Suppression of Experimental Lung Colonization of a Metastatic Variant of Murine Colon Adenocarcinoma 26 by a Monoclonal Antibody 8F11 Inhibiting Tumor Cell-induced Platelet Aggregation

Yoshikazu Sugimoto, Masahiko Watanabe, Tomoko Oh-hara, Shigeo Sato, Toshiyuki Iose, and Takashi Tsuruo

Abstract

We have previously established and characterized two monoclonal antibodies, 8F11 and 20A11, that recognize an M, 44,000 membrane glycoprotein of metastatic murine colon 26 cells. Both monoclonal antibodies inhibit platelet aggregation induced by the tumor cells in vitro. In this report, the inhibitory effect of 8F11 on lung colonization of i.v.-inoculated tumor cells was examined. The i.v. administration of 8F11 suppressed lung colonization of NL-17, a highly metastatic variant of colon 26. Inhibition of NL-17 lung colonization by 8F11 was dose dependent with a maximum of 80% inhibition at a dose of 800 µg (11, 12). We have focused our interest on the arrest of circulating tumor cells at distant organs and subsequent proliferation of metastatic tumor cells. Tumor cells interact with various host cells in the vascular compartment. Among them, platelets have been shown to play an important role in the successful formation of metastasis of some tumor types (4, 5). Tumor cells inoculated i.v. into experimental animals have been demonstrated to induce platelet aggregation in vivo and cause thrombocytopenia (6, 7). Calcium channel blockers have been reported to inhibit both platelet aggregation in vitro and lung colony formation of tumor cells in vivo (8–10). A synthetic oligopeptide, GRGDS, and antibodies against von Willebrand factor have also been shown to inhibit tumor cell-platelet interaction and tumor metastasis (11-12). These observations have been supported by the findings that platelets enhance the adhesion of tumor cells to subendothelial matrices (13–15). Many investigators have examined the direct relationship between the metastatic potential and platelet-aggregating activity of tumor cells. In some reports a direct relationship between tumor cell-induced platelet aggregation and metastatic potential has been shown (16–18), while in other studies this correlation was not observed (19, 20). The reasons for this discrepancy have not been fully elucidated. Nevertheless, platelet aggregation is thought to be an important determinant for the process of tumor metastasis in some tumor systems.

In previous studies, we established several high or low metastatic clones of murine colon adenocarcinoma 26 (21) and demonstrated that platelet-aggregating activity of tumor cells is a requirement for successful metastasis (17). Recently, we generated two monoclonal antibodies, 8F11 and 20A11, against NL-17, a high metastatic clone of colon 26 with high platelet-aggregating activity. These antibodies inhibit platelet aggregation induced by the tumor cells and recognize an M, 44,000 membrane sialoglycoprotein (22). In the present study we show the inhibitory effect of the monoclonal antibody 8F11 on lung colonization of NL-17 cells in vivo. This observation indicates that platelet aggregation mediated by the M, 44,000 protein is directly involved in the lung colonization of NL-17 cells.

Materials and Methods

Materials. Protein A-Sepharose 4B was obtained from Pharmacia (Uppsala, Sweden). ImmunoPure F(ab')2 preparation kit was a product of Pierce (Rockford, IL). Apyrase was purchased from Sigma Chemical Co. (St. Louis, MO). [methyl-3H]Thymidine (91 Ci/mmol) was from Amersham Japan, Ltd. (Tokyo, Japan). All other agents were of the highest purity available.

Animals and Tumor Cells. Female BALB/c and BALB/c x DBA/2 F1 (hereafter called CD2F1) mice were obtained from Charles River Japan, Inc., Tokyo, Japan, and female BALB/c-nu/nu athymic nude mice were from Nippon CLEA Inc. (Tokyo, Japan). Mice of 8–10 weeks of age were used throughout these experiments. NL-17, a high metastatic clone of murine colon adenocarcinoma 26, was maintained in RPMI 1640 medium supplemented with 5% fetal bovine serum.

Monoclonal Antibody. The monoclonal antibody 8F11 (IgG2a) was obtained from ascitic fluid of the hybridoma-bearing BALB/c-nu/nu mice. The antibody was purified by precipitation with 50% saturated ammonium sulfate and by protein A-Sepharose 4B column chromatography under a protocol of the supplier. The F(ab')2 fragment of 8F11 was prepared by using an ImmunoPure F(ab')2 preparation kit (Pierce) according to the protocol of the supplier. The F(ab')2 fragment was further subjected to protein A-Sepharose column chromatography to eliminate undigested antibody. Purity and protein concentration of the antibody and the F(ab')2 were confirmed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (23).
Assay of Experimental Metastasis. NL-17 cells were harvested by brief exposure to HBSS containing 0.05% trypsin and 0.02% EDTA. The cells were washed by light centrifugation (400 × g, 5 min) and resuspended in HBSS supplemented with 1% BALB/c serum. The cells were kept on ice for 10 min and then adjusted to 2.5 or 5 × 10^5 cells/ml (depending on experiments) (17, 21). Under these conditions, >95% of the cells excluded trypan blue dye. The mice were given i.v. injections of 0.2 ml of the tumor cell suspension via the lateral tail vein. 8F11 whole antibody or the F(ab')2 fragment of 8F11 was given i.v. at various doses before or after the tumor inoculation. Lung metastasis was examined on day 21 after the tumor inoculation (17, 21).

Assay of Tumor Cell Retention in the Lung. The effect of 8F11 on the retention of radiolabeled tumor cells in the lung was examined after tail vein injection of 8F11 antibody and labeled NL-17 cells as described previously (17, 24). NL-17 cells were incubated with [methyl-3H]thymidine (91 Ci/mmol) for 16 h at a concentration of 2.5 µCi/ml (17). The labeled tumor cells were harvested and 5 × 10^4 cells containing 7.47 × 10^4 dpm of radioactivity were injected i.v. as described above. At various times after injection, the mice were sacrificed and the lungs were excised. The lungs were solubilized in 2 ml of Protosol (New England Nuclear, Boston, MA) and decolorized by adding 500 µl of 30% H2O2. The radioactivity was determined in 10 ml of ACS II (New England Nuclear) in a Beckman LS7500 liquid scintillation system equipped with automatic quench compensation. The number of tumor cells retained in the lung was calculated based on the radioactivity of the lung and the specific radioactivity of the labeled NL-17 cells (17).

Platelet Aggregation. PRP was prepared as previously described (22). Briefly, fresh blood was drawn from CD2F1 mice and immediately mixed with heparin (final concentration, 25 units/ml). The heparinized PRP was centrifuged for 7 min at 400 × g. PPP is a yellowish supernatant and PRP forms a white band between PPP and Percol layer. The platelet count in PRP was adjusted to 1 × 10^11 cells/ml by adding PPP. Cultured NL-17 cells were harvested after brief treatment with 0.05% trypsin and 0.02% EDTA in HBSS containing 10 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (pH 7.3), centrifuged, counted, and adjusted to 1 × 10^6 cells/ml. PRP was added to the cell suspension to degrade ADP.

Platelet aggregation was measured turbidimetrically by an NKK HEMA TRACER I (Niko Bioscientific Co., Tokyo, Japan). NL-17 cells were incubated with 8F11 whole antibody or the F(ab')2 fragment of 8F11 at various concentrations on ice for 20 min. PRP (200 µl) was incubated in a cuvette at 37°C under constant stirring in the aggregometer. After 5 min, 10 µl of NL-17 cell suspension pretreated with 8F11 was added, and the change in light transmittance was monitored for 15 min.

RESULTS

Inhibition of Experimental Lung Colonization of NL-17 Cells by 8F11. The effect of 8F11 on the formation of pulmonary metastasis after i.v. inoculation of NL-17 cells was examined (Table 1). 8F11 antibody was given i.v. 15 min before the systemic inoculation of NL-17 cells. The inhibitory effect of 8F11 was dose dependent, and the strongest inhibition of the lung metastasis was observed at the highest dose tested, 800 µg/mouse (Table 1). More than 100 µg/mouse of 8F11 was required for the inhibition of NL-17 lung colonization.

The effect of 8F11 timing on subsequent inhibition of metastasis was examined (Table 2). 8F11 given i.v. 120–15 min before NL-17 inoculation and simultaneously with NL-17 inoculation efficiently inhibited the formation of lung metastasis (Table 2). Significant inhibition was still observed when 8F11 was given 15 min after the tumor inoculation. 8F11 given 120 min after the tumor inoculation induced only a marginal effect.

The abbreviations used are: HBSS, Hank's balanced salt solution without calcium and magnesium; PRP, platelet-rich plasma; PPP, platelet-poor plasma.

### Table 1 Dose-dependent inhibition of experimental lung metastasis of C26-NL-17 by a monoclonal antibody 8F11

<table>
<thead>
<tr>
<th>Dose of 8F11 (µg/mouse)</th>
<th>Mean ± SD</th>
<th>% of control</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>76 ± 27</td>
<td>100</td>
<td>48-123</td>
</tr>
<tr>
<td>25</td>
<td>81 ± 16</td>
<td>107</td>
<td>59-101</td>
</tr>
<tr>
<td>50</td>
<td>64 ± 23</td>
<td>84</td>
<td>46-102</td>
</tr>
<tr>
<td>100</td>
<td>20 ± 7*</td>
<td>26</td>
<td>13-30</td>
</tr>
<tr>
<td>400</td>
<td>13 ± 5*</td>
<td>17</td>
<td>7-20</td>
</tr>
<tr>
<td>800</td>
<td>7 ± 4*</td>
<td>9</td>
<td>0-20*</td>
</tr>
</tbody>
</table>

* Significant (P < 0.05) by t test as compared to the control group (dose 0).
* Two mice were tumor free on day 21.

### Table 2 Time-dependent inhibition of experimental lung metastasis of C26-NL-17 by a monoclonal antibody 8F11

<table>
<thead>
<tr>
<th>Time of 8F11 injection (min before or after tumor inoculation)</th>
<th>Mean ± SD</th>
<th>% of control</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>−120</td>
<td>5 ± 4*</td>
<td>7</td>
<td>0-11</td>
</tr>
<tr>
<td>−15</td>
<td>7 ± 9*</td>
<td>9</td>
<td>0-20</td>
</tr>
<tr>
<td>0</td>
<td>10 ± 10*</td>
<td>13</td>
<td>2-24</td>
</tr>
<tr>
<td>+15</td>
<td>16 ± 4*</td>
<td>21</td>
<td>12-21</td>
</tr>
<tr>
<td>+120</td>
<td>35 ± 8</td>
<td>46</td>
<td>34-72</td>
</tr>
<tr>
<td>Control</td>
<td>76 ± 27</td>
<td>100</td>
<td>48-123</td>
</tr>
</tbody>
</table>

* Significant (P < 0.05) by t test as compared to the control group.

### Table 3 Pulmonary retention of i.v. injected NL-17 cells with or without 8F11 injection

<table>
<thead>
<tr>
<th>[3H]Thymidine-labeled NL-17 cells retained in the lung (% of injected cells)</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>8F11</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td>83 ± 11*</td>
</tr>
<tr>
<td>2 h</td>
<td>59 ± 4</td>
</tr>
<tr>
<td>+</td>
<td>44 ± 6*</td>
</tr>
<tr>
<td>+</td>
<td>4 ± 1*</td>
</tr>
</tbody>
</table>

* Mean ± SD.
* Significant (P < 0.05) by t test as compared to the control groups.

Entrainment of Tumor Cells in the Lung. The effect of 8F11 administration on the entrapment of NL-17 cells in the lung was examined after i.v. inoculation of 5 × 10^4 radiolabeled NL-17 cells (Table 3). When the mice were treated with 8F11 (800 µg/mouse) 15 min before tumor inoculation, NL-17 cells were retained less in the lung as compared to the control group. The highest effect was observed 24 h following tumor cell injection. Tumor retention at this late stage of entrapment seems to be more important for the actual formation of metastasis. These results indicate that 8F11 can inhibit tumor metastasis by inhibiting the pulmonary arrest of tumor cells through the inhibition of tumor cell-platelet interaction.

Effect of 8F11 F(ab')2 on Platelet Aggregation and Metastasis. To discriminate the effect of 8F11 on platelet aggregation from the possible activation of host-immunocompetent cells, F(ab')2 fragments of 8F11 were prepared. The F(ab')2 fragment preparation used in this study contained no detectable amount of whole antibody on sodium dodecyl sulfate-polyacrylamide gel electrophoresis (data not shown). The effect of 8F11 and...
the F(\(ab\)')\(_2\) fragment on platelet aggregation induced by NL-17 cells was examined (Fig. 1). 8F11 whole antibody slightly prolonged the lag time of the platelet aggregation induced by NL-17 cells at 0.1 mg/ml and caused complete inhibition of aggregation at 1 mg/ml (Fig. 1A). This result was in accordance with our previous report (22). Similar inhibitory effects were observed with the F(\(ab\)')\(_2\) fragment of 8F11 (Fig. 1B). The F(\(ab\)')\(_2\) fragment showed a marginal effect on platelet aggregation at 0.1 mg/ml, caused a significant retardation at 0.3 mg/ml, and completely inhibited platelet aggregation induced by the tumor cells at 1 mg/ml.

The effect of the 8F11 F(\(ab\)')\(_2\) fragment on the formation of pulmonary metastasis after i.v. inoculation of NL-17 cells was examined. The F(\(ab\)')\(_2\) fragment of 8F11 (800 \(\mu\)g/mouse) given i.v. 15 min before the inoculation of tumor cells significantly inhibited lung colonization (Table 4). This observation indicates that a mechanism unrelated to the immune system of the host is involved in the inhibitory effect of 8F11 on lung colonization and strongly supports our hypothesis that 8F11 inhibits the interaction of tumor cells with platelets, causing the inhibition of lung colonization. However, the inhibitory effect of the F(\(ab\)')\(_2\) fragment of 8F11 on lung colonization was slightly weaker than that of 8F11 whole antibody, and immune defense mechanisms may be partly involved in the inhibition of lung colonization of NL-17 cells.

![Figure 1](image)

**Fig. 1.** Effect of 8F11 whole antibody (4) or the F(\(ab\)')\(_2\) fragment of 8F11 (8) on platelet aggregation induced by NL-17 cells. In A, NL-17 cells were incubated on ice for 20 min with 0.1–1 mg/ml of 8F11 whole antibody, and the platelet-aggregating activity was examined. a, control; b, 0.1 mg/ml; c, 0.3 mg/ml; d, 1 mg/ml. In B, NL-17 cells were incubated on ice for 20 min with 0.1–1 mg/ml of the F(\(ab\)')\(_2\) fragment of 8F11, and the platelet-aggregating activity was examined. a, control; b, 0.1 mg/ml; c, 0.3 mg/ml; d, 1 mg/ml.

**Table 4** Inhibition of experimental lung metastasis of C26-NL-17 by a F(\(ab\)')\(_2\) fragment of 8F11

Mice were given 800 \(\mu\)g of 8F11 whole antibody i.v. or the F(\(ab\)')\(_2\) fragment of 8F11, and 15 min later NL-17 cells (5 \(\times\) 10\(^6\) cells/mouse) were inoculated. Lung colonization was examined on day 21 after the tumor inoculation. Six mice were used for each group.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Injection</th>
<th>Mean ± SD</th>
<th>% of control</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>8F11</td>
<td>i.v.</td>
<td>85 ± 21</td>
<td>100</td>
<td>70–119</td>
</tr>
<tr>
<td>8F11</td>
<td>i.v.</td>
<td>30 ± 18*</td>
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<td>11–49</td>
</tr>
<tr>
<td>8F11</td>
<td>i.v.</td>
<td>42 ± 5*</td>
<td>49</td>
<td>32–50</td>
</tr>
</tbody>
</table>

* Significant at \( P < 0.05 \) by \( t \) test as compared to the control group.

Effect of the Removal of the Excess Antibody. In the experiments of inhibition of metastasis described above, we injected a large amount of 8F11 antibody (up to 800 \(\mu\)g/mouse) i.v. into BALB/c mice. In these experiments, excess antibody in the blood might possibly react with normal cells and affect the function of normal cells and/or the interaction between normal cells and circulating tumor cells and then cause the inhibition of experimental lung colonization of NL-17 cells. In order to rule out this possibility, we tested the lung-colonizing ability of NL-17 cells which were pretreated with 8F11 antibody and then washed with HBSS to remove excess antibody.

NL-17 cells (2.5 \(\times\) 10\(^6\) cells/ml in HBSS supplemented with 1% serum from BALB/c mice) were treated with 8F11 antibody (4 mg/ml) on ice for 20 min, centrifuged (400 \(\times\) \( g \), 5 min), and resuspended in HBSS supplemented with 1% BALB/c serum. For a control experiment, 8F11-treated NL-17 cells were centrifuged and resuspended in the same solution containing 8F11 antibody (4 mg/ml). In this experiment, homotypic aggregation of NL-17 cells did not occur.

Lung-colonizing activity of NL-17 cells was inhibited by 8F11 antibody when tumor cells were free from excess antibody (Table 5). This result clearly indicates that the interaction between normal cells and 8F11 antibody is not responsible for the inhibition of lung colonization.

**DISCUSSION**

In previous studies we have established several high or low metastatic clones from murine colon adenocarcinoma 26 (21) and demonstrated that platelet aggregation induced by the tumor cells was an indispensable event for the lung colonization (9, 17). Two monoclonal antibodies, 8F11 and 20A11, have been established, which showed stronger reactivity to a high metastatic clone, NL-17, with high platelet-aggregating ability than to a low metastatic clone, NL-14, with low platelet-aggregating ability. These monoclonal antibodies inhibited the platelet aggregation induced by the tumor cells. Both antibodies were shown to recognize an A/r 44,000 membrane protein. In previous studies we have established several high or low metastatic clones from murine colon adenocarcinoma 26 (21) and demonstrated that platelet aggregation induced by the tumor cells was an indispensable event for the lung colonization (9, 17). Two monoclonal antibodies, 8F11 and 20A11, have been established, which showed stronger reactivity to a high metastatic clone, NL-17, with high platelet-aggregating ability than to a low metastatic clone, NL-14, with low platelet-aggregating ability. These monoclonal antibodies inhibited the platelet aggregation induced by the tumor cells. Both antibodies were shown to recognize an A/r 44,000 membrane protein. In the present study, we have demonstrated that one of the antibodies, 8F11, inhibited experimental lung colonization of NL-17 cells.

In the clinical situation colon cancers most often metastasize to the liver via the portal circulation, with the exception of the tumors that arise from the distal portion of the rectum. The colonization of circulating tumor cells to specific organs is supposed to be determined partly by the preferential adhesiveness of tumor cells to target organs (25–27). In addition, organ-derived growth regulatory factors are also involved in the selective growth of tumor cells at the secondary organs (28–32). Metastatic variants of colon adenocarcinoma 26 used in this

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**Table 5** Effect of the removal of excess 8F11 antibody on the experimental lung metastasis of C26-NL-17

NL-17 cells (5 \(\times\) 10\(^6\) cells/0.2 ml) were treated with 8F11 antibody (4 mg/ml) on ice for 20 min, washed, and inoculated i.v. at 5 \(\times\) 10\(^6\) cells/mouse with or without 8F11 antibody (4 mg/ml, 800 \(\mu\)g/mouse). Lung colonization was examined on day 21 after the tumor inoculation. Six mice were used for each group.

<table>
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* Significant at \( P < 0.05 \) by \( t \) test as compared to the control group.
study metastasize mainly to the lung when tumor cells were inoculated i.v. or s.c. (21). Liver and ovary metastasis occurred at relatively low rates (21). Colon 26 tumor cells cannot metastasize via the portal circulation, because primary colon 26 tumor do not proliferate in colon. In this study, we examined the role of platelet-aggregating activity in the metastasis formation in vivo. For this purpose, we injected lung-metastasizing colon 26 cells via the lateral tail vein, although this system might not reflect natural pathogenesis of metastasis of colon tumor.

Three mechanisms have been proposed to describe platelet aggregation induced by tumor cells. The first mechanism for platelet aggregation is mediated by thrombin generation (33-36) and can be inhibited by thrombin antagonists (37, 38). In a previous report, we showed that the thrombin inhibitors, hirudin and MD805, marginally affect platelet aggregation induced by NL-17 cells (22). The second mechanism for platelet aggregation is mediated by ADP released from tumor cells (16, 38, 39). In the present study, we used apyrase to avoid the involvement of ADP on tumor cell-induced platelet aggregation in vitro. The third mechanism requires the direct interaction between tumor cells and platelets (16, 22, 40, 41). 8F11 is thought to inhibit this mechanism of platelet aggregation by interfering with the interaction between the M, 44,000 protein of NL-17 cells and platelets.

The M, 44,000 protein reactive with 8F11 antibody possesses a similar molecular weight as tissue thromboplastin (42-47). Tissue thromboplastin is a ubiquitous cell surface glycoprotein. Tissue thromboplastin accelerates the coagulation of plasma via the extrinsic route and aggregates platelets through the generation of thrombin (42, 43, 45-47). Crude membrane preparations from NL-17 cells possess the ability to shorten the coagulation time of citrated plasma. This fact suggests that NL-17 cells might also possess tissue factor activity. However, 8F11 antibody (2 mg/ml) does not inhibit the procoagulant activity of membrane fractions from NL-17 cells or from normal mouse lung, indicating that 8F11 does not inhibit the generation of thrombin. Therefore, the inhibitory effect of 8F11 on NL-17 cell-induced platelet aggregation is supposed to be independent of thrombin generation. Moreover, thrombin inhibitors hirudin (up to 300 units/ml) or MD805 (up to 20 μM) show only marginal inhibitory effects on the platelet aggregation induced by NL-17 cells. Because we have not yet determined the primary structure of the M, 44,000 protein, we cannot deny the possibility that the M, 44,000 protein is identical to tissue thromboplastin. At this moment, however, it is unlikely because the 8F11 antibody inhibits NL-17 cell-induced platelet aggregation without inhibiting thrombin generation.

The antimaltastatic effect of 8F11 whole antibody seems to be mediated not only by the inhibition of platelet-tumor cell interaction but also by the activation of the immune system of the host. 8F11 is an IgG2a antibody, and this isotype has been shown to possess strong activity to promote tumor cell killing (48, 49). Many investigators have reported on the antimaltastatic activity of monoclonal antibodies through activation of immunocompetent cells (50-52). We have shown that the F(ab')2 fragment of 8F11 could inhibit tumor cell-induced platelet aggregation in vitro and experimental lung metastasis in vivo. This result clearly indicates that activation of the immune system of the host is not required for the antimaltastatic activity of 8F11. However, we cannot exclude the possible participation of immunocompetent cells on the 8F11 inhibitory effect on experimental lung colonization of NL-17 cells. Another possible mechanism for 8F11 antimaltastatic activity is direct growth inhibition of tumor cells. However, we observed that 8F11 did not have a significant effect on the growth of NL-17 cells either in culture conditions or as an s.c. tumor.

First we examined the antimaltastatic effect of 8F11 antibody in the presence of excess antibody. In such conditions, interaction between 8F11 antibody and normal cells may affect the lung colonization of NL-17 cells. Indeed, 8F11 antibody reacts with the M, 40,000 protein of the membrane fraction of normal mouse lung. However, the antimaltastatic effect of 8F11 was not diminished when excess antibody was washed out. This result suggests that direct binding of 8F11 with NL-17 cell surface is indispensable for the inhibition of lung colonization of NL-17 cells.

Platelets have been reported to enhance the adhesion of tumor cells to subendothelial matrices (13-15). Interaction of tumor cells with platelets was shown to enhance the entrapment of tumor cells to secondary organs (5, 6). Additionally, platelets are known to secrete platelet-derived growth factors which are known to promote the growth of high metastatic clones of colon 26 (53). Tumor cell growth at the final stage of metastasis is an important event, and many growth factors and putative receptors affect the metastatic ability of colon 26 cells (17, 32, 54, 55). The role of tumor cell interactions with platelets on subsequent tumor cell growth is an interesting subject for further analysis.

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REFERENCES


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INHIBITION OF PLATELET AGGREGATION AND METASTASIS


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