子宮內膜異位之形成與淋巴細胞之相關

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引言

子宮內膜異位症是造成生殖年齡女性不孕及疼痛的一種疾病。雖然有許多研究都希望找出其成因，但事實上只有部分被了解。基於許多累積的證據顯示：子宮內膜異位症源於月經逆流至腹腔的假說是最廣泛被接受的。然而月經逆流在大部分的女性身上都會出現，但為何只有少部分女性會形成子宮內膜異位症呢?所以從病理學形成的角度作探討，可發現幾個過程，如異位內膜細胞的存活、著床及增生，都是值得探討的。而許多影響這些過程的因子，如：hormone、growth factor、cytokines 及 prostaglands 以及在子宮內膜異位病灶中的 immune cells、endometrials epithelial cells、stromal cells 及 vascular endothelial cells 都是值得去做探討的。而這些因子中 immune cells 對 endometrials cells 的排斥及接受被認為扮演著決定性的角色。除了這直接的角色外，immune cells 所分泌的多種 cytokines 對於的增生，發炎反應及 angiogeneis 都有一定的貢獻。另外研究發現在子宮內膜異位病灶上含有許多種類的 immune cells，如 T 及 B lymphocytes、nature killer cells 、macrophages 及 mast cells，這都指出這些 immune cells 在子宮內膜異位症中潛在的意義。

T lymphocyte

1, when cytotoxic T lymphocytes do not respond to autologous endometrium. Endometriosis Deuelops.

基本上 T lymphocytes 分為 cytotic T cells 及 helper T cells，一些相關的研究指出 T lymphocyte 對於字體移植的 endometrials cells 缺乏反應時，可能出現子宮內膜異位症。傳統的研究利用恆河猴進行子宮內膜組織自體移植至皮下進行實驗。發現子宮內膜異位組比健康組的移植部位有較少的 lymphocytes 數目。在人類的研究中也有同樣的結果。基於以上的研究，藉由矯正 T lymphocyte 對於 endometrials cell 之 cytoxicity 的缺陷可作為子宮內膜異位症的治療策略。事實上這些 T lymphocyte cytoxicity 的缺陷可藉由 recombinant 的 interleukin-2 去刺激週邊血流中的 lymphocytes 而得到矯正。進而證實 interleukin-2 對於子宮內膜異位症具有治療的潛力。而在 Rat model 中 endometriosis 的病灶也會因 IL-2 提升了 lymphocyte 的數目而使得病灶變小。

另一種機轉則認為 endometriotic cell 會分泌 Fasl，進而能逃過 cytotoxic T lymphocyte 的攻擊，Fas 會和 lymphocyte 上的 receptor 結合而導致 lymphocyte apotosis，而使得週邊之 lymphocyte 數量減少而逃過其攻擊。有趣的是子宮內膜異位女性的腹腔液及血清中有較高濃度的 IL-8 及 CCL-2，而這些成份正可以引導 endometriotic stromal cell 榨出 FasL。事實上將 Jurkat cells(T lymphocyte cell line) 和事先以 IL-8 及 CCL-2 處理過的 endometriotic stromal cell 共同培養下則出現 apotosis 之情形。而在具有 advanced satge endometriosis 之女性的腹腔液中，亦可見到較高之 FasL 之濃度。總之於 endometriosis 女性的腹腔液中的某些因子，直接或非直接地藉由刺激 endometriotic cell 的作用使得 cytotoxic T lymphocyte apotosis 而讓 endometriosis 可以存活下來。

2, Helper T-cell Activity & Pecreased in Endometriotic PF

除了 cytotoxic T lymphocyte 之外，$CD8^+$ T cell (helper T cells) 或 $CD4^+$ T cellsu 也被發現子宮

內膜異位症患者的腹腔液會減少其功能。在研究中發現在 endometriosis 的腹腔液中 CD4:CD8 的比例呈現降低之情形。雖然 $CD4^+$ T cell 的濃度呈現上升的情形，但事實上具有活性的 $CD4^+$ T cells 和 $CD8^+$ T cells 一樣是降低的。在一個研究中顯示，將 THP1 cell (monocytic cell line)和具有 endometriosis 的腹腔液一起培養，則會降低其分泌 MHC class Ⅱ 和 CD80/CD86 (這些分子可刺激 T cell 活性)。這結果顯示在含 endometriosis 的腹腔液中有某些潛在因子可影響 antigen-presenting cells (monocyte lineages) 的作用，因而減少了 helper T-cell 的活性。可能的因子應該是 IL-10，因為 IL-10 neutralization 則具有此作用。進而顯出在含 endometriosis 的腹腔液中具有活性的 $CD4^+$ T cells 之降低和高濃度的 IL-10 是有相關的。

3, Th1 and Th2 cells

將近 20 年前，一個新的 Th cell 之分類出現(Th1 及 Th2 cells)。Th1 cells 主要作用在製造大量 interferon-γ，引起 delayed hypersensitivity 的作用，及活化 macrophages 和抵抗細胞內的病原體。而 Th2 cell 主要在製造 IL-4 及 IgE; 及引出 eosinophils 及幫忙清除寄生蟲。自從這個分類被提出後免疫學家則利用此兩中分類之平衡，不論是全身性的或局部性的去解釋各種不同的生理及病理的情形。而在子宮內膜異位的研究中發現，在週邊 Lymphocytes 的 IL-4 及 IL-10 的表現變得強烈而 interferon-γ 的製造則降低。所以指出 endometriosis 中 Th1/Th2 cell 的平衡是偏向 Th2。這一發現可能因為在 endometriosis 中 IL-4 的分泌對 Th2 cell 有正向迴匱之關係所造成。

4, Th17 cell and Regalator T (Treg) cells

Th17 cells 是在 Th1、Th2 cells 以外的 T helper cell。它可快速地藉由活化及移出 neutrophils 而引起發炎反應。而在 endometriosis 的研究中亦發現 Th17 cells 存在腹腔液中，而 Th17 cells 所分泌的 IL-17 可刺激 endometriosis stromal cells 之增生及 IL-8 和 cydooxygensase-2 的表現。另外也有研究指出 IL-17 出現在 endometrial cyst 的 fluid 中，而且發現在具有 aromatase 反應的 endometriosis 中有較高的 IL-17 含量。Treg cell 則被發現主要作用在抑制免疫系統的活性，藉此維持免疫系統的平衡，及對於 self-antigen 的容忍。在健康女性的 secretory phase 時 Treg cell 的量則明顯降低，但在 endometriosis 女性則無此現象。而此現象指出子宮內膜異位症患者在月經來時，此未降低總量的 Treg cell 則會壓制體內的免疫細胞的新生，進而減少對這些 endometrial cell 攻擊，使得這些回流的 endometrial cell 可以存活及著床。

5, The effect of Hormonal Therapy on T lymphocyte

利用 GnRHa 去壓低體內的 Estrogen 廣泛地被使用在 endometriosis 的治療。主要認為 estrogen 能維持 endometriotic cell 的增生。但 estrogen 的壓制也會改變體內免疫系統，進而對子宮內膜異位的治療有所貢獻。有研究報告指出 GnRHa 的使用可使週邊血液中 T lymphocyte 的量及腹腔液中 T lymphocyte 的量及活性增加。而子宮內膜異位患者週邊血液中 IL-4 製造的增加及 interferon-γ 製造的降低都可因為 GnRHa 的使用而獲得矯正。這些研究的結論指出 GnRHa 的使用，不只直接在 endometriotic cell 並且也在改變免疫環境上有所貢獻。

6, T Lymphocytes in Animal model of Endometriosis

狒狒(baboon)是最常被用來做 endometriosis 研究的動物，狒狒本身自己可產生子宮內膜異位症，亦可藉由自體移植子宮內膜組織而產生。在研究中發現，在週邊血液中不論是自發性或人為誘導子宮內膜異位的個案，活化的 $CD4^+$ T cells 含量都會升高。但在腹腔液研究中，誘導子宮內膜異位個案的 $CD8^+$ T cells 含量並未升高。可見腹腔液中 leukocyte 的改變是為原因性的，而非續發性的。不過許多研究的發現都顯示這些範例都不足以單一地解釋所有病理的變化，所以更多的研究去探討這複雜的病理變化是必需的。

B lymphocytes

最早有關於患有子宮內膜異位女性 B lymphocyte 活性增加的報導在 1980 年。 同年亦有研究者指出女性患有子宮內膜異位者有 C3 及 IgG 沉澱在子宮內膜組織而血清中補體的數量則減少。此結果指出局部的自體免疫反應產生，並消耗掉補體。之後便有許多學者著重在 B lymphocyte 於子宮內膜異位發病機轉的角色之研究。特別在自體免疫反應的研究上最常見。其中包括二類自身抗體，第一類是針對子宮內膜所產生的抗體，第二類則是各種不同常見的自體免疫反應的抗體。

1, Autoantibody Specific to the Endometrium

Wild 及 Shivers 是第一個提出在子宮內膜異位女性的血清中找到 anti-endometrial antibody 的研究者。同樣的，Fernandez-Shaw etal.指出 anti-endometrial antibody 在有子宮內膜異位女性的血清中比正常女性的血清中常出現。Mathur etal.則提出針對子宮內膜組織的 IgA、IgG antibody 不只存在血清中，也存在子宮內膜異位女性的子宮頸及陰道的分泌物當中。他們也發現子宮內膜中引起 autoantibody 反應的真正 antigen 是內膜中的運鐵蛋白 (transferrin)及 α-2-HS glycoprotein。

2, Antibody commonly observed in Autoimmune Diseases

常見的 autoantibodies 如 antinuclear antibodies 也都在具有子宮內膜異位的女性身上發現。有一研究報告指出在 31 個子宮內膜異位的女性中，針對 16 種抗原中至少有一種發生反應而 64.5%出現 IgG 自體抗體，而 45.2%出現 IgM 自體抗體。這結果顯示子宮內膜異位和不正常的 polyclonal B-cell 反應是有相關的。藉由此發現亦可作為解釋子宮內膜異位和不孕症的關係。例如這些抗體並不止和 endometrium 發生反應也和胚胎和精蟲發生反應。不過這些自體抗體的反應到底是發病的初始原因或是附帶的現象至今仍不清楚。

3, B1 cell

B1 cell 是 B lymphocyte 的一個 subclasses，而且已知 B1 cell 在週邊血清中會自我更新。傳統研究中發現 endometriotic 病灶中的 B lymphocyte 的量非常少。不過最近利用 flow cytometry 的分析發現 B1 cell 及 total B lymphocytes 在 endometriosis 組織的量遠比在子宮內膜的量高。此外在腹腔液中 B1 cell 的量也較高。而後續也有研究指出在子宮內膜異位病灶具有較豐富之 plasma cell。此 cell 一般認為是由 B1 cell 來的。

綜合上述，無庸置疑的是 B lymphocyte 對 endometrium 不論是 specific 或 non-specific

都會產生auto-antibody，另外也可是子宮內膜異位成因的一環。

NK-cells

1, NK Cells Cytotoxic Activity is Reduced in Endometriosis

一般而言，NK-cells是對腫瘤或微生物細胞產生排斥反應而生。只要是靠釋放出細胞質中的蛋白質顆粒以誘導細胞凋零以破壞標靶細胞。而和endometriosis有關是起源於某個研究指出週邊血液中的NK-cells有能力破壞endometrial cells。此研究顯示NK-cells可破壞月經逆流中的endometrial cells。當NK-cells活性降低時便可能使得endometriosis產生。事實上後續的研究顯示NK-cells的cytotoxic activity在endometriosis中是降低的。而且在endometriosis患者的週邊血液中NK-cells對endometrial cells的cytotoxic能力也消失了。此外這種NK-cells cytotoxic能力的降低和endometriosis的嚴重程度是有相關的。而在腹腔液中亦發現NK-cells cytotoxic activity降低之情形。

2, Factors Modulate NK Cells Cytotoxic Activity in Endometriosis

Oostelynck etal.發現子宮內膜異位患者之腹腔液比沒有子宮內膜異位患者之腹腔液更有抑制NK-cells cytotoxic的效應。而進一步的研究顯示，對於IL-2具有拮抗作用的free IL-12P40在子宮內膜異位患者的腹腔液中較一般人有較高之含量。一般而言IL-2可誘導出NK-cells的cytotoxity。所以有可能free IL-12P40是子宮內膜異位患者腹腔液中壓抑NK-cells cytotoxity的因子之一。在endometriosis tissue的培養中發現其上清液具有抑制NK-cells的作用。而且由endometriosis患者的子宮內膜間質細胞培養的上清液較正常患者的上清液對NK-cells有較強之抑制作用。此結論表示，雖然真正物質尚未被完全找出，但可以知道不論是子宮內膜異位細胞或子宮內膜細胞只要被子宮內膜異位症影響，便具有壓抑NK-cells cytotoxic activity的能力。

3, Altered NK-cells Inhibitory Receptors in Endometriosis

為了控制NK-cells對於標的細胞過度的cytotoxic activity，NK-cells本身出現有inhibitor receptor，稱為killer cell inhibitor receptor (KIRs)。在嚴重的子宮內膜異位患者之腹腔液中可KIR3DL1,KIR2DS1,KIR2DL1的含量明顯較健康者高。而在週邊血液中，子宮內膜異位患者之KIR2DL1含量亦高於健康的人。此情形可能可用來解釋子宮內膜異位患者之NK-cells cytotoxic activity降低之原因。

4, Impact of Surgical/Medical Therapy on of NK-cells Function

手術或藥物治療能否改善NK-cells的活性是一個有趣的話題。不過已知手術並不會改善NK-cells的activity，因此可知NK-cells的活性不足是原發性的而非次發性的。而不同於手術GnRHa的治療可增進週邊血液中NK-cell的活性及數目。有趣的是在GnRHa療程中若NK-cells的活性較低者則有較高之復發率。這結果呈現NK-cell的活性降低應是子宮內膜異位症的原因而非續發的變化。而hormone的治療能促進NK-cells的活性而可預防再復發。雖然人類的結果尚未出

爐，但在 rats 的研究中可見 dienogest 及 danazol 也都可以增強 NK-cells 的活性。

綜合上述，受損的 NK-cells cytotoxic activity 可能是子宮內膜異位發生的原因。而已形成之子宮內膜異位對 NK-cells 活性的影響可促使疾病的進行。而 hormone therapy 可促進 NK-cells 的作用進而可控制疾病的變化。

總結：

許多的證據都顯示免疫細胞中的淋巴這一系列對子宮內膜異位症扮演著重要的角色。一般來說，即使並不清楚這到底是成因還是 endometriosis 所造成的，還是認為在子宮內膜異位患者的免疫能力是受到壓抑的 除了免疫細胞直接作用在抵制子宮內膜異位，免疫細胞也藉由引起發炎反應，及促使子宮內膜細胞的增生，對子宮內膜異位的發展有所貢獻。這些發現都讓我們可藉由調節免疫細胞的功能去作為治療的方針。更多的研究可促使更了解子宮內膜異位的成因，及發展出更新的治療方法，去幫助那些遭遇子宮內膜異位的婦女。

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