**Proteomic profiling of the cell surfaceome identifies new theranostic targets for cancer cells driven by hyperactive mTORC1 signaling**

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**Abstract:**

Aberrantly high mTORC1 signaling is a known driver of many cancers and human disorders, yet pharmacological inhibition of mTORC1 rarely confers durable clinical responses. To explore alternative therapeutic strategies, herein we conducted a proteomics survey to identify cell surface proteins upregulated by mTORC1. A comparison of the surfaceome from *Tsc1*$^{-/-}$ versus *Tsc1*$^{+/+}$ mouse embryonic fibroblasts revealed 59 proteins predicted to be significantly overexpressed in *Tsc1*$^{-/-}$ cells. Further validation of the data in multiple mouse and human cell lines showed that mTORC1 signaling most dramatically induced the expression of the proteases neprilysin (NEP/CD10) and aminopeptidase N (APN/CD13). Functional studies showed that constitutive mTORC1 signaling sensitized cells to genetic ablation of NEP and APN, as well as the biochemical inhibition of APN. And the APN antibody was also developed via phage-display technology, the $^{89}$Zr labelled APN antibody could be applied to image the Tsc1-null human bladder subcutaneous tumors in vivo via PET/CT. In summary, these data show that mTORC1 signaling plays a significant role in the constitution of the surfaceome, which in turn may present novel therapeutic strategies.