從腫瘤轉移機轉談甲狀腺未分化癌藥物治療之進展

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摘　要

絕大多數癌症是死於轉移而非腫瘤本身，因此瞭解轉移的機轉是現今很重要的研究課題。早在十九世紀，有一位Paget學者，提出一個種子與土壤的假說(seed and soil hypothesis)來解釋轉移現象，即擴散的癌細胞如種子，必須有適合其生長的特殊土壤（目標器官），才能成功順利地長成而轉移腫瘤。癌細胞病理上，猶如寄生蟲，需要依賴並利用宿主環境，才能自我存活。腫瘤爲了成功轉移，本身會運用各種策略，除了血管新生作用之外，還有其它機轉，比如由上皮細胞轉型成間質細胞（epitheilial-to-mesenchymal transition, EMT）以更具移行力和侵犯力，也能適應各種不同環境轉換不同細胞形態的高度可塑能力。而腫瘤與其所處的宿主微環境（microenviorment），包括纖維母細胞、免疫細胞和胞外間質等，都有緊密的交互作用，也會決定並影響腫瘤轉移的進程。關於癌細胞爲什麼會轉移到特定的目標器官，近來有研究證據支持細胞激素及其對應受體，類似發炎機轉的理論。也有研究提出癌症幹細胞的觀念。甲狀腺未分化癌爲一有高轉移率與死亡率的癌症，傳統的治療方式包括手術、放射線治療、化學治療或其合併治療，效果非常不理想，病患經診斷後平均只能存活三個月。透過對於癌轉移機轉的更多認識，現在有許多分子標靶的藥物研究進行中，在人體試驗上的效果令人期待。

關鍵詞：癌症轉移（Cancer metastasis）
機轉（Mechanism）
甲狀腺未分化癌（Anaplastic thyroid cancer, ATC）
標靶療法（Target therapy）

前言

癌症的死亡原因，絕大多數 (約90%) 病人是死於轉移，而非腫瘤本身。腫瘤要成功地轉移至遠處，盡其所能要運用各種策略以完成下列幾個步驟：(1) 脫離原腫瘤並移行 (migrate) 進入血液或淋巴系統 (intravasation)、(2) 定位及辨認要移轉的目標位置並轉出血液或淋巴系統 (extravasation)、 (3) 建立好轉移基地，並長成新的腫瘤。由於目前分子醫學的進步，愈來愈瞭解癌轉移的機轉，也開發出愈多的標靶藥物

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來對抗癌症。

甲狀腺未分化癌是最難治療的甲狀腺癌，也是存活期最短的癌症之一，雖然放射線療法有效，但病人卻容易因轉移而死亡，因此若能了解轉移的機制，並加以抑制，甲狀腺未分化癌的治療就會變得較爲容易。

癌細胞轉移運用的多種策略

1.上皮細胞轉型成間質細胞 (epithelial-to-mesencymal transition, EMT)

癌細胞爲了會變得更具有侵犯(invasiveness) 和移行的能力，進而遠處擴散(dissemination) ，轉移細胞會與原腫瘤脫離細胞間的連結，也會由原本上皮細胞 (epithelial cell) 的表面的分子標記及細胞特質轉換成間質細胞 (mesenchymal cell) 的型態，如表一所列，這現象稱爲 epithelial-to-mesenchymal transition (EMT)[1-3]。

不同的腫瘤類型會有不同侵犯周邊組織的型式[4]，組織學上發現主要有兩大類型。第一種類型爲單一細胞侵犯型（single cell invasion)，在腫瘤周邊組織會發現單一或散落的癌細胞。第二種類型爲集體細胞侵犯型（collective cell invasion)，即發現癌細胞成群結集在一起，而非單獨行動。第一種單一細胞侵犯型主要會以類纖維母細胞（fibroblast-like)或類白血球細胞(leukocyte-like)模式在胞外間質（extracellula matrix, ECM)上移行。類纖維母細胞模式具有下列幾個特性：(1)像纖維母細胞的型態、(2)細胞間連結消失、(3)侵犯能力及細胞與胞外間質的交互作用較強，例如細胞表面表現較多的integrin和蛋白質水解酶（proteases)、(4)細胞分裂能力低[5]。黑色素細胞瘤（melanoma)即屬此型[2]，會在 ECM上挖隧道前進。相反地，類白血球細胞像阿米巴式（ameboid)的移動，和胞外間質的交互作用較弱，不需要依賴蛋白質水解酶分解 ECM，而是靠自己能變形通過 ECM上的隙縫而前進[6]，有些血液腫瘤和神經內分泌腫瘤（如肺小細胞癌）等[2]即屬此類。

集體細胞侵犯型即侵犯組織的癌細胞仍保留細胞彼此間的連結。而這集合細胞中，比較特殊的是位於侵犯前端（invading front）的細胞群，它們細胞表面會表現較多的integrin，和ECM有較強的連結，也有較多能分解胞外間質的matrix metalloproteinase（如MT1-MMP、urokinase plasminogen activator（uPA）、uPA receptor、MMP-2等）[7]。這現象與胚胎發育過程中的型態發育機轉可能相仿。

2.癌細胞之可塑性（Tumor cell plasticity）

癌細胞的可塑性很強，是指它爲了完成轉移的目的，可以在不同的環境中轉換成不同的細胞型態，除了前面所提到的EMT，間質細胞的型態也會因所處的環境中有蛋白質水解酶抑制劑，而轉換成不需依賴水解酶的阿米巴

表一：上皮細胞與間質細胞的差異性

上皮細胞		間質細胞	
表面分子標記	細胞特質	表面分子標記	細胞特質
E-cadherin	Epithelial	N-cadherin	Fibroblastic
Cytokeratins	Nonmotile	Vimentin	Motile
ZO-1	Noninvasive	NCAM	Invasive
Occludin	Anoikis (apoptosis triggered by lack of attachment to a substrate)	Snail	Scattering
Desmoplakin	Polarized	Twist	Anoikis resistance
		Fibronectin	Low proliferation
		MMP-2, -3, -9	Nonpolarized
		Integrin $\alpha_v\beta_6$	

Adapted from Yilmaz M, Christofori G, Lehembre F. Distinct mechanisms of tumor invasion and metastasis. Trends Mol Med 2007; 13: 535-41.

細胞型態。所以癌細胞有能力依所處的微環境(microenvironment)不同，而去轉換不同的侵犯模式，比如處在不同的抗癌藥物的環境下[8]。當抵達要轉移的目的地時，穿出血管後，間質細胞型態又可以轉換成原來上皮細胞的型態(mesenchymal-to-epithelial translation, MET)[9]，生成新的腫瘤。

3.宿主微環境（microenviorment）的重要性

病理學上，癌症病理其實跟寄生蟲很類似，需要依賴並利用宿主環境，才能自我存活。腫瘤爲了自己轉移成功，除了可能有EMT和能適應各種不同環境的高度可塑性等機轉，腫瘤與其所處的宿主微環境(microenviorment)，包括纖維母細胞、免疫細胞和胞外間質等，都有緊密的交互作用，也會決定和影響腫瘤轉移的進程。例如有許多研究發現把低度轉移能力的癌細胞曝露在有致癌轉移訊號的微環境中，會轉變成有高度的侵犯和轉移能力[10-16]。而不同個體基因的差異性也會造成不同的宿主微環境，微環境中致癌和抑癌因子的差異，會影響到腫瘤的轉移能力[17,18]。

胞外間質中的纖維母細胞在癌轉移上也有很重要的角色。纖維母細胞會分泌許多間質(matrix)，而胞外間質的構成內容可能會決定腫瘤會轉移到那個器官[19]。例如 fibronectin堆積的增加可以做爲導引轉移的訊號[20]。轉移處胞外間質內matrix metalloproteinases和matrix metalloproteinase inhibiors濃度的消長也會影響到腫瘤是否會轉移[21,22]。

4. 細胞激素（cytokines）

免疫細胞會被吸引到發炎的地置，是因爲細胞和發炎位置間有細胞激素與細胞激素受體（receptor）互相吸引的作用力存在[23]。而目前仍然不太清楚癌細胞爲什麼會轉移到特定的目標器官，有各種嘗試解釋的假說，較多的證據支持把發炎機轉的『細胞激素（cytokines）與細胞激素受體（cytokine receptors）交互作用』用在解釋轉移機轉，即癌細胞會運用許多種細胞激素來告訴它要轉移到何處[24]。以乳癌細胞爲例，細胞表面會表現很多如 CXCR4和 CCR7等細胞激素受體，而發現乳癌常轉移的器官，也表現較多的會相吸引的細胞激素如 CXCL12/SDF-1α和CCL21/6kine等[25]。胃癌和攝護腺癌的轉移也被發現有互相作用的細胞激素及其相對應受體的存在[26,27]。腫瘤細胞會分泌血管內皮生長因子VEGF（vascular endothelial growth factor）、TGF-β、TNF-α（tumor necrosis factor-α, TNF-α）等細胞激素來誘導肺部內皮細胞表現S100A8及S100A9等 chemoattractants來幫助癌細胞轉移[28]。但相反地，如果目標器官無法表現相對應的細胞激素或相對應受體，轉移就不會成功[29]。因此，目標器官上間質細胞所表現的激素或相對應受體，能控制轉移速率[30]。

5.癌細胞轉出血管（extravasation）

癌細胞會黏附在血管內皮細胞，之後再移行出血管而侵入周邊組織。其分子機制迄今仍不甚清楚。可能的機轉是：（1） 癌細胞會與內皮細胞上的特定表面受體結合、（2）血小板的協助角色。血循中的癌細胞會利用血小板來躲避α-腫瘤壞死因子的毒殺而增加存活度[31]，並幫助腫瘤栓塞至遠端的小血管。血小板也可以促進癌細胞在與內皮細胞黏附之後的血管新生作用，如此可以促進轉移腫癌的生長[32-35]。在動物實驗上，也發現阿斯匹靈可以抑制癌之轉移，可能是因降低癌栓塞的發生率和血管新生作用[36-38]。許多腫瘤癌細胞會過度表現血管內皮生長因子，是最重要的血管新生因子，會增加血管內皮細胞的通透性，促進癌細胞的轉出血管[39]。

6.癌症幹細胞(cancer stem cells)

早在1889年，Paget[40]提出一個種子與土壤的假說(seed and soil hypothesis)來解釋轉移現象，即擴散的癌細胞如種子，必須有適合其生長的特殊土壤(目標器官)，才能成功順利地長成而轉移腫瘤。Paget的假說現在有愈來愈多研究證據的支持。近年來發現，癌症進展過程中，轉移癌細胞並非是晚期才會出現的，而是在很早期就有了。有研究指出可能有癌症的幹細胞(cancer stem cells)或初發細胞(cancer-initiating cells, CIC)的存在，和幹細胞類似，它們具有自我更新(self-renewal)的能力且會形成腫瘤。原發的腫瘤上可能有一群CIC的細胞，會離開原腫瘤而扮演像種子的角色到遠處長成轉移腫瘤[41,42]。

CIC形成的機轉可能是源自：(1)正常幹細胞的癌化(oncogenic transformation)、(2)前驅細胞(progenitor cell)的轉型突變、(3)癌細胞與幹細胞的融合(fusion of cancer cells with stem cells)、(4)癌細胞轉成未分化型態(dedifferentiaton of cancer cell)[42]。癌症幹細胞的存在，目前研究者已經在血癌、乳癌、肺癌、前列腺癌、胰臟癌、腦癌等癌症找到證據[43-47]。若能找到並深入瞭解各種癌症其幹細胞之特性，癌轉移之治療會有極大的突破性發展。

7.血管新生(angiogenesis)

血管新生(angiogenesis)在正常人體生理上，比如胚胎發育、傷口癒合、女性月經週期等，都有極重要的角色。在腫瘤的生長與轉移機轉上，血管新生也同樣有很重要的角色。隨著腫瘤長大，它不再只依靠滲透作用來獲取養分，必須透過血管新生作用來供給。血管新生機轉是個精密調控的動態平衡，包括腫瘤與微環境的交互作用。血管新生因子〔如VEGF, basic fibroblast growth factor (bFGF), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), placental growth factor (PlGF), matrix metalloproteinases (MMPs)〕和內生性的抑制血管生成因子(如thrombostatin, angiostatin, tumstatin)會彼此交互作用來抑制血管新生。腫瘤若突變失去抑癌基因(如P53)或是處於缺氧或發炎的環境中，便會刺激血管新生。內皮細胞會受到刺激而增生並移行至腫瘤內部並形成新的腫瘤血管。腫瘤也會過度分泌 VEGF, VEGF還會使骨髓的內皮細胞前驅細胞增生移行並分化成血管內皮細胞[48]。同時，源自造血幹細胞的單核球細胞和巨噬細胞除了分泌血管新生因子之外，也會分泌蛋白質水解酶去構築新的腫瘤血管網絡。

腫瘤的新生血管和正常血管不同，它非常曲折，有大小不一的管徑和分支分流。而管壁細胞是腫瘤細胞與內皮細胞的組合，管壁外圍的平滑肌細胞缺乏內皮細胞並擁有高度複製能力和分泌血管新生因子，包括VEGF[49,50]。雜亂的血管分支和動靜脈分流會增加缺氧壓力，也會促進血管新生[51]和血管通透性增加[52]。血管壁基底膜的不連續相連接和缺乏良好的淋巴循環，常會造成腫瘤的過高組織壓力(interstitial pressure)[49]，會影響抗癌藥物的作用。

甲狀腺未分化癌藥物治療新進展

絕大多數(90%)罹患甲狀腺未分化癌(anaplastic thyroid cancer, ATC)的病人於診斷時就已經有腺體外擴散現象，而且75%在病程中會有遠處轉移[53,54]。ATC不管腫瘤體積大小、是否有淋巴或遠處轉移，致死率均非常高。美國癌症聯合會(AJCC)都將它歸爲Stage IV[55]。目前的治療方式包括手術、放射線治療、化學治療或其合併治療，但效果非常不理想，病患經診斷後平均只能存活三個月。由於超過一半的ATC病人在確診時已有癌轉移，因此化學治療的角色是很重要的，過去臨床上常用doxorubicin的單一療法，目前療法會使用多種藥物組合 (如cisplatin、bleomycin、melphalan、paclitaxel等)，但迄今仍無有效的療法，基礎醫學目前對於甲狀腺癌，包括ATC，致癌分子機轉有愈來愈多的瞭解，也因此有愈來愈多的分子標靶藥物陸續投入活體外、動物或人體的研究與試驗，簡介各類型標靶藥物與研究最新結果，整理如表二：

1.以 Ras蛋白導向之訊息傳遞路徑阻斷劑

細胞生長訊息傳遞路徑tyrosine kinase-Ras-Raf-MEK之異常活化可發生於約七成的甲狀腺癌，因此爲重要的標靶治療目標[56]。

其中關鍵步驟之一，Ras蛋白要依附到細胞膜上需要一種稱爲 "脂肪酸轉移酵素"（farnesyl protein transferase, FPTase）將Ras蛋白質脂化（farnesylation），才能進行接下來的訊息傳遞。脂肪酸轉移酵素抑制劑，如manumycin，即是抑制Ras蛋白質的脂化，使得這樣的訊息傳導不容易進行，達到抑制癌細胞的效果。不論是manumycin單獨使用或協同paclitaxel、doxorubicin、cisplatin等傳統化療藥物試驗，於活體外研究顯示能抑制ATC細胞株生長[57]。於活體腫瘤異種移植老鼠(xenograft mouse model)研究， manumycin與paclitaxel合併使用能使抑制ATC腫瘤生長和血管新生[58]。

表二：目前治療甲狀腺未分化癌，實驗上(in vitro或 in vivo或臨床試驗)的有效藥劑

類別	機轉	藥劑名	參考文獻
以Ras蛋白導向之訊息傳遞路徑阻斷劑	抑制脂肪酸轉移酵素	Manumycin	in vitro[57] in vivo[58]
	抑制Raf kinase	Sorafenib (Bay 43-9006)	in vitro[59]Phase II trial 結果尚未發表
酪胺酸激酶抑制劑	拮抗VEGF的單株抗體	Bevacizumab (Avastin)	in vivo[60]
	抑制EGF receptor tyrosine kinase	Gleevec (imatinib, ST151)	in vitro[61,62]Phase II trial 進行中
	抑制EGF receptor tyrosine kinase	Gefitinib (Iressa, ZD1839)	in vitro[63-67]Phase II trial 結果無效[68]
	雙重抑制EGF受體及VEGFR受體酪胺酸激酶	AEE788	in vitro & in vivo[69]
血管新生抑制劑	與tubulin結合之蛋白	Combrestatin A4 phosphate	in vitro & in vivo[70] Phase I trial 結果有效[71]
細胞凋亡誘發劑	阻滯細胞週期促凋亡	Aplidine	in vivo[72]
	抑制Integrin ligase	QLT0267	in vitro[73] in vivo[73]
	抑制Proteasome	Bortezomib	in vitro[74]
	抑制Rho蛋白的geranylgeranylation	Lovastatin	in vitro[75]
熱休克蛋白90抑制劑	抑制細胞生長訊息傳遞	17-AAG	in vitro[76]
組織蛋白去乙醯酶抑制劑	抑制調控細胞生長分化基因的轉錄	FK228	in vitro[77]
		SAHA	in vitro[78]
促癌細胞分化	機轉未明	Lovastatin	in vitro[79]

另一作用標靶位置是抑制 Raf kinase的活性，如 Sorafenib (Bay 43-9006)。活體腫瘤異種移植老鼠研究顯示亦能使抑制 ATC腫瘤生長和血管新生[59]。目前有針對 ATC與已轉移甲狀腺乳突癌之phase II臨床試驗進行中，但結果尚未發表。

2.酪胺酸激酶抑制劑 (tyrosine kinase inhibitors)

甲狀腺癌會表現過量的 receptor tyrosine kinase (RTK)，如血管內皮生長因子(vascular endothelial growth factor, VEGF)、表皮生長因子(epidermal growth factor, EGF)等，這與腫瘤血管新生作用發生有密切相關。

使用拮抗VEGF的單株抗體，Bevacizumab (avastin)在活體腫瘤異種移植老鼠研究顯示能抑制ATC腫瘤生長[60]。另一酪胺酸激酶抑制劑 Gleevec(imatinib, ST1571) 於活體外細胞株研究有爭議[61,62]，但目前有進行中的phase II 臨床試驗。而 EGF receptor tyrosine kinase抑制劑，如 Gefitinib(Iressa, ZD1839)，雖然於活體外細胞株研究單獨使用或合併 Gleevec，能抑制ATC[63-67]，但在 phase II 臨床試驗結果還是令人失望[68]。AEE788能雙重抑制EGF受體及VEGFR受體酪胺酸激酶活性，於活體外細胞株研究顯示能抑制生長並誘使凋亡，在活體腫瘤異種移植老鼠研究中單獨使用或合併paclitaxel顯示均能抑制ATC腫瘤生長[69]。

3.血管新生抑制劑(antiangiogenic agents)

Combrestatin A4 phosphate(CA4P)是與tubulin結合的蛋白質，能干擾血管新生。不論在活體外細胞株[70]、活體腫瘤異種移植老鼠研究[70]、phase I 臨床試驗[71]均顯示有很好抑制 ATC的效果，但 phase II 臨床試驗結果尚未發表。

4.細胞凋亡誘發劑(apoptosis-inducing agents)

Aplidine能抑制癌細胞蛋白質和DNA合成、停滯於細胞週期G1 phase、並誘發細胞凋亡。Aplidine於活體腫瘤異種移植老鼠研究上顯示能抑制 ATC腫瘤生長[72]。

Integrin ligase是參與中介細胞生長與生存的訊號，在一些癌細胞會被過度表現。QLT0267是透過抑制integrin ligase進而抑制癌細胞生長並誘發凋亡，在活體外細胞株和活體腫瘤異種移植老鼠研究顯示能抑制 ATC[73]。

Ubiquitin-proteasome 路徑是細胞內分解蛋白質之主要路徑。Bortezomib能抑制 proteasome在活體外細胞株研究顯示會促使ATC凋亡[74]。

Lovastatin爲3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor，一種史他汀類降血脂藥，透過抑制Rho蛋白的geranylgeranylation，於活體外細胞株研究顯示會促使ATC凋亡[75]。

5.熱休克蛋白90抑制劑(heat shock protein 90 inhibitors)

熱休克蛋白90是一能穩定生長因子受體及其訊息傳遞分子的伴護蛋白(chaperone)。透過抑制熱休克蛋白90，能抑制細胞生長的訊息傳遞進而導致細胞死亡。17-Allylamino-17-demethoxygeldanamycin (17-AAG)爲熱休克蛋白90抑制劑，在活體外細胞株研究發現能誘使ATC細胞死亡，但非凋亡[76]。

6.組織蛋白去乙醯酶抑制劑(Histone deacetylase inhibitor)

組織蛋白去乙醯酶能使細胞核染色質緻密化，抑制調控細胞生長分化基因的轉錄。FK228爲組織蛋白去乙醯酶抑制劑，在活體外ATC細胞株研究發現能抑制生長[77]。另一組織蛋白去乙醯酶抑制劑 Suberoylanilide hydroxamic acid (SAHA)，活體外 ATC細胞株研究亦發現能抑制其生長 [78]。

7.促癌細胞分化劑

促進ATC自未分化轉變成較高之分化程度，將可減少其轉移機率及有利於使用原子碘來做較有效的治療。Lovastatin於活體外 ATC細胞株研究發現能促進其分化[79]。

8.基因治療(gene therapy)

喪失抑癌基因p53或其功能是甲狀腺分化癌轉成未分化癌的重要機轉。利用腺病毒攜帶p53基因引入未分化癌細胞株，活體外及動物活體研究發現可恢復對傳統化療藥物的反應[80]。

9.清除癌症幹細胞(cancer stem cell eradication)

傳統的癌症發生理論，即所謂的 "多重階段致癌模式(multi-step carcinogenesis model)，而癌症幹細胞的致癌理論是因癌症幹細胞可以自我更新而不斷複製，以提供源源不絕已分化的癌細胞。癌症幹細胞的存在，目前研究者已經在血癌、乳癌、肺癌、前列腺癌、胰臟癌、腦癌等癌症找到證據[43-47]。近來也有愈來愈多研究支持甲狀腺癌幹細胞的存在[81]，雖然目前還不太清楚其特性，但如果將來能直接選擇對準癌幹細胞的抗癌藥物，再配合傳統藥物治療後，將使癌細胞沒機會再復發，大大地增加治癒率，爲未來最具潛力的研究方向。

結語

癌症的進程，從原發腫瘤的生長至最終遠處轉移的發生，中間各個步驟的分子機轉已經不再像一個黑箱，而是愈來愈清楚了。標靶藥物的開發，除了血管新生的抑制劑之外，未來應會有更多針對腫瘤的基因表現、抑制EMT、抑制intravasation或extravasation、改變宿主的微環境、改變或干擾相關的細胞激素或其對應受體、抑制癌症幹細胞的產生等各種不同機轉。以甲狀腺未分化癌爲例，已有學者發現PPAR gamma agonists (rosiglitazone和ciglitazone)能誘發細胞發生EMT某種程度的逆轉[82]，不要轉成有高度侵襲和轉移性的間質細胞型態。根據Paget在十九世紀(1889)提出的『種子與土壤假說』[40]，我們希望能發展新療法去破壞種子，阻止種子的散播，防止適合種子生長的土壤形成。

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The Mechanism of Cancer Metastasis and Advances in Potential Treatment for Anaplastic Thyroid Cancer

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Most cancer deaths are caused by metastasis rather than the primary tumor. Therefore, nowadays, it is crucial to understand the mechanism of metastasis more and more. Early in the nineteenth century, Paget postulated the "seed and soil" theory to explain the phenomenon: the disseminating cancer cells ("seed") need to find the appropriate microenviorment in target organs ("soil") for metastatic growth. Pathologically, as parasites, the cancer cells exploit the host and survive depending on the host environment. Cancer cells can use multiple strategies to metastasize successfully. Besides angiogenesis, other mechanisms exemplified as epithelial-to-mesenchymal transition (EMT) making cells more migratory and invasive, and exhibiting marked cell plasticity for adaptive switch in different host environment. There is also a close crosstalk and interaction between cancer cells and the host microenvironment (including fibroblasts, immune cells, and extracelluar matrix). The interaction will determine and influence the progression of cancer at all stages. Regarding why cancer cells would metastasize to the specified distant organ, recently, there are emerging evidences supporting the chemoattraction theory (the attraction between cytokines and its corresponding receptors), as the mechanism of inflammation. There are also accumulating evidences supporting the concept of cancer stem cells. Anaplastic thyroid cancer (ATC) has very high metastasis and mortality rates among all human cancers. Conventional treatments for ATC include surgery, radiation therapy, chemotherapy, or their combination. Current treatment results are very disappointing and the patients' average survival period is only three months after establishing diagnosis. Recently, because of the better understanding the mechanism of metastasis, there are various potential target therapy medicines for ATC conducted in vitro or in vivo experiments. The future clinical trial results may be promising.(J Intern Med Taiwan 2008; 19: 472-480)