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Loss of core-fucosylation of SPARC impairs collagen binding and contributes to COPD

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease with high morbidity and mortality worldwide. Although several mechanisms to account for deleterious immune effects were proposed, molecular description for the underlying alveolar structural alterations for COPD is lacking. Here, silencing of α 1,6- fucosyltransferase (Fut8), the enzyme for core-fucosylation and highly expressed in lung stem cells, resulted in alveolar structural changes in lung organoids, recapitulating COPD. Site-specific mass spectrometry analysis demonstrated that the secreted protein acidic and rich in cysteine (SPARC), which binds collagen, contains a core-fucosylation site in its VCSNDNcfK glycopeptide. Biacore assay showed markedly reduced collagen binding of SPARC lacking core-fucosylation. Molecular dynamics analysis revealed that core-fucosylation of SPARC induced dynamic conformational changes in its N-glycan, allowing terminal galactose and N- acetylglucosamine to interact with K150, P261 and H264 residues, thereby promoting collagen binding. Site-specific mutagenesis of these residues also resulted in low affinity for collagen binding. Moreover, loss of collagen and decline of core- fucosylation were observed in COPD lung tissues. These findings provide a new mechanistic insight into the role of core-fucosylation of SPARC in cell-matrix communication and contribution to the abnormal alveolar structures in COPD.

Biography

John Yu is a Distinguished Chair Professor and Director of the Institute of Stem Cell and Translational Cancer Research at CGMH. He also serves as a Distinguished Visiting Research Fellow at the Institute of Cellular and Organismic Biology, Academia Sinica, where he was the Director from 2002 to 2009. Additionally, he is the founding President of the Taiwan Society for Stem Cell Research. He has held numerous positions on various committees, including those of the International Society for Stem Cell Research (ISSCR) in the USA and the Steering Committee of the Asia-Pacific Stem Cell Network. He has also served as an advisor for Stem Cell Biology at Kumamoto University. Previously, he was the Director of Experimental Hematology at the Scripps Research Institute from 1998 to 2002. He has received several prestigious awards, including the Established Investigator Award from the American Heart Association.

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