Antigenic Cancer Cells that Escape Immune Destruction Are Stimulated by Host Cells

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ABSTRACT

Cancers induced by UV light in murine skin often regress completely when transplanted into normal syngeneic recipients and grow progressively only in T-cell-deficient hosts. Heritable cancer variants that grow progressively and kill normal mice occasionally evolve in vivo. It is surprising that most of these variants appear to retain their antigenicity and immunogenicity. We have compared three such variants (4102-PRO, 6132A-PRO, and 6134-PRO) with the parental tumors to determine why the variants acquired progressive phenotypes without antigen loss. We found that all three variants grew substantially faster than the parental tumors in T-cell-deficient hosts; one variant, 6132-PRO, also grew faster in vitro. Furthermore, the growth of all of the variants was stimulated by soluble factors released by tumor-induced peritoneal exudate cells, and all attracted more leukocytes than the parental cells. Finally, pretreatment of mice with antigranulocyte antibody reduced the growth of variant but not parental 4102 and 6134A tumors. The treatment reduced the growth of both the parental and the variant 6132A lineage cells. We found no evidence for acquired resistance of variant tumors to immune destruction by a host defense mechanism. The parental cells did not grow faster in beige nude mice deficient in natural killer and αβ T cells or in SCID mice deficient in B and T cells. The variant parental cells had a similar sensitivity to lysis by polyinosinic-polycytidylic acid-induced natural killer cells or thiglycollate- and LPS-induced macrophages. Together, our results are consistent with the notion that these variants escape from immune destruction in vivo by attracting leukocytes that stimulate tumor cell growth.

INTRODUCTION

The mechanisms of escape of antigenic tumor cells from immune destruction have been explored in multiple tumor models. Generally it is assumed that, preceding the escape, heritable changes had occurred that allowed the cancer cells to escape, but rarely are the parent transformed cells from which the more malignant variant developed available. An exception are the tumors induced in mice by UV light that kill the original host but cannot grow progressively in normal (i.e., non-UV-irradiated) mice (1) unless these mice are first depleted of T cells (1, 2) or the tumor cells undergo heritable changes (3). Comparing the parental tumor cells (regressor, RE) with the heritable variants (progressor, PRO) may allow identification of the critical changes in tumors that acquire progressive growth. It is surprising that we have found that for the majority of these variants, neither loss of antigen-presenting molecules nor loss of an antigen recognized by cytolytic CD8+ T cells seems to be the mechanism accounting for escape from destruction by the immune system of the normal host (3).

In addition to CD8+ CTL, it is known that immune effectors such as antibodies, cytokines, macrophages, NK cells, granulocytes, and γδ T cells can destroy cancer cells (for reviews, see Refs. 4 and 5), and conceivably escape of some variants may result from increased resistance to these effectors. In fact, one of the antigen-retention variants, 4102-PRO, grew faster than the parental tumor in nude mice (6), consistent with the notion that this variant had become resistant to effector cells other than αβ T cells. However, elimination of granulocytes inhibited the growth of this variant in vitro and in nude mice (6) and allowed rejection by the T-cell-competent host (7). Furthermore, the variant attracted inflammatory cells and was also stimulated in vitro by such cells, as well as by defined growth factors that can be released by such cells (6). This raised the possibility that the 4102-PRO variant escaped by acquiring sensitivity to paracrine growth stimulation by an inflammatory environment induced by the variant. It remained undetermined, however, whether this phenotype or resistance to immune effectors other than αβ T cells was the primary reason for escape, and whether this phenotype was expressed by other PRO cells. In the present paper, we demonstrate that (a) the variants do not show increased resistance to immune surveillance mediated by B cells, macrophages, NK cells or γδ T cells; (b) the selection for variants that show reduced growth after depletion of granulocytes is not unique to the 4102-PRO tumor but is also found for antigenic variants of other independently induced UV tumors; and (c) the changes found are characteristic of only those variants selected in vivo rather than in vitro.

MATERIALS AND METHODS

Mice and Tumors. Athymic nu/nu mice and beige nude mice were purchased from Frederick Cancer Research Facility (Frederick, MD). SCID mice were bred in the FMI facility at the University of Chicago (Chicago, IL). Breeder SCID mice were originally obtained from IMDYNE (San Diego, CA). 4102-regressor (RE), 6132A-RE, 6134A-RE, 6130-RE, and 6139B-RE tumors were induced by UV light, adapted to culture in CMEM, and maintained as described (2, 3). These tumors are called regressors because they are rejected by normal euthymic mice but grow regularly in nude mice (1, 2). 4102-progression (PRO), 6132A-PRO, 6134A-PRO, and 6139B-PRO (in vivo) were selected in vivo (i.e., they survived rejection from a pool of RE cells that were injected into euthymic mice). These tumors were then adapted to culture as described (2). 6130-PRO and 6139B-PRO (in vitro) were selected from their parental RE tumor cell lines in vitro using specific CTLs to select for antigen loss as described (3). All PRO variants grow in the majority of C3H mice, which are challenged with these tumor fragments.

Assay for Quantifying Viable Cells. To assess cell growth, 20 μl of MTT solution (5 mg/ml) were added to each well of a 96-well plate containing 100 μl of medium (after removal of 100 μl of the original medium) for 4–6 h, followed by 100 μl of 10% SDS plus 0.01 N HCl. Absorbance was read on an ELISA reader at 570 nm, subtracting the background at 650 nm.

Tumor Growth in Vivo. Tumor cells (5 × 10⁶) were injected s.c. into the flanks of 3–4 athymic nude mice. Tumor growth was measured every 3–4 days with a caliper. Size in cm³ was calculated as (ab²)/2 where a, b, and c are the longest, intermediate, and shortest dimensions of the tumor, respectively.

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2 To whom requests for reprints should be addressed, at Department of Pathology, University of Chicago, Chicago, IL 60637.
3 A tumor that is immunologically rejected when transplanted into normal mice after transient growth. By this measure, a regressor is nonmalignant in vivo by attracting leukocytes that stimulate tumor cell growth.
4 The abbreviations used are: CTL, cytolytic T lymphocytes; NK, natural killer; CMEM, MEM plus 10% FCS; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazo- lium bromide; poly I:C, polyinosinic-polycytidylic acid; PEC, peritoneal exudate cells; MLC, mixed lymphocyte culture.

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three orthogonal diameters. This formula is derived from the formula for the volume of an ellipsoid:

$$ V = \frac{4}{3} \pi abc $$

**Assay for Cytotoxicity.** Target cells ($5 \times 10^4$) were incubated with 100 µl $^{51}$Cr (sodium chromate at 1 mcg/ml) for 1 h at 37°C. Effector cells were serially diluted in a volume of 100 µl of CMEM in flat-bottomed (for macrophage assays) or V-bottomed (for CTL and NK assays) microtiter plates. Labeled tumor target cells were washed 4 times with CMEM and resuspended in CMEM at $5 \times 10^4$ cells/ml. One hundred µl of this suspension were added to each well of effectors. Cultures were incubated for 4.5 (for CTL and NK cells) or 16 (for macrophages) h at 37°C, 7.5% CO$_2$ in a humidified incubator. After incubation, 100 µl of supernatant from each well were collected and analyzed for radioactivity using a y-counter (Micromeda Systems, Inc., Horsham, PA). The percentage of specific lysis was calculated by the formula:

$$ \text{lysis} = \frac{(\text{experimental release} - \text{spontaneous release})}{(\text{maximum release} - \text{spontaneous release})} \times 100 $$

Spontaneous release was ≤15% of maximum. Maximum release was determined by detergent lysis of targets.

**Generation of Mixed Lymphocyte Tumor Cell Cultures.** C3H/HeN MTT$^+$ mice were immunized twice by i.p. injections of $1 \times 10^7$ tumor cells 7 days apart. Spleens were aseptically removed 14 days after the last injection and made into single cell suspensions using sterile tissue grinders. RBC were lysed with Tris-ammonium chloride (0.83%), and spleen cells were washed 2 times with CMEM. Tumor cells were treated with mitomycin C for 45 min at 37°C and washed 3 times. Cultures consisted of $8 \times 10^8$ spleen cells and $4 \times 10^5$ treated tumor cells in 3 ml of RPMI 1640 supplemented with 10% non-heat-inactivated FCS, 1% penicillin/streptomycin, 0.1% gentamicin, and 5 × $10^{-3}$ M ß-mercaptoethanol. Cultures were incubated for 6 days at 37°C in 16 × 125-mm round bottomed tissue culture tubes.

**Induction of NK Cells.** NK cells were induced by i.p. administration of poly I:C (as described in Ref. 8). Athymic nude mice were given injections of 100 µg of poly I:C diluted in saline. Spleens were aseptically removed 18 h later and processed as described above for mixed lymphocyte tumor cell cultures. Spleen cells were used directly as effectors in a 4.5-h cytolyis assay. YAC cells were used as a positive control for sensitivity to NK cells.

**Induction of Peritoneal Macrophages.** Macrophages were lavaged from the peritoneal cavities of C3H/HeN mice given injections 3–5 days earlier with 2 ml of Brewer's thioglycolate broth (aged until green as described in Ref. 9). Lavaged cells were recovered by injecting 5 ml of sterile PBS i.p. with a 5 ml syringe and 20-gauge needle, massaging the abdomen, and aspirating the fluid with the same syringe. Assays with macrophages were done in CMEM supplemented with 10% secondary MLC supernatant and 10µg/ml lipopolysaccharide. Nonadherent cells were removed and replaced with fresh assay medium before $^{51}$Cr-labeled target cells were added to the plates. Plates were incubated for 16 h. MRVNu cells (8, 9) were used as controls for resistance to macrophage lysis.

**Coculture of Tumor Cells with PEC.** Naive PEC were lavaged from nude mice as described above. The cells were sedimented at 1500 rpm in a clinical centrifuge and resuspended in 10 ml of CMEM. The inhibition assays included 20% secondary MLC supernatant to stimulate the inflammatory cells. Two-fold dilutions of PEC were done in triplicate in 96-well flat-bottomed plates. Tumor cells ($1 \times 10^7$) were added to each well. It was important that pipette tips were changed after each dilution to accomplish effective dilution of the observed effects. Plates were incubated at 37°C in 7.5% CO$_2$ for 4 days at which time an MTT assay was performed. Percent tumor growth was calculated as:

$$ \text{percent growth} = \frac{(\text{experimental absorbance} - \text{spontaneous absorbance})}{(\text{maximum absorbance} - \text{spontaneous absorbance})} \times 100 $$

The absorbance of tumor cells alone was the average of 8 wells.

**Transwell Assay.** To measure stimulation of tumor cells by a secreted factor, transwell plates were used (Costar 3413, Cambridge, MA). The top wells are equivalent in size to those in a 96-well plate and are covered on the bottom by a filter with a 0.4-µm pore size. Tumor cells ($1 \times 10^7$) were added to each top well in a volume of 100 µl CMEM. The top wells were suspended over a 24-well plate containing $5 \times 10^6$ PEC in 1 ml CMEM. PEC were induced by giving nude mice injections of $5 \times 10^6$ RE cells i.p. 3 days earlier. Similar results were also seen with PEC from naive mice. After 4 days of incubation, top wells were transferred to a new plate, and MTT was added as before. The index of stimulation was calculated as:

$$ \text{index of stimulation} = \frac{(\text{average absorbance of tumor cells cultured with PEC})}{(\text{average absorbance of tumor cells cultured in CMEM})} $$

Data represent the average of 3 wells ±SEM.

**Chemoattraction Assay.** Medium conditioned for 24 h by $1.5 \times 10^5$ tumor cells in 10 ml of CMEM was added to two bottom wells of modified Boyden chambers (Neuro Probe, Cabin John, MD). Thioglycollate-elicited PEC ($2 \times 10^5$) were added to the top chamber in a volume of 200 µl approximately 24 h after thioglycollate was injected i.p. At this time about 50% of the PEC are granulocytes. The PEC were suspended in either fresh CMEM (to test for directional movement) or in the same tumor cell-conditioned media as in the lower chamber (to distinguish from increased random movement). The top chambers with the PEC were separated from the lower chambers by a polycarbonate filter with a pore size of 5 µm (Neuro Probe). Chambers were incubated for 90 min. Unimmigrated cells were washed off the tops of filters by aspirating the 200 µl of medium containing the PEC, wiping filters with a Q-tip, adding distilled water with a squirt bottle, and repeating three times. Filters were stained by dipping them into a staining solution (Diff-Quick; Baxter, McGaw Park, IL). Cells that had migrated through the filter pores were counted using a magnification of X400, and the average of six fields from the duplicate filters ±SEM was plotted.

**Recovery of Cells from the Peritoneal Cavity.** PEC were harvested from nude mice that had received $5 \times 10^5$ tumor cells 3 days previously. For depletion of granulocytes, 200 µl of ascites fluid from nude mice bearing IgG2b rat antinouse granulocyte (anti-Gr-1) hybridoma RB6-8C5 [a gift of Dr. Robert Coffman (10)] were given i.p. 2 days before tumor challenge. PEC were removed as described for macrophage induction. The recovered cells were sedimented at 225 × g for 5 min, resuspended in 12 ml of CMEM, and put into 24-well culture dishes. The recovered tumor cells were allowed to grow for 10–12 days in culture, at which time an MTT assay was performed. Only tumor cells remained viable at this time.

**RESULTS**

**Progressor Variants Derived in Vivo, but not in Vitro, Have Increased Growth in Nude Mice Despite Similar Growth in Vitro.** We first compared the in vitro exponential growth rates of the 3 parental regressor tumors with the in vivo derived progressor variants. RE and PRO pairs of both 4102 and 6134A grew at the same exponential rate (Fig. 1A). Thus, for 4102 and 6134A, there does not appear to be an intrinsically faster growth rate for PRO tumors that could explain their improved survival in vivo. In repeated experiments, however, 6132A-PRO grew faster than the parental 6132A-RE (Fig. 1A).

We next compared the growth of the RE and PRO pairs in nude mice, which lack αβ T cells. As expected, 6132A-PRO grew significantly faster than 6132A-RE in vivo as well (Fig. 1B). However, both 4102-PRO and 6134A-PRO also grew faster than the parental tumors in nude mice (Fig. 1B), despite the similar growth rates in vitro. This confirms earlier data for 4102 (6) and indicates that, for at least these two tumors, the reason for the growth differences between RE and PRO pairs must lie in the tumor cell interactions with host components.

It was important to determine whether the faster growth in nude mice was a common characteristic among PRO variants in general, or if it was a particular property of variants selected by the hosts in vivo. To test this, we compared the growth rates of parental RE tumors 6130 and 6139B with their PRO variants that had been selected for antigen loss in vitro using cytolytic T cells. Both of these PRO variants grew at the same rate or slower than the parental tumors in nude mice (Fig. 2), even though they had similar growth rates in vitro. 6139B has...
Another PRO variant, which was selected in vivo. This variant has also lost a CTL-recognized antigen like the one selected in vitro. Even though such a loss might in itself suffice to allow this variant to grow progressively in normal mice, it also grew much faster than the parental 6139B-RE in nude mice (Fig. 2), indicating that faster growth in nude mice is a characteristic of PRO variants derived in vivo, regardless of whether an antigen was also lost. Confirmation of the antigenic phenotypes of these tumors is shown in Fig. 3. Tumor-specific CTLs elicited in response to immunization with the parental RE tumor cells recognize the PRO variants of 4102, 6132A, and 6134A but not an unrelated control. In contrast, anti-6130-RE- and anti-6139B-RE-specific CTLs do not recognize the PRO variants, indicating that they have lost their tumor-specific antigens, consistent with previous results (2).

Antigen-retaining PRO Variants Remain Sensitive to Non-T-Cell Host Defenses. Both 4102 and 6134A RE and PRO pairs consistently grew at the same exponential rate in vitro. It was possible, therefore, that these PRO variants could grow faster in vivo because they were no longer sensitive to inhibition by non-T effector cells, (e.g., NK cells, B cells, macrophages, and granulocytes), which might slow the growth of sensitive cells in nude mice; furthermore, sensitivity of the regressors to such cells may be critical for slowing regressor tumor growth in normal mice during the time when specific T-cell responses are being generated. To test this general possibility, tumor cells were injected into SCID mice (which lack B cells and T

Fig. 3. Demonstration of antigen loss or retention by progressor variants of UV-induced regressor tumors used in this study. Cytotoxic activity of cultured spleen cells from C3H mice shows antigen retention by 4102-PRO, 6132A-PRO, and 6134A-PRO, and antigen loss by 6130-PRO and 6139B-PRO (in vivo). C3H/HeN mice were immunized twice by injection of 1 × 10^7 RE tumor cells i.p. 7 days apart. Spleens were removed 14 days after the last tumor cell challenge. Spleen cells were prepared and cultured as described in "Materials and Methods." Six days later, a T^111Cr-release assay was performed using PRO, RE, and an unrelated tumor cell line as a control for specificity.
cells) and into beige nude mice (which have approximately a 100-fold decrease in NK lytic activity). If any of these cell types inhibited the growth of the parental tumors, then tumor growth rates should increase to be similar to that of PRO tumors. Instead, the differences in growth rates in both strains mimicked the rate of growth in nude mice (Fig. 4). In vitro, the RE and PRO variants were equally sensitive to lysis by poly I:C-induced NK cells and had a similar sensitivity to lysis by lipopolysaccharide-activated macrophages (Fig. 5). Similar results were observed in a 4-day cytostasis assay. Fig. 6A shows that both 4102-RE and 4102-PRO were equally sensitive to growth inhibition by PEC activated with a 20% secondary MLC supernatant in vitro, although again, 6132A-PRO was somewhat less sensitive to inhibition than the parental cells. 6134A-RE and 6134A-PRO were both equally inhibited by PEC that did not have to be activated in vitro (Fig. 6B). Taken together, these data suggest that loss of sensitivity to inhibition than the parental tumors. 6134A-RE and 6134A-PRO have similar growth characteristics as 4102-PRO (i.e., they grew more rapidly than the parental tumors in vivo, remained sensitive to non-T-cell host defenses, and attracted inflammatory cells in vitro), we wanted to determine whether the PRO cells could also be recovered in greater numbers than RE cells from the peritoneal cavities of nude mice after only 3 days of growth. Fig. 8 shows that the recovery of PRO tumor cells from peritoneal cavities was higher than that of RE tumor cells, although the difference was not as large for 6132A-RE and PRO. As seen previously for 4102 (6), treatment of nude mice with an anti-granulocyte antibody 2 days before tumor cell injection resulted in a dramatic decrease in the recovery of all PRO tumor cells and 6132A-RE tumor cells, as determined by measuring the outgrowth of tumor cells in vitro from the reisolated peritoneal exudate.

The PRO Variants Are Able to Attract and Be Stimulated by Factors Released by Tumor-Induced PEC of the Host. It remained possible that coculturing PEC with 20% secondary MLC supernatant might activate the PEC to be lytic, although such activation may not occur in vivo. We therefore repeated the 4-day cytostasis assay in the absence of this supernatant. Using this method, the 4102 and 6132A-PRO cells were no longer inhibited but actually grew better in the presence of PEC (Fig. 6B). The effect was more pronounced for 4102-PRO and was not observed for 6134A-PRO. In contrast, each of the parental RE tumor cells lines was still inhibited. To determine whether tumor-induced PEC produced soluble factors that stimulated tumor growth, PEC were incubated with tumor cells in transwell plates. Fig. 7A shows that each of the PRO tumors could be stimulated by PEC when separated by a porous membrane, even though 6134A-PRO is inhibited when in direct contact with these PEC. 6132A-RE and 6132A-PRO were equally stimulated, whereas both 4102-PRO and 6134-PRO seemed to be more sensitive to this stimulation than were their parental tumors.

If inflammatory cells affect tumor growth, attraction to the local tumor environment may be necessary. We performed chemotaxis assays using conditioned media from tumor cells to see whether RE and PRO tumor pairs could attract PEC differently in culture. Conditioned media from each of the PRO variants consistently attracted more PEC than those from their corresponding RE tumors (Fig. 7B). Thus, the PRO variants can attract inflammatory cells in vitro and can be stimulated by factors produced by these cells. This confirms earlier findings with the 4102 tumor (6) and suggests that this phenomenon of tumor stimulation by host leukocytes is not unique to this tumor but is commonly found with other PRO variants of UV-induced regressor tumors.

An Antigranulocyte Antibody Decreases the Recovery and Outgrowth of PRO Tumor Cells from the Peritoneal Cavity. We had previously found that treatment of nude mice with an anti-granulocyte antibody before tumor challenge could decrease the recovery of 4102-PRO cells from the peritoneal cavities of these mice (6). Because 6132A-PRO and 6134A-PRO have similar growth characteristics as 4102-PRO (i.e., they grow more rapidly than the parental tumors in vivo, remained sensitive to non-T-cell host defenses, and attracted inflammatory cells in vitro), we wanted to determine whether the PRO cells could also be recovered in greater numbers than RE cells from the peritoneal cavities of nude mice after only 3 days of growth. Fig. 8 shows that the recovery of PRO tumor cells from peritoneal cavities was higher than that of RE tumor cells, although the difference was not as large for 6132A-RE and PRO. As seen previously for 4102 (6), treatment of nude mice with an anti-granulocyte antibody 2 days before tumor cell injection resulted in a dramatic decrease in the recovery of all PRO tumor cells and 6132A-RE tumor cells, as determined by measuring the outgrowth of tumor cells in vitro from the reisolated peritoneal exudate.
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Fig. 6. The growth of antigen-positive PRO and RE tumor cells in the presence of peritoneal exudate cells. A, both the RE and the PRO tumor cells are inhibited when exposed to PEC activated in vitro with secondary MLC supernatant. PEC were harvested from nude mice and plated in triplicate with 1 x 10^6 tumor cells/well at the indicated ratios in the presence of 20% secondary MLC supernatant. After 4 days, an MTT assay was performed. Percent growth is plotted as average absorbance of tumor cells + PEC divided by the average absorbance of tumor cells alone X 100. Variation between triplicate wells was <10%. B, effects of unelicited, non-activated PEC on the growth of antigen-positive PRO and RE tumor cells. PEC were harvested from nude mice and plated in triplicate with 1 x 10^6 tumor cells/well at the indicated ratios in the absence of secondary MLC supernatant so as not to activate the PEC. After 4 days, an MTT assay was performed as in A.

DISCUSSION

Our results suggest that certain tumors escape immune destruction by the normal host by selecting for sensitivity to stimulation by host cells rather than through gaining resistance to immune effectors. All of the three variants analyzed retained the CTL-recognized unique tumor antigens and grew more rapidly than the parental tumors in nude mice, thus making resistance to T cells an unlikely mechanism of escape. Selection for variants with these characteristics required growth in vivo, which may make our analysis more relevant to problems occurring in the host. We found no evidence that an increased resistance of the variants to immune surveillance mediated by NK cells, antibodies, macrophages, and extrathymic T cells accounted for the progressive phenotype, even though these immune effectors can restrain the growth of certain cancer cells in vivo (for review, see Refs. 4 and 5). Instead, we observed that the variants (and 6132A-RE) were stimulated in transwell chambers by factors released by inflammatory cells and that the variants attracted more of these cells than did the parental tumors. Elimination of granulocytes inhibited the recovery and growth of tumor cells from the peritoneal cavity. Thus, we propose that the variants selected in vivo can escape T-cell destruction by the normal host because they induce conditions in which they grow faster than they can be eliminated. Indeed, our recent finding that elimination of granulocytes allows the normal C3H host to reject 4102-PRO tumor cells (7) agrees with the notion that acquisition of sensitivity to stimulation by the host is the primary reason for the escape.

Granulocytosis in the peripheral blood and granulocyte infiltration into tumors occurs in a variety of human and experimental cancers...
suspension was plated at 0.5 ml/well in a 24-well plate. An MTT assay was done after injection i.p. into naive or antibody-treated mice. After 3 days, PEC were lavaged in both 6132A-PRO and the parental regressor. 6132A-RE grows slower in vitro and i/i vivo than the two other regressor tumors we studied. The 6132A-PRO tumor variant grows faster than regressor variant cells in T-cell-deficient mice and whether our progressor variants produce high levels of prostaglandin E2. In any case, our study provides evidence that three independently induced host-selected variant tumors are stimulated by host leukocytes and have not become resistant to cytolytic cells. Countering this stimulation by the host can inhibit tumor growth (6) and can lead to tumor rejection (7). However, exploitation of this concept for tumor therapy or prevention in a clinical setting will require identification of defined growth factors and cytokines involved in this paracrine stimulatory loop so that selective inhibitors can be applied that have fewer or less serious side effects than eliminating granulocytes.

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