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学位の種類	博士（医学）
報告番号	甲第１５３１号
学位記番号	第１１０２号
氏名	孫　佳
授与年月日	平成 28 年 3 月 25 日
学位論文の題名	SCF(Fbxo22)-KDM4A targets methylated p53 for degradation and regulates senescence （細胞老化過程における p53 標的遺伝子 Fbxo22 の機能解析） Nature communications. 2016 Feb 12;7:10574
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SCF^{Fbxo22}-KDM4A targets methylated p53 for degradation and regulates senescence

Recent evidence has revealed that senescence induction requires fine-tuned activation of p53, however, mechanisms underlying the regulation of p53 activity during senescence have not as yet been clearly established. We demonstrate here that SCF^{Fbxo22}-KDM4A is a senescence-associated E3 ligase targeting methylated p53 for degradation. We find that Fbxo22 is highly expressed in senescent cells in a p53-dependent manner, and that SCF^{Fbxo22} ubiquitylated p53 and formed a complex with a lysine demethylase, KDM4A. Ectopic expression of a catalytic mutant of KDM4A stabilizes p53 and enhances p53 interaction with PHF20 in the presence of Fbxo22. SCF^{Fbxo22}-KDM4A is required for the induction of p16 and senescence-associated secretory phenotypes during the late phase of senescence. $Fbxo22^{-/-}$mice are almost half the size of $Fbxo22^{+/-}$mice owing to the accumulation of p53. These results indicate that SCF^{Fbxo22}-KDM4A is an E3 ubiquitin ligase that targets methylated p53 and regulates key senescent processes.