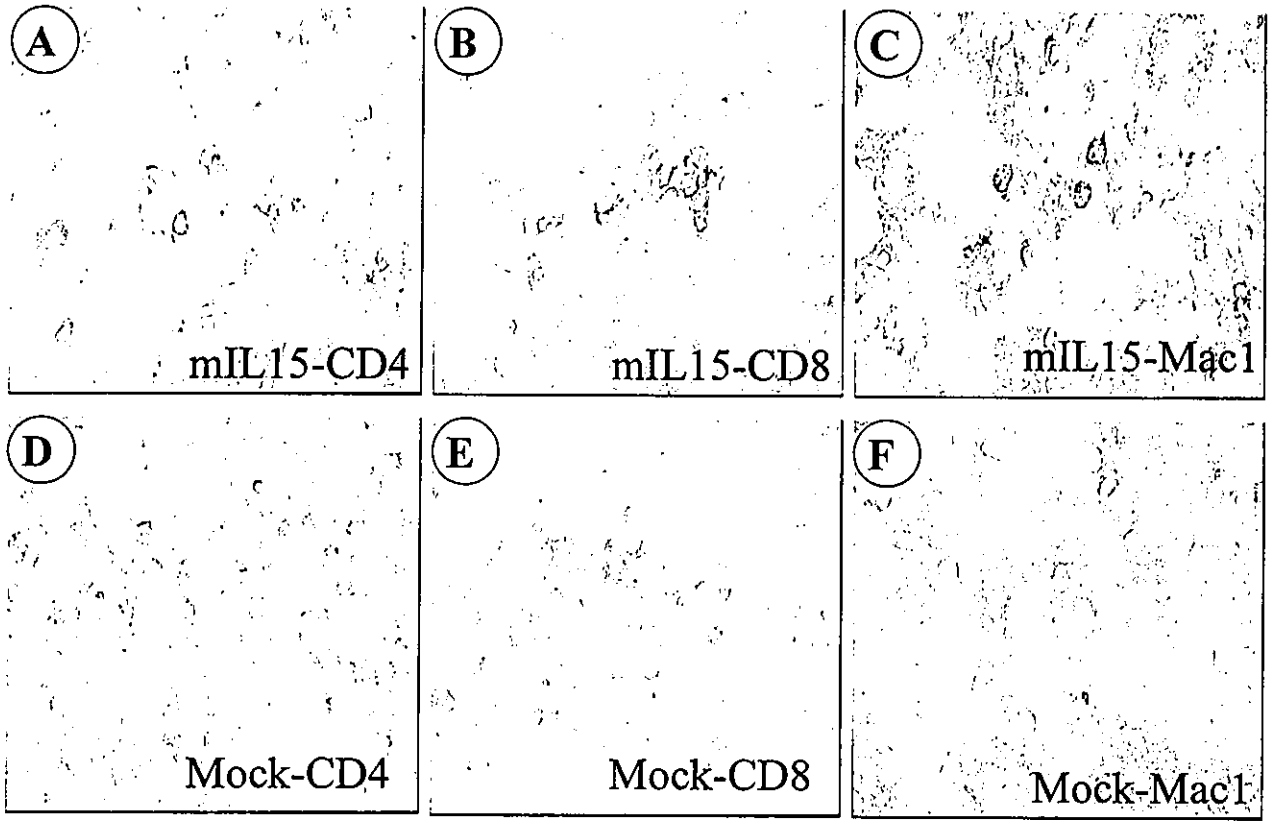

Figure 5. Immunohistochemical analysis of tumor implantation sites in BALB/c mice 14 days after subcutaneous injection of colon 26/mIL-15-4 cells (A-C) and mock transfectants (D-F). Staining with L3/T4 (CD4) (A), KT15 (CD8) (B) and Mac-1 (CD11b) (C) revealed infiltration of CD4$^+$ and CD8$^+$ lymphocytes and Mac-1-positive monocytes, respectively. Such infiltration was not observed in mice treated with mock transfectants (D-F).

Fourteen days after subcutaneous injection of colon 26/mIL-15-4 cells infiltration of CD4$^+$ and CD8$^+$ lymphocytes and Mac-1-positive monocytes was observed at the site of injection (Fig. 5). These findings were supported by previous reports that described the function of IL-15 in proliferation and functional activation of T, B and NK cells (3,4) and monocytes (29). To further clarity of anti-tumor mechanisms, we performed *in vivo* depletion of NK cells, CD4$^+$ and CD8$^+$ T cells. The anti-tumor effects of colon 26/mIL-15-4 cells were partially abrogated by treatment with anti-CD8$^+$ antibodies but not by depletion of NK cells or CD4$^+$ T cells (Fig. 4). In CD8$^+$ T cell-depleted mice, colon 26/mIL-15-4 cells disappeared temporarily, but re-grew 1 month after implantation. These results indicate that inoculation of IL-15-secreting tumor cells may mediate initial anti-tumor effects through CD8$^+$ T cells, CD4$^+$ T cells, NK cells and a variety of immunocompetent cells and that long-lasting specific immunity is mediated only through CD8$^+$ T cells. However, Meazza *et al* (30) reported that TS/A tumor cells, which secrete high levels of IL-15, reduced tumorigenicity, and that depletion of CD8$^+$ T cells or NK cells abrogated the efficacy of IL-15. This inconsistency may be due to differences in IL-15 between murine and human. Although murine and human IL-15 cross-react, there is only 73% amino acid identity between murine and human IL-15 (1). Therefore, it may be more appropriate to use murine IL-15 in murine studies. Indeed, Yajima *et al* (31) reported that murine IL-15 transgenic mice have anti-tumor activity against MHC class I-negative and -positive malignant melanoma through augmented NK activity and cytotoxic T-cell response, respectively. The present study is the first to show that murine tumor cells secreting high levels of murine IL-15 can mediate complete rejection of weakly immunogenic tumor cells and induce long-lasting specific anti-tumor immunity.

These results suggest that IL-15 is important in tumor immunity and that IL-15 may be an excellent candidate for a tumor-vaccine adjuvant for boosting CD8$^+$ memory T cells as therapy for weakly immunogenic human cancers.

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特集 コンセンサス 胆嚢癌の治療

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免疫逃避機構

tumor escape in immune responses

腫瘍細胞においては腫瘍特異抗原や腫瘍関連抗原が発現しているにもかかわらず，腫瘍組織は増殖し，宿主の生命を脅かす。これは腫瘍組織が宿主の免疫監視機構をかいくぐる免疫逃避機構をもっているからに他ならない。

HLA class I抗原の発現低下

腫瘍細胞の免疫逃避機構として，腫瘍抗原の発現低下があげられる。

腫瘍細胞表面に腫瘍抗原が提示されるためには，まず腫瘍抗原蛋白が細胞内に存在し，イムノプロテアソームによりプロセシングを受けて蛋白が提示ペプチドとなり，transporter associated with antigen processing (TAP)により細胞内輸送され，HLA-A，B，Cならびにβ_2-microgloburin (β_2m)と結合して腫瘍細胞表面に提示されることが必要である。class I 発現を認めない分子機構として，まずβ_2mの不活化があげられる。この場合には抗原提示が不可能となるため，特異的腫瘍免疫誘導は不可能となる。腫瘍抗原のプロセシング機能低下の要因として，low molecular weight polypeptide proteasome subunit (LMP)，multicatalytic endopeptidase complex-like-1 (MECL-1)，PA28などのプロテアソームサブユニットの発現の低下ないしは欠失があげられる。TAPに代表される細胞内輸送機能の低下も知られている。限局癌が浸潤癌，転移癌へと進展する過程においてもHLAの発現は低下し，悪性度・免疫逃避機構が助長される。このように，HLA class I発現を認めない腫瘍に対してはMHCに依存しない免疫監視機構が重要となり，MHC非拘束性様式で腫瘍を認識・攻撃する効果細胞の増強が重要となる。

免疫抑制物質の産生

腫瘍局所において，腫瘍産生因子あるいは腫瘍間質に存在する免疫細胞や間質細胞から産生される免疫抑制物質(TGF-β，IL-6，IL-10，PGE_2)などの作用により，腫瘍局所の免疫監視機構や全身の免疫能が低下する。これが腫瘍の逃避機構の一因となっている。免疫系は大きくtype 1(細胞性免疫)ならびにtype 2(液性免疫)に分類することができるが，抗腫瘍免疫はtype 1(細胞性免疫)が担っている。腫瘍局所に浸潤したマクロファージ(M)は腫瘍局所環境によりtype 2 Mへと誘導される。Type 2 Mが産生するIL-6やIL-10はヘルパーTリンパ球(Th)のうちTh2を誘導し，細胞性免疫は抑制される結果となる。さらに，Thから産生されるIL-4，IL-10，IL-6などのいわゆるTh2系サイトカインはtype 2 Mを誘導するため，癌患者の抗腫瘍免疫はさらに抑制される結果となる。一方，癌免疫療法により強力な抗腫瘍エフェクターの誘導に成功しても，癌局所におけるTGF-βなどの免疫抑制物質により抗腫瘍活性が不活化され，十分な抗腫瘍効果が得られない。

腫瘍細胞におけるFas ligandの発現

Fas発現細胞はFas ligandとの結合刺激により，アポトーシスに陥るとされている。通常リンパ球はFas ligandを発現しており，腫瘍細胞に発現しているFasに結合してアポトーシスに陥らせると考えられている。これとは逆に，腫瘍細胞に発現したFas ligandがリンパ球上に発現したFasを刺激してリンパ球をアポトーシスに陥らせる機構が，腫瘍の免疫逃避機構の一つとして報告されている。

表1 腫瘍の免疫逃避機構

1. HLA class I 抗原の発現低下
   a. 腫瘍抗原蛋白分解酵素の発現低下
   b. 細胞内輸送機構の不活化
   c. β_2-microgloburin の不活化
2. 腫瘍細胞および浸潤免疫細胞からの免疫抑制物質の産生
   a. TGF-β
   b. IL-6
   c. IL-10
   d. PGE_2
3. 腫瘍細胞における Fas ligand の発現