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"Shedding Light on Mertk Post-Translational Cleavage and Signaling"

By

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Thursday, December 1st, 2022
12:00 P.M.
Cancer Center G-level Conference Room, Zoom

https://rutgers.zoom.us/j/91854467344?pwd=dThoekZ6bkRicGVwc3ZvOHRhbVYwUT09
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ABSTRACT

Tyro3, Axl, Mertk (abbreviated TAM receptors), comprise a family of homologous type I receptor tyrosine kinases that have important roles homeostatically in the resolution of inflammation, but also can function as oncogenic tyrosine kinases that drive malignant features in cancer cells. In particular, Mertk, expressed on a variety of macrophage subsets including tumor associated macrophages, has an important role in efferocytosis (the clearance of apoptotic cells) and in doing so, promotes an immunosuppressive tumor microenvironment that contributes to immune evasion and cancer progression. In this thesis, I explore the regulation of Mertk by post-translational proteolytic cleavage processing events, a process that is not well understood in the context of cancer biology. We investigate the regulation of Mertk cleavage as well as whether Mertk cleavage opposes tumor growth, possibly by limiting cell surface localization of Mertk on tumor-associated macrophages. We provide evidence that, after an initial cleavage event mediated by ADAM17, the remaining Mertk fragment that includes the transmembrane domain (mb-cMertk), undergoes a subsequent γ-secretase cleavage event. γ-secretase cleavage occurs in the transmembrane domain of its substrates and accordingly releases an intracellular cytosolic fragment. Cytosolic fragments from other γ-secretase cleavage substrates have been implicated in signaling and transcription (such as Notch signaling) and therefore the potential function of the Mertk fragment produced by γ-secretase cleavage (cyto-cMertk) was explored. Using MG132, an inhibitor of proteasome degradation, we provide evidence that cyto-cMertk is a labile intracellular fragment that is rapidly degraded, suggesting that stabilization is required for functionality. In addition to the homeostatic nature of Mertk cleavage, Mertk is regulated by a separate mechanism following Gas6-mediated receptor binding, whereby Mertk bound by γ-carboxylated Gas6 (and to a lesser extent non-γ-carboxylated Gas6) resulted in the degradation of surface Mertk and total Mertk. Through mutations preventing ADAM17 cleavage and Mertk phosphorylation, we determined that this loss of Mertk is independent of both cleavage and receptor activation. Finally, the screening and testing of several small molecule inhibitors targeting the interface between Gas6 and Mertk (and other members of the TAM family of receptors) will be discussed. Overall, our data suggests that Mertk activity is regulated by homeostatic proteolysis and ligand-mediated degradation, to control receptor signaling.