiation. ■

Shlien A, Campbell BB, de Borja R, Alexandrov LB, Merico D, Wedge D, et al. Combined hereditary and somatic mutations of replication error repair genes result in rapid onset of ultra-hypermutated cancers. Nat Genet 2015 Feb 2 [Epub ahead of print].

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