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Evolution of resistance to ALK targeting therapies in NSCLC

Background: Targeted therapies, including inhibitors of oncogenic tyrosine kinase activity of EML4-ALK fusion (ALK-TKI), ultimately fail due to the evolution of acquired resistance. Whereas the research community has gained reasonable mechanistic understanding of the end products of this evolution, evolutionary dynamics and trajectories remain unexplored. This knowledge gap reflects the dominance of an assumption that resistance emerges as the result of a binary (epi) mutational switch. Consequently, relapse of the disease could be reduced to a selective expansion of resist-ant clones, and little can be done clinically to interfere. However, this assumption remains mostly untested, and it conflicts with complex evolutionary trajectories observed in evolved therapy resistance in bacteria. Results: We investigated evolution of resistance toward multiple clinically relevant ALK-TKI using in vitro models of EML4-ALK+ lung cancers. Exposure of EML4-ALK+ cell lines to different clinically relevant ALK-TKI leads to rapid and reproducible development of resistance. The resistance evolves gradually, originating from weakly resistant precursors and culminating in (near) complete loss of growth inhibition. Even though the end products of this evolution converge to pan-ALK-TKI resistance, different ALK-TKI select for predictably distinct molecular adaptations, associated with distinct cross-sensitivities. Conclusions: Evolution of resistance to ALK-TKI represents a gradual, Darwinian process rather than all or nothing switch followed by expansion of fully resistant cells. Distinct ALK-TKIs exert overlapping, but different selective pressures, resulting in different evolutionary trajectories. Our observations suggest that explicit consideration of evolutionary dynamics could lead to the development of novel approaches to block or delay evolution of resistance.