An Achilles Heel in Oncogenic Ras

Yamaguchi, Evan

Mutations in the genes encoding Ras GTPases are major drivers of human cancers. Despite 30 years of intensive research, no compounds directly targeting Ras proteins have been developed. Previous studies unexpectedly revealed that synthetic analogs of the C-terminal alpha-helix of K-Ras inhibit the growth of Ras-dependent cancer cells. However, the molecular mechanisms of this inhibition remain unknown. Firstly, it has been concluded that the helix 5 of K-Ras is an uncommon interface to which effector proteins bind. However, exceptions do exist. A previously uncharacterized interaction between the focal adhesion kinase (FAK) and K-Ras has been displayed. Further investigation of this interaction could produce novel therapeutics for FAK and K-Ras driven cancers. Secondly, a role for helix 5 in Ras function and a new mechanism of Ras activity regulation has been uncovered. In the proposed mechanism, the helix 5 of Ras mediates signaling between the membrane-attached hypervariable region of Ras and the active site. This would be regulated by movement of helix 5, resulting in a loose association of helix 5 with the rest of Ras. This loose association would allow helix 5 analogs to bind to the region of Ras where helix 5 normally resides. The proposed mechanism not only serves to provide an explanation for the dependence of Ras activity on membrane association, but also presents a novel opportunity in inhibition of Ras signaling. This data suggests a promising approach for the development of inhibitors for thus far ‘non-druggable’ Ras and offers effective therapeutics for many untreatable tumor types.

Awards Won: