Shc 在 thrombin 誘導肺部上皮細胞 IL-8/CXCL8 表現所扮演的角色

The Role of Shc on Thrombin-Induced IL-8/CXCL8 Expression in Lung Epithelial Cells

中文摘要

蛋白質經後修飾作用 (post-translational modification) ，使其具有不同功能與特性，藉此調節細胞生理活性。其中以 ubiquitination 和 SUMOylation 形成機制最爲相似，皆使用多個酵素將標的蛋白質接上 ubiquitin 或 SUMO。研究顯示，標的蛋白質上 ubiquitin 透過特定離胺酸 (Lysine) 形成多個 Ub-Ub 鍵結，稱之 poly-Ub chains，而 ubiquitin 上不同 Lysine 所形成 poly-Ub 鍵結代表不同的生理意義。

在 SUMOylation 研究中發現，SUMO 也會在標的蛋白質上形成 poly-SUMO chains。目前已知在低等真核生物中 poly-SUMO chains 與酵母菌孢子的形成有關。此外，在高等真核生物中也發現了生理壓力下會促使 poly-hSUMO-1 chains 形成之現象。但目前仍不清楚 SUMO-1 上哪個 Lysine 與形成 poly-hSUMO-1 chains 有關以及 poly-SUMO-1 chains 在高等真核生物中所代表的意義。

因此，本研究首先將 hSUMO-1 所有離胺酸全都突變成精胺酸，稱爲 K0，以 K0 當控制組來觀察單一離胺酸還原之 hSUMO-1，K1 至 K11，並探討 hSUMO-1 上哪些離胺酸可能是 hSUMO-1 上形成聚合鏈之分支點。結果發現，當標的蛋白質進行 SUMOylation 修飾時，除了標的蛋白質上之離胺酸會連結一個 hSUMO-1 之外，而且 hSUMO-1 本身也會進行 SUMOylation 修飾，透過 hSUMO-1 上之 Lys 17、Lys 23、Lys 25、Lys39、Lys45、Lys46、Lys 48、Lys 78 進行 SUMOylaiton，其中又以 Lys48 主要是形成 SUMOylation 之位置，而且這些分支點可能是形成 poly-SUMO-1 chains 之位置。因此，本研究之結果可提供 hSUMO-1 與 hSUMO-1 如何進行連結，藉此可進一步探討 poly-SUMO-1 chains 對於高等真核生物之生理意義。

英文摘要

The post-translational modification, such as phosphorylation, methylation, acetylation, ubiquitination, and SUMOylation plays a vital role in altering properties and functions of cellular protein. Among these modifications, ubiquitination and SUMOylation share a similar mechanism of a set of three catalytic enzymes facilitating the conjugation of ubiquitin or SUMO protein to the target protein. Recent studies showed that ubiquitination occurs on the specific lysine site of target proteins and different ubiquitination formation linkages represent unique biological significances. In the field of SUMOylation studies, scientists also observed poly-SUMO chains formation. This phenomenon is vital in yeast spore formation. Besides, poly-SUMO chains formation was regulated under physiological stress. However, it is still unclear at the biological significance of poly-SUMO chains formation and which lysine of SUMO-1 is involved in poly-SUMO chains formation. In this study, human cell lines were used to investigate the biological functions of poly-SUMO chains and the branch point of poly-SUMO chains formation.

In order to identify which lysine of hSUMO-1 is the branch point for poly-SUMOylation, we initially mutated all lysine on hSUMO-1 to arginine, which is K0 hSUMO-1. We then compared SUMOylation pattern of the different single lysine revertant of hSUMO-1, which are called K1~K11, with K0. We found that hSUMO-1 can be modified by SUMOylation through Lys17, Lys23, Lys25, Lys39, Lys45, Lys 48, and Lys78 of hSUMO-1. Among the SUMO modified lysines, Lys48 seemed to be the major SUMOylation site, suggesting that these branch points might be potential SUMOylaion sites for poly-SUMO-1 chains. These results offer new insight into conjugation of hSUMO-1 and study of the biological functions of poly-SUMO-1 chains.