MS04 Structure in Cancer Biology

MS4-02

Anaplastic Lymphoma Kinases and ligands: Structure, mechanism and antagonism in cancer and metabolism

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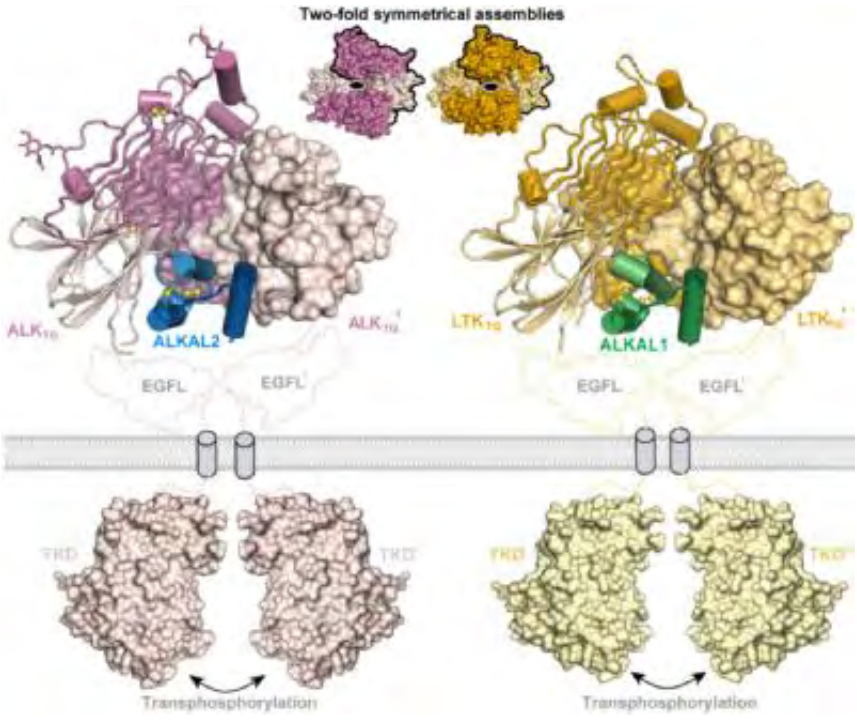
Abstract

Anaplastic lymphoma kinase (ALK) and the related leukocyte tyrosine kinase (LTK) are recently deorphanized receptor tyrosine kinases. Together with their activating cytokines, ALKAL1 and ALKAL2 they are involved in neural development, cancer and autoimmune diseases. Furthermore, mammalian ALK recently emerged as a key regulator of energy expenditure and weight gain. Despite such functional pleiotropy and growing therapeutic relevance structural insights into ALK and LTK and their complexes with cognate cytokines have remained scarce. To facilitate our mechanistic understanding of ALK/LTK function and therapeutic targeting, we pursued crystal structures of ALK/LTK-cytokine complexes. Our structures revealed unprecedented protein architectures and receptor-cytokine assemblies, whereby a single cytokine molecule without any apparent symmetry dimerizes ALK and LTK proximal to the cell membrane to initiate signalling. The cytokine-binding segments of human ALK and LTK comprise a novel architectural chimera of a permuted TNF-like module that braces a glycine-rich subdomain featuring a hexagonal lattice of long polyglycine type II helices. The cognate cytokines ALKAL1 and ALKAL2 are monomeric three-helix bundles, yet their binding to ALK and LTK elicits similar dimeric assemblies with two-fold symmetry, that tent a single cytokine molecule proximal to the cell membrane. We show that the membrane-proximal EGF-like domain dictates the apparent cytokine preference of ALK. Assisted by these diverse structure–function findings, we propose a structural and mechanistic blueprint for complexes of ALK family receptors, and thereby extend the repertoire of ligand-mediated dimerization mechanisms adopted by receptor tyrosine kinases.

References

De Munck S., Provost M., Kurikawa M., Omori I., Mukohyama J., Felix J. Bloch Y. Abdel-Wahab O., Bazan J.F., Yoshimi. A., Savvides S.N.* Structure and mechanism of cytokine-mediated activation of ALK family receptors. Nature (2021), 600:143-147.

ALK/LTK-cytokine complexes



ALK/LTK complexes are novel among RTK