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ENHANCEMENT OF TUMOR GROWTH AFTER PARTIAL HEPATECTOMY AND BLOOD TRANSFUSION

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Female adult BUF rats (6–8 weeks) received Sham operation (Sham); 70% hepatectomy (PH); Sham or PH with blood transfusion (BT or PH+BT). BUF 7316A hepatoma cells were inoculated subcutaneously in the neck of rats on the operation day. Tumor size was measured from day 7 to 20 after inoculation. Sera and splenic adherent cell harvested on day 5 from Sham and PH rat were added into Mixed Lymphocyte Cultures (MLR). The result showed that tumor growth in PH or BT rats was significantly promoted as compared to that in Sham rats ($P<0.01$, $P<0.05$). The most marked enhancement of tumor growth was observed in PH+BT rats ($P<0.001$). Sera and splenic adherent cell from PH rat significantly inhibited MLR ($P<0.05$). Those results suggest that partial hepatectomy and blood transfusion are responsible for the enhancement of tumor growth. Some immunosuppressive factor might be produced in the process of liver regeneration, and blood transfusion might have an additive immunosuppressive effect.

Key words: Hepatectomy, Blood transfusion, Tumor cell, Immunosuppression.

Recently there are many reports from surgeons that a rapid growth of residual tumor sometimes occurs shortly after liver resection,[1] but the factors which enhanced the tumor growth are not as yet clear. It is known the liver plays a important role in the immune system and the immunological disturbance may occur in the process of liver regeneration after liver damage or hepatectomy.[2] Many reports have showed that blood transfusion can suppress the recipients immune response and increase the recurrence of malignancies after operation.[3] Experiments were performed to examine the enhancement effect and mechanisms of tumor growth after partial hepatectomy and blood transfusion.

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MATERIALS AND METHODS

Tumor Cell Line

Syngeneic to BUF rats 7316A hepatoma cell line was utilized in this studies (From Japan Osaka University Medical School). Tumor cells were grown in the RPMI-1640 complete culture medium with 10% FCS for 3–4 days at 37 ℃ in 5% CO_2.

Animals

Falmal Baffalo (BUF; $RT1^b$) rats (6–8 weeks) were used as tumor recipients and all serum and cell isolation procedures. Male adult Wistar Shionogi (WS; $RT1^k$) rats were used as blood donors. Each experimental rat received 2 ml blood of WS rat with preservative-free heparin (1 U/ml) by vena cava injection at the procedure of operation.

Experimental groups

BUF 7316A hepatoma cells 1×10^7/ml in heterogenous growth were harvested and suspended in Hanks' Balanced salt solution. Each rat was inoculated subcutaneously 1 ml in the neck. Tumor volume were obtained by measurement of length and width during the period from day 7 to 20 after the inoculation. At the time of inoculation, four operation groups were performed (n=6). 1. Sham operation (Sham); 2. 70% hepatectomy (PH) as described by Higgins and Anderson;[4] 3. Sham with blood transfusion (BT); 4. PH with blood transfusion (PH+BT).

Collection of Serum and Spleen Adherent Cells

Blood and spleen were obtained from Sham and PH rats after 5 days operation. Pooled blood was stand at room temperature and clot at 4 ℃ for eight h. respectively. Serum was isolated by centrifuged for 10 min. at 2000 r/min. Splenic lymphocyte separated by regular method was suspended in the RPMI-1640 complete culture medium and incubated for one h. at 37 ℃ 5% CO_2 in a plastic flask. Noadherent cells were removed by 3 time washing and adherent cells were collected through cell craper.

Mixed Lymphocyte Cultures (MLR)

Sera and adherent cells from Sham and PH rat were diluted with different concentrations and added into each culture well of MLR. Naive BUF rat spleen T-cell (2×10^5/well) was cultured with irradiated (20 Gy) WS rat spleen cells (4×10^5) in 96 well plates at 37 ℃ 5% CO_2 for 5 days. During the last eight h. of incubation, each well was pulsed with 1 μ Ci of ^3H thymidine. The uptake of ^3H thymidine was counted by liquid scintillation techniques. Statistical analyses of all data were done using student's *t* test.

RESULTS

Effect of Partial Hepatectomy and/or Blood Transfusion on Tumor Growth

The different tumor size was seen in each groups from 7 days after inoculation (Figure 1). The increase of tumor size in both PH rats and BT rats was significantly greater compared with Sham rats ($P>0.01$, $P>0.05$). The largest tumor size was observed in rats with PH+BT group ($P>0.001$).

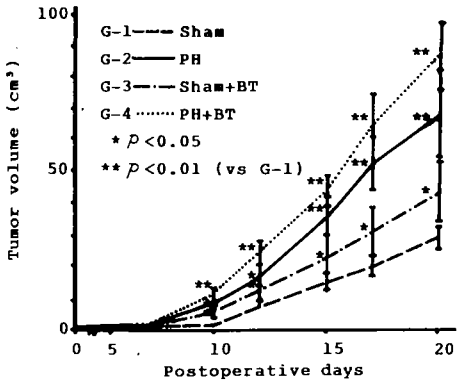

Fig. 1. Curved line of tumor growth.

Effect of Sera and Splenic Adherent Cells on MLR

Sera from PH rats after 5 days operation had inhibitory effect on MLR (Figure 2). In the concentration of over 0.8%, the inhibitory effect was significant compared with Sham rats ($P>0.05$). As show in Figure 3, the splenic adherent cells from PH rats had similar inhibitory effect on MLR ($P>0.05$).

DISCUSSION

The result in this study that the growth of transplanted 7316A hepatoma cells in rats were enhanced after PH and BT demonstrated that partial hepatectomy and blood transfusion might be responsible for the rapid recurrence of residual liver tumor after liver resection in clinic.

Since Opelz were the first to report that blood transfusion have an beneficial effect on renal allograft survival,[5] many subsequent studies proved that blood transfusion have an immunosuppressive effect. A decreased immune response after blood transfusion were reported in both specific and nonspecific immunoregulatory mechanism which include decreased natural killer cells, increased T-suppressor and

monocytic suppressor cells activity,[6] and antiidiotypic antibodies directed against T-cell antigen-specific receptors.[7] Recently research showed the leukocytes bearing class II MHC antigens in the transfused allogenic blood may be important in modifying host immune defeuse.[8] The immunomodulation induced by blood transfusion might produce a more favorable host environment for the proliferation of tumor cells.

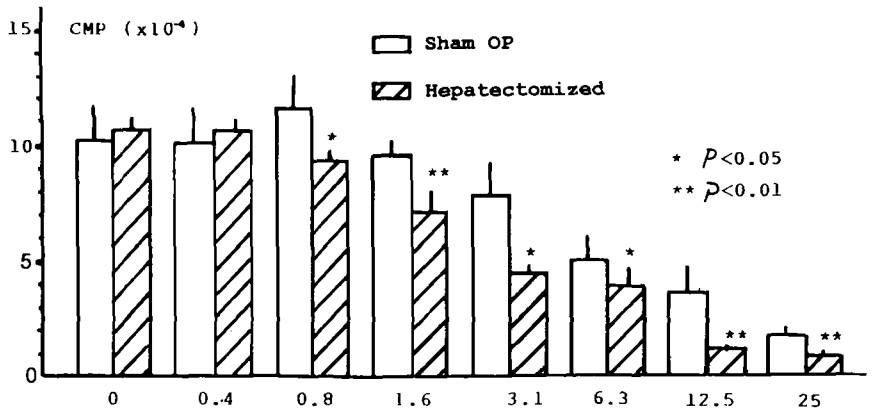

Fig. 2. Inhibitory effect of serum on MLR.

Fig. 3. Inhibitory effect of adherent cell on MLR.

The mechanisms of tumor growth enhanced after partial hepatectomy remain speculative. Lagualia believed the immunological disturbances may occur in the process of liver regeneration after liver damage or hepatectomy. Considerable evidence is that allograft rejection is reduced in the recipients who had hepatic

disturbance after transplantation.[2] Pinto et al. have reported that the immune response are decreased after partial hepatectomy in animal.[9] Our result that sera and splent adherent cells from hepatectomized rats have significant inhibitory effect on MLR demonstrated the immunosuppressive mechanism may occur in the process of lover regeneration. This immunomodulating effect may be caused not by external materials like blood transfusion but by some inhibitory factor produced in the process of liver regeneration. The inhibitory factor might come from splenic adherent fraction such as macrophage and existed in sera modify immune response by inhibited the proliferation of lymphocyte. It might be responsible for enhancement of tumor growth after liver resection.

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