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梅嫩蛋白在神經內分泌瘤扮演之角色

曾嶔元[1,2]

[1]國泰綜合醫院病理暨檢驗醫學部，台北，台灣

[2]輔仁大學醫學系，台北，台灣

摘要

胰臟神經內分泌瘤最常見的突變發生在*MEN1*基因上。人類*MEN1*基因位於染色體11q13.1上，轉譯出610個氨基酸之「梅嫩蛋白（menin）」。*MEN1*是一種抑瘤基因（tumor suppressor gene），其梅嫩蛋白透過其它的蛋白質分子來間接地表現其作用。在眾多與梅嫩蛋白交互作用的蛋白質中，MLL（mixed lineage leukemia）蛋白是相當特殊的一種，因為梅嫩蛋白透過它而執行表觀基因學之作用。藉由此機轉，梅嫩蛋白誘發*p27*和*p18*基因的表現，但抑制週期素（cyclin）D1的表現。由於p27和p18會阻擾細胞週期的進行，而週期素D1卻可促進細胞週期的進行。因此，*MEN1*是一種抑制細胞生長的抑瘤基因。此可部分解釋，為什麼*MEN1*基因突變與胰臟神經內分泌瘤的發生有關。（生醫2014;7(2):99-104）

關鍵字：精神經內分泌瘤、*MEN1*基因、梅嫩蛋白（menin）、抑瘤基因（tumor suppressor gene）、表觀基因學

前言

胰臟的神經內分泌瘤約44%有*MEN1*基因的突變[1]。即便是偶發性的胰臟神經內分泌瘤，也有22%至34%的案例出現*MEN1*基因的突變[2-3]。近年來有一大型的研究，分析100例的偶發性的胰臟神經內分泌瘤，再度肯定*MEN1*基因的突變並不罕見，因為25%的偶發性胰臟神經內分泌瘤有*MEN1*基因的突變[4]。人類*MEN1*基因在染色體11q13.1上，*MEN1*基因有10個外顯子，其轉錄之mRNA長2.8 kb，而轉譯出610個氨基酸之67Kd的蛋白[5]。此蛋白名為「梅嫩（menin）」，此名湊巧與某一不相干之比利時城市的法語名稱相同。

*MEN1*為抑瘤基因

大約95%家族性「第一型多發性內分泌瘤（multiple endocrine neoplasia type 1 syndrome）」

通訊作者：曾嶔元 教授
電話：886-2-2690-7965 ext 2518
傳真：886-2-2691-9800
地址：106 台北市仁愛路四段280號 病理暨檢驗醫學部
電子郵件：jeffbucknell@gmail.com

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的病人，有*MEN1*基因之「異合（heterozygous）種系突變（germline mutation）」[6]。亦即，這些許病人的*MEN1*對偶基因之一有「種系突變」，另一對偶基因則出現「體突變（somatic mutation）」[5]。目前文獻上記載的*MEN1*基因突變已超過一千多種。

因為當*MEN1*兩個對偶都因突變而失去功能時（biallelic inactivation）病人就會罹患第一型多發性內分泌瘤，所以*MEN1*基因為如假包換的「抑瘤基因（tumor suppressor gene）」。梅嫩蛋白之抑瘤作用是透過抑制細胞的增殖來達到的。實驗已證明過度表現的梅嫩蛋白，可抑制被RAS轉形的NIH3T3細胞在軟膠（soft agar）內形成群落（clonogenicity）；梅嫩蛋白也可抑制此細胞在裸鼠內的生長[7]。此外，以反義（antisense）cDNA來減少梅嫩蛋白的表現，就可以增加老鼠十二指腸之「類隱窩（crypt-like）」細胞的增殖[8]。

對於梅嫩蛋白是如何抑制細胞的增殖，此問題困擾生物醫學專家多年。因為梅嫩蛋白序列極為特殊，細胞內無類似結構之蛋白質[5]。因此，無法從已知之蛋白功能來推測梅嫩蛋白之功能。

從演化的角度來看，酵母菌和秀麗隱桿線蟲（*Caenorhabditis elegans; C. elegans*）都沒有梅嫩蛋白[9-11]，所以梅嫩蛋白的功能並不是所有生命之基本所需。然而，從果蠅到人類都有梅嫩蛋白，顯然梅嫩蛋白在較複雜的生物細胞中扮演重要的角色。果蠅的梅嫩蛋白與人類的梅嫩蛋白有47%的相似性；斑馬魚（zebrafish）和老鼠（mice）的梅嫩蛋白則和人類的梅嫩蛋白分別有75%和98%的相似性[11-15]。顯然，梅嫩蛋白在不同複雜度的生物中演化出特定的序列，這表示它在不同的生物中可能扮演不同的功能。

不令人意外地，近年來的研究發現，梅嫩蛋白直接或間接地影響某些生理現象，如胚胎的發育[16]、細胞的分化[17]、細胞的增殖7、凋亡[18]、DNA修復[19-20]和荷爾蒙或代謝的機能[21]。

梅嫩蛋白為細胞核內分子

雖然在正常情況下，有少量梅嫩蛋白出現在細胞質和細胞膜上[22-23]，但基本上，梅嫩蛋白所在的位置是細胞核。由梅嫩蛋白C端有「核向訊號（nuclear localisation signal; NLSs）」的存在，我們就知道它就是核內蛋白。目前*MEN1*的無義突變（missense mutation）和框架內佚失突變（in-frame deletions）都未犯及NLS處[2,24-32]，所以這類突變都不會影響梅嫩蛋白移往細胞核。不過梅嫩蛋白之斷尾突變（truncating mutation）則全都犯及NLS，所以斷尾之梅嫩蛋白則會停留在細胞質。

梅嫩蛋白位於細胞核內，有機會影響基因的表現。近年來，研究發現梅嫩蛋白似乎是透過與它交互作用的蛋白質分子來間接地表現其作用。目前已知能和梅嫩蛋白交互作用的分子包括：JunD（和梅嫩蛋白之密碼子1-40、139-242和323-428接觸）、NF-kB（密碼子305-381）、SMAD3（密碼子40-277和477-610）、RPA2（密碼子1-40和286-448）、NM23H1（密碼子1-486）、Pem（密碼子278-476）、ASK（密碼子396-610）、mSIN3A（密碼子371-387）和FANCD2（密碼子219-395）。以上有些是轉錄因子，如JunD[33-35]、NF-κB[36]和Pem[37]。梅嫩蛋白可和這些轉錄因子交互作用而影響其對基因轉錄的調節。以上有些分子和DNA修復或複製有關，如FANCD2[19]和RPA2[20]。前者即為「范可尼貧血互補群D2（Fanconi anemia complementation group D2）」，後

者則為「複製蛋白A2（replication protein A2）」。

梅嫩蛋白也和核內受體交互作用，如ERα[38]、PPARγ[39]和VDR[40]，所以梅嫩蛋白也可調節核內受體介導的轉錄。此外，梅嫩蛋白還可與細胞骨架（cytoskeletal）蛋白如「膠原原纖維酸性蛋白（glial fibrillary acid protein; GFAP)」[23]、波形蛋白（vimentin）[23]和IQGAP1[41]等交互作用。

最令人注意的是，有些染色質修飾蛋白也可與梅嫩蛋白交互作用。例如MLL（mixed lineage leukemia）[42-48]、EZH2[49]和組蛋白去乙醯酶（histone deacetylases; HDACs）[33-34,50]。

近年來，晶體學研究（crystallographic study）發現梅嫩蛋白的三度空間立體結構像手掌，能抓住MLL蛋白的N端[51-52]。梅嫩蛋白和MLL的關係甚至可解釋其抑制細胞增殖的機轉。

MLL為梅嫩蛋白的鑰匙

前述指出梅嫩蛋白的三度空間立體結構像隻手掌，在其中央凹陷處可抓住MLL蛋白N端的5-44號氨基酸殘基[42]。因此，看起來像是手（梅嫩蛋白）拿著鑰匙（MLL蛋白）開　細胞的功能。當梅嫩蛋白發生突變而不和MLL形成複合體時[44]，即失去了正常該有的功能了。

MLL是果蠅「三胸群（trithorax group）」的同源基因。MLL蛋白的C端有SET區（SET domain），亦即有「斑駁抑制（suppressor of variegation）」[53]、「zeste加強子（enhancer of zeste）」[54]和「三胸（trithorax）」[55])。SET區為許多與染色質有關的蛋白所共有的結構，它具有組蛋白H3K4甲基轉移酶（histone H3 lysine 4 methyltransferase; HMT）之活性[44,48,56-57]。HMT的作用可產生單、雙或三甲基化。其中三甲基化的H3K4（trimethylated H3K4; H3K4m3）常出現於哺乳動物的起動子[58]。通常H3K4m3被認為是一種標誌，代表該處染色質之轉錄作用是活躍的。

梅嫩蛋白拿著MLL這根鑰匙要開或關那一扇門？近年來的研究指出，它們打開了*p27*和*p18*，但關上了週期素（cyclin）D1。p27和p18都是週期素依賴性激酶（cyclin-dependent kinase; CDK）之抑制劑[59]，p27可阻擾細胞週期由G1進入S，而p18則作用在G1晚期。有研究發現，失去p27和p18的功能會導致多處內分泌組織的增生[60]。

有觀察發現，胰島素瘤（insulinoma）的*p27*表現量低[45]；而且*p27*的種系突變會導致內分泌瘤症候群[61]。至於*p18*，亦有研究發現*p18*和*MEN1*双重剔除之老鼠會長出胰島素瘤[62]。在內分泌細胞裡，梅嫩蛋白和MLL的複合體會落腳到*p27*和*p18*基因座而調控其表現。當*MEN1*基因佚失或突變時H3K4甲基化程度就會減少，因而*p27*及*p18*的表現也隨著下降[63]。此外，如同ING2一般[64]，梅嫩蛋白也可能結合到H3K4m3而抑制週期素D1的表現，的確有研究發現，減少梅嫩蛋白的表現可導致週期素D1過度表現[8]。

雖然梅嫩蛋白可影響p27和p18的表現，但是此現象在骨髓細胞中卻不會發生[47]。另外也有研究指出，失去*MEN1*基因的肝細胞，也不會造成肝細胞的腫瘤[65]。顯然，梅嫩蛋白的抑瘤作用是有組織的侷限性。更進一步來看，以胰臟當例子，雖然梅嫩蛋白可

在內分泌及外分泌細胞中表現，但是當*MEN1*基因出問題而失去正常功能時，只有內分泌細胞會增殖[66]。

結語

近年來，研究發現梅嫩蛋白是透過與它交互作用的蛋白質分子來影響細胞的增殖。因此，當*MEN1*基因突變而完全失去其功能時，梅嫩蛋白就會間接地造成細胞增殖的失控。本文所述之神經內分泌瘤發生機轉相當簡單，足以讓我們對此疾病得到鳥瞰式的了解。但我們必須了解，所有的腫瘤（包括神經內分泌瘤），其致病機轉都不可能如此單純的。2010年的研究報告即指出，98%的胰臟神經內分泌瘤有染色體的異常[67]。顯然除了*MEN1*外，神經內分泌瘤還有其它的基因突變。這些基因在神經內分泌瘤的發生上扮演什麼角色？是否與表觀基因學之作用有關？若是如此，那麼表觀基因學異常所致之腫瘤在臨床上是否與其它的腫瘤不同，這值得我們進一步探討。

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