Marmara University Faculty of Engineering
Department of Bioengineering

SEMINAR

28 February 2020
10:00-12:00
MÜ – Göztepe Kampüsü – Mühendislik Fakültesi
MB144 – Konferans Salonu

Ozlem Keskin is a professor in the Chemical and Biological Engineering Department at Koc University, Istanbul. Before, she was a postdoctoral fellow at the National Cancer Institute-National Institutes of Health, U.S.A., during 1999− 2001. She received her Ph.D. degree in Chemical Engineering in 1999, at Bogazici University, Istanbul. She is a member of the Science Academy, Turkey and recipient of several awards including the Science Award, Turkey, 2012 and UNESCO-L'OREAL Co-Sponsored Fellowship Award for Young Women in Life Sciences, 2005. She is an associate editor in Plos Comp Biol, Plos One and BMC Structural Biology. Her work focuses on understanding the principles of protein−protein interactions (PPIs), the molecular mechanisms, physical principles and dynamics of macromolecular systems. She co-heads the Computational Systems Biology (COSBI) group aiming to construct protein interactomes by integrating atomistic details of protein-protein interfaces and mechanistic understanding of signaling pathways. (http://home.ku.edu.tr/~okeskin). Her work received more than 9000 citations according to Google scholar.

Effect of Oncogenic K-Ras4B dimerization on downstream MAPK and Akt signaling

Ras activates effectors that transmit receptor-initiated signals. K-Ras4B may dimerize through the β- and α-interfaces, mapped to Switch I and effector binding regions and the allosteric lobe, respectively. We chose $KRas4B^{G12D}$ as control and its double mutants K101D/R102E and R41E/K42D to assess the impact of KRas4B mutants on dimerization and function. R41 and R102 are found in several adenocarcinomas in Ras isoforms. Site-directed mutagenesis, cellular localization experiments and molecular dynamics (MD) simulations are performed. α-interface K101D/R102E double-mutations reduced dimerization, but only slightly reduced pERK levels. β-interface R41E/K42D mutants did not affect dimerization but blocked pERK. Both mutants increased downstream pAkt levels in cells. They further altered ERK- and Akt-regulated expression of *EGR1*, *JUN*, and *BCL2L11*. The results underscore the role of the α- and β-interfaces in homodimerization and effector binding, respectively. MD simulations showed that the membrane and the hypervariable region interact with both interfaces, inhibiting homodimerization and effector binding. We conclude that dimerization is not necessary but enhances MAPK signaling.