Role of Mononuclear Cells and Inflammatory Cytokines in Pancreatic Cancer-Related Cachexia

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Abstract

Background and Purpose: The mechanism behind aggressive development of cachexia in patients suffering from pancreatic cancer is not well understood. In this study, we investigated which factors are associated with the cachectic status of the patients and evaluated cachexia-promoting capacity of cancer and inflammatory cells.

Experimental Design: DNA microarray analysis and quantitative reverse transcription-PCR were used to screen for cachexia-associated factors in pancreatic specimens obtained from non-cachectic and cachetic patients diagnosed with pancreatic ductal adenocarcinoma. The expression pattern of the most prominently altered cachexia-associated factor, interleukin-6 (IL-6), was further analyzed in patients sera by ELISA, in pancreatic specimens by immunohistochemistry, and in a coculture system by quantitative reverse transcription-PCR using pancreatic cancer cell lines T3M4 (IL-6 positive) and Panc-1 (IL-6 negative) and peripheral blood mononuclear cells (PBMC) obtained from donors and noncachetic and cachetic patients.

Results: Among numerous analyzed factors, IL-6 was significantly overexpressed in pancreatic specimens and elevated in serum of cachectic patients. The coculture system revealed that pancreatic cancer T3M4 cells but not Panc-1 cells were able to stimulate IL-6 exclusively in cachectic PBMC (by 14-fold) and this triggering was reduced by half in the presence of IL-6-neutralizing antibodies.

Conclusion: IL-6 represents a prominent cachexia-associated factor in pancreatic cancer. IL-6 overexpression in cachetic patients is related to the ability of certain tumors to sensitize PBMC and induce cytokine expression in cachetic PBMC.

Pancreatic cancer is presently the fifth leading cause of cancer-related death in Western industrialized countries, with a 5-year survival rate far under 5% (1, 2). The reason this disease is so aggressive and devastating remains unclear but the cause is probably multifactorial. Our understanding of the aggressive growth behavior of pancreatic cancer has increased in past years. A variety of molecular alterations contributing to pancreatic cancer have been identified. These include growth-promoting factors, activation of invasion-promoting factors, early metastasis formation, and factors contributing to chemo-therapy and/or radiotherapy resistance (3–6). Chemotherapy has only a limited effect on the progression of the disease and cannot cure pancreatic cancer patients (5).

Despite our increasing knowledge about the molecular background of pancreatic cancer, the causes of cachexia, which affects almost all pancreatic cancer patients at an early or later tumor stage, remain unknown (7, 8). Cachexia is mainly characterized by anorexia and the loss of adipose tissue and skeletal muscle mass. The word “cachexia” is derived from the Greek words “kakos,” meaning “bad,” and “hexis,” meaning “condition” (9). About half of all cancer patients show a cachexia syndrome, with the frequency higher in patients with solid tumors (10). Pancreatic and gastric cancer patients have the highest frequency of developing cancer-associated cachexia (11). The reasons why pancreatic cancer patients develop cachexia are still not fully understood.

Several concepts have been proposed to explain why pancreatic cancer patients develop cachexia, but these are controversial and not conclusive. One theory is that dysregulation in the neuropeptide pathway of leptin, neurotensin, which is involved in body weight regulation, is a major mechanism. The orexigenic and anorexigenic neuropeptides in the leptin pathway decrease or increase sympathetic nerve activity, respectively, which regulates energy expenditure by activating thermogenesis in brown adipose tissue and possibly in other sites, such as white adipose tissue and muscle, through induction of the mitochondrial uncoupling protein UCP-1 and the newly identified UCP-2 and UCP-3 proteins (12–14). Because the leptin pathway is closely connected to the homeostasis of fat and muscle tissue, dysregulation by...
stimulatory or inhibitory cytokines could consequently lead to cachexia (15).

Another theory is that dysregulation of a lipid- and protein-mobilizing factor plays a crucial role in cancer cachexia (15, 16). Catabolic tumor products such as the so-called lipid-mobilizing factor, which is most probably produced by the tumor and the proteolysis-inducing factor, directly stimulate tissue breakdown and contribute to the development of cancer cachexia. Additionally, the induction of lipolysis by lipid-mobilizing factor is associated with an increase in the intracellular level of cyclic AMP, possibly formed in response to activation of adenylate cyclase, which induces a breakdown of adipose tissue into fatty acids (17). In addition, the proteolysis-inducing factor induces protein degradation (amino acids) in skeletal muscle (18).

Despite their differences, both these concepts of the development of cachexia propose that the ongoing stimulus to fat and protein degradation is due to dysregulation of cytokines, especially tumor necrosis factor-α (TNF-α), INF-γ, intereleukin-1 (IL-1), and IL-6 (15, 18, 19). TNF-α and in part IL-6 activate proteolysis, insulin resistance, apoptosis, and the nuclear factor-κB pathway and contribute via these catabolic processes to cachexia (19, 20). Therefore, the term “cytokine driven” is often used in connection with cachexia. In pancreatic cancer cell lines, high expression of IL-6 and IL-8 could be shown, possibly explaining the particularly high rate of cachexia in patients with pancreatic cancer (21).

However, a central but still unanswered question is whether the tumor or the reaction of the host to the tumor is the source of or the reason for the induction of cachexia in cancer patients. Additionally, it is still not clear whether the tumor or the host is the production site of the above-mentioned cytokines (22). Therefore, in this study, we aimed to identify cachexia-promoting factors in pancreatic cancer by applying DNA microarray analysis. Identified factors were further studied and quantified to identify the pathophysiologic mechanisms responsible for inducing cachexia in pancreatic cancer patients.

**Patients and Methods**

Cachexia in pancreatic cancer patients was defined as loss of >10% body weight within the 6 months before operation. Furthermore, the postoperative Union Internationale Contre le Cancer classification sixth edition, there were two stage II, five stage III, and one stage IV pancreatic adenocarcinomas.

Of these eight pancreatic cancer patients, four patients had cachexia, with a weight loss between 13% and 27% of their initial body weight, and four patients experienced no significant weight loss (weight loss between 0% and 5% of their initial body weight).

Additionally, tissue samples were obtained from six male and two female chronic pancreatitis patients (median age 46 years; range 38-51 years). All individuals had histologically confirmed alcohol-induced chronic pancreatitis.

For use as normal controls, pancreatic tissue samples were obtained through an organ donor program from eight previously healthy individuals (five male donors, three female donors; median age, 50 years; range, 37-69 years) who were free of any pancreatic disease.

**DNA microarray analysis.** The HuGeneFL DNA array from Affymetrix, Inc. (Santa Clara, CA) was used. It contained about 7,000 gene sequences representing 5,600 full-length human genes. The sequences were selected from three database exemplars from Unigene supplemented with additional genes from the Genbank and the Institute for Genomic Research (Rockville, MD).

Total RNA was extracted by the guanidine isothiocyanate method from snap-frozen human tissues. Polyadenylate RNA was isolated using Oligo(dT)-cellulose kits from Amersham Pharmacia Biotech (Piscataway, NJ). Polyadenylate RNA (2.5 μg) was converted into double-stranded cDNA by reverse transcription (Life Technologies, Grand Island, NY) using the T7-T24 primer [5'-GCCACGTAATGTTAATAC-GACTCATAATGGACGGCGG (df24)]. The double-strand cDNA product was cleaned up by a phenol/chloroform/isooamyI extraction using phase lock gels (Eppendorf, Westbury, NY). Double-stranded cDNA was converted into cRNA using the in vitro transcription MEGAscript T7 kit from Ambion (Austin, TX) and biotinylated nucleotides as described (23). The in vitro transcription product was purified using RNasey mini columns from Qiagen (Valencia, CA) and fragmented as described (23). Hybridization of fragmented in vitro transcription products to oligonucleotide arrays was done as suggested by the manufacturer (Affymetrix). All 24 pancreatic tissue samples (eight normal, eight chronic pancreatitis, eight pancreatic cancer) were subjected to RNA extraction and transcript profiling.

**Pancreatic tissues for quantitative reverse transcription-PCR analysis.** Normal pancreatic tissue samples were collected from 21 individuals (median age, 49 years; range, 41.5-60.0 years) through an organ donor program where no recipient was available for the pancreas. Additionally, 34 chronic pancreatitis patients (median age, 58 years; range, 49.5-63.5 years) served as a second control group. Pancreatic cancer tissues were obtained from 33 patients. Fourteen of these (median age, 66 years; range, 58.8-72.5 years) had no cachexia before the operation and 19 (median age, 72 years; range, 68-78.5 years) had cachexia. Regarding the postoperative Union Internationale Contre Cancer classification, there were five stage I, seven stage II, one stage III, and one stage IV patients without cachexia and two stage I, 14 stage II, and three stage III patients with cachexia.

**Interleukin-6 immunohistochemistry and ELISA.** For interleukin-6 immunohistochemistry, 4-μm-thick tissue sections of paraffin-embedded pancreatic cancer tissue were used. For immunohistochemistry of IL-6, the mouse anti-human IL-6 antibody from R&D Systems GmbH (Wiesbaden, Germany) was used. To block unspecific activity, slides were treated with preimmune goat serum. For negative control, consecutive sections were exposed to mouse IgG1. DAKO antimouse polymer-HRP0 and DAKO Envision+ detection system (DAKO Diagnostics AG, Zürich, Switzerland) were applied for signal visualization. Evaluation of these sections (patients without cachexia, n = 9; patients with cachexia, n = 11) was done by two independent pathologists blinded to the purpose of the study.

For quantitative determination of human IL-6 in serum of patients without (n = 27) and with (n = 14) cachexia, the commercially
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available IL-6 enzyme immunoassay from Immuno-Biological Laboratories (Hamburg, Germany) was used.

**Identification of relevant genes.** Primary analysis of microarray data was done using the Affymetrix GeneChip software. All genes on the DNA microarray were then checked for a significant increase or decrease in the mRNA expression in patients with and without cachexia. Additionally, genes which were differentially expressed in patients with and without cachexia were compared with those in patients with chronic pancreatitis and normal controls. An increase/decrease in the differential expression was defined as a change of at least 3-fold versus respective controls. Second, all differentially expressed genes were checked for any known or reported association with cachexia.

Quantitative reverse transcription-PCR (RT-PCR) was used to confirm the expression of the selected genes.

**Reagents and materials for coculture experiments.** RPMI 1640, PBS solution, trypsin-EDTA, and penicillin-streptomycin solution were purchased from Invitrogen Life Technologies Cell Culture (Karlsruhe, Germany). Fetal bovine serum was purchased from PAN Biotech GmbH (Aidenbach, Germany). Culture plates and cell culture inserts with 1-μm pore-sized position emission tomography membranes were purchased from BD Biosciences (Heidelberg, Germany). A neutralizing human IL-6 antibody was obtained from R&D Systems. The MagNA Pure LC RNA Isolation Kit I and the First-Strand cDNA Synthesis Kit for cells (Roche Applied Science) or tissues (Aidenbach, Germany) was used. A standard curve from different representative plasmids was used to calculate the number of copies of the amplified product. Finally, the number of specific amplicons was further normalized to the average expression of two housekeeping genes (Cyclophilin B and HPRT) per microliter of input cDNA.

**Statistical analysis.** Primary analysis of the DNA microarray data was done using the Affymetrix GeneChip software. Data were calculated as mean ± SE unless indicated otherwise. For statistical analysis, the Mann-Whitney test and Pearson’s correlation test were used. The statistical package SPSS for Windows from SPSS, Inc. (Chicago, IL) was used for all statistical analyses. P < 0.05 was considered statistically significant.

**Results**

DNA microarray analysis including 5,600 human genes identified four genes which showed significant differences between cancer samples, normal controls, and chronic pancreatitis and between samples of pancreatic cancer patients with or without cachexia. In detail, islet amyloid polypeptide was significantly decreased, whereas neuropeptide Y Y3 receptor, neurotensin, and IL-6 were significantly increased in tumors of pancreatic cancer patients with cachexia compared with tumors of pancreatic cancer patients without cachexia. Further analysis of the DNA microarray data additionally identified 12 genes that have been described previously to be altered in tumor cachexia. However, none of these genes were altered in the pancreatic cancer samples compared with normal controls or chronic pancreatitis nor was any difference seen between pancreatic cancer patients with or without cachexia.

**Further analysis of cachexia genes by quantitative reverse transcription-PCR analysis.** To verify the results of the DNA microarray analysis, quantitative RT-PCR analysis was done in tumor samples of noncachectic (n = 14) and cachectic (n = 19) pancreatic cancer patients and in tissues of patients with chronic pancreatitis (n = 34) and normal controls (n = 21). In contrast to the DNA microarray, the quantitative RT-PCR analysis revealed that in a larger sample size, islet amyloid polypeptide, neuropeptide Y Y3 receptor, and neurotensin did not show any significant differences between patients with or without cachexia. However, IL-6 mRNA expression was significantly increased (P < 0.01) in tumor samples of cachectic in comparison with noncachectic pancreatic cancer patients. Furthermore, IL-6 was significantly elevated in patients with cachexia compared with patients with chronic pancreatitis and normal controls. The mean number of copies was 908.9 ± 344.9 (mean ± SE) in the noncachectic group, 5,646.0 ± 1,839.0 in the cachexia group, 781.0 ± 209.1 in patients with chronic pancreatitis, and 287.6 ± 76.6 in normal controls (Fig. 1).

**Interleukin-6 immunohistochemistry in pancreatic tissues.** To localize IL-6 in tissues, immunohistochemical staining was done in pancreatic cancer sections of patients with and without...
Fig. 1. Quantitative real-time PCR mRNA expression of islet amyloid polypeptide (IAPP), neurotensin, neuropeptide Y Y₃ receptor (NPY Y₃), and IL-6 in normal pancreas tissue, chronic pancreatitis tissue, and pancreatic cancer tissue of patients without and with cachexia. P values for patients without and with cachexia are expressed.

Cachexia. Tissue areas surrounding the tumor exhibited no IL-6 immunoreactivity. In contrast, IL-6 immunoreactivity was strongly present in the cytoplasm of pancreatic cancer cells, whereas IL-6 immunoreactivity for noncancerous tissue structures was completely negative. Inflammatory cell infiltrates revealed only weak IL-6 immunostaining (Fig. 2A and B). Comparison of tissue sections of pancreatic cancer patients with and without cachexia revealed a much stronger IL-6 immunohistochemical signal in cancer cells of patients with cachexia (Fig. 2D and C).

**Interleukin-6 serum levels.** IL-6 serum levels were measured in patients with (n = 27) and without (n = 14) cachexia. There was a significant difference (P < 0.04) between the two groups. The IL-6 serum levels were significantly higher in pancreatic cancer patients with cachexia (median, 8.06 pg/mL; 25th/75th percentile, 2.32/11.77 pg/mL) compared with the noncachectic group (median, 3.7 pg/mL; 25th/75th percentile, 2.80/6.92 pg/mL).

**Coculture of peripheral blood mononuclear cells with pancreatic cancer cell lines.** IL-6 mRNA expression was measured following isolation of PBMCs from pancreatic cancer patients with and without cachexia and normal controls. IL-6 mRNA levels in PBMCs of normal controls and pancreatic cancer patients without cachexia were comparable. In contrast, PBMCs of pancreatic cancer patients with cachexia exhibited a marked reduction in IL-6 mRNA levels compared with normal controls (Fig. 3A).

To further evaluate potential interactions between pancreatic cancer cells and immune cells, coculture experiments were carried out next using Panc-1 and T3M4 pancreatic cancer cell lines. IL-6 mRNA expression analysis by quantitative RT-PCR revealed no IL-6 mRNA expression in Panc-1 cells (0.09 ± 0.05 mRNA copies/μL), whereas T3M4 cells showed moderate IL-6 mRNA expression levels (14.04 ± 2.63 mRNA copies/μL).

Coculture of PBMCs of pancreatic cancer patients with and without cachexia and of normal controls with Panc-1 cells resulted in a slight but not significant increase in IL-6 mRNA levels in all PBMC subsets. PBMCs of controls exhibited 313.3 ± 37.1 mRNA copies/μL, PBMCs of patients without cachexia exhibited 86.2 ± 59.1 mRNA copies/μL, and PBMCs of patients with cachexia exhibited 75.3 ± 56.8 copies/μL of IL-6 mRNA after a 24-hour coincubation with Panc-1 cells (Fig. 3B).

Coculture of T3M4 with PBMCs of pancreatic cancer patients with cachexia resulted in a significant 14-fold up-regulation (P < 0.002) of IL-6 mRNA expression in PBMCs. In contrast, coculture of T3M4 with PBMCs of pancreatic cancer patients without cachexia or with normal controls did not result in a change of IL-6 mRNA expression in the respective PBMCs. The number of IL-6 mRNA copies was 20.0 ± 5.4 in PBMCs of normal controls, 18.0 ± 9.4 in patients without cachexia, and 259.6 ± 113.9 in patients with cachexia (Fig. 3C). To gain further insights into the IL-6-dependent mechanism of cachexia development in pancreatic patients, we investigated a link between deregulated IL-6 expression and acute-phase response. Cyclic AMP receptor protein levels were higher in cachectic versus noncachectic patients (20.6 ± 15.3 versus 6.6 ± 2.25 μg/μL), but this did not reach statistical significance. However, systemic cyclic AMP receptor protein levels correlated significantly with the IL-6 mRNA expression of the PBMCs activated by T3M4 in vitro (P < 0.04).

In summary, the IL-6 mRNA expression of PBMCs of patients with cachexia was low if PBMCs were cultured alone and could be significantly stimulated in coculture with the pancreatic cancer cell line T3M4 (Fig. 4). The IL-6 mRNA expression profile of Panc-1 and T3M4 itself did not change after coculture with the PBMCs of patients without or with cachexia or after coculture with normal controls (data not shown).

Additionally, the IL-6 mRNA expression by the PBMCs of cachectic patients in coculture with T3M4 could be reduced by up to 60% if a neutralizing antibody was added. The numbers of copies were 313.3 ± 238.3 without the IL-6 antibody and 135.8 ± 103.4 with the IL-6 antibody (Fig. 5).

**Discussion**

Cachexia occurs frequently in patients with malignant diseases and has a strong effect on the clinical course, quality of life, and survival of these patients (10, 11). Although every physician is aware of the clinical picture of cachexia, our understanding of the factors initiating cachexia and of the underlying pathomechanisms that maintain this syndrome is still very limited (27). Recent publications have postulated various hypotheses to explain the initial steps in cachexia. Cachexia-associated factors have been isolated from the urine.
of patients suffering from cachexia, and injection of these factors in mice induced lethal cachexia. In addition, there is evidence of a dysregulation of neuropeptides that are involved in orexigenic and anorexigenic pathways in humans (28–34). Despite these theories, there is also evidence that cytokines, especially IL-6 and TNF-α, play a central role in the pathomechanisms of cachexia (35). IL-6 is a cytokine with a plethora of actions ranging from inflammation over neural development to bone metabolism. With regard to cancer cachexia, some studies indicate positive effects of IL-6 treatment in the therapy of malignancies (36). On the other hand, recent studies raise strong evidence that IL-6 is involved in the development of cancer cachexia and have shown quite success in the treatment of cachexia with human anti-IL-6 antibody.
tumors were implanted s.c. in wild-type mice and IL-6 cachexia than host-derived cytokines. In this study, MCG 101 are quantitatively more important in the development of in which Cahlin et al. showed that tumor-derived cytokines

(37). In pancreatic cancer patients, high IL-6 serum levels have been associated with poor prognosis, increased tumor size, and loss of weight (21, 38, 39).

There is currently no generally accepted definition of cachexia. However, an unintentional weight loss of >5% to 10% of total body weight over a maximum of 6 months is generally accepted as a strong indicator for cachexia (40). To ensure a clear definition of cachectic patients, in our study, we included patients in the cachexia group only when they had an unintentional weight loss of >10% of their "normal" weight in the past 6 months.

Our first goal in this study was to identify and to further analyze factors that may contribute to cachexia. Surprisingly, gene chip analysis of resected pancreatic cancer tissue including 5,600 human genes revealed a significant difference between patients with and without cachexia in only four factors (IL-6, NPY-Y3 receptor, neurotensin, and islet amyloid polypeptide) which were either increased or decreased. Because by quantitative RT-PCR analysis only IL-6 could be confirmed as being differentially expressed in patients with and without cachexia and between patients with cachexia and patients with chronic pancreatitis or normal controls, we focused our further experiments on identifying mechanisms which are involved in IL-6 regulation (41–43).

According to expression analysis, the tumor itself seems a major source of cachectic factors in pancreatic cancer. IL-6 immunohistochemistry revealed an almost exclusive staining in pancreatic cancer cells. IL-6 serum levels were significantly elevated in pancreatic cancer patients with cachexia compared with noncachectic patients or normal controls. Altogether, these findings underline that the tumor itself plays an important role in the production of cachexia-inducing cytokines.

Our present findings are supported by a recent animal study in which Cahlin et al. showed that tumor-derived cytokines are quantitatively more important in the development of cachexia than host-derived cytokines. In this study, MCG 101 tumors were implanted s.c. in wild-type mice and IL-6 knockout mice and then tumor growth and weight loss were studied. Wild-type tumor-bearing mice developed cachexia because of rapid tumor growth, which were both attenuated in IL-6 gene knockouts. In addition, carcass weight loss was not improved by the omission of host cytokine (TNF-α, IL-12, or IFN-γ) except for IL-6 (44).

To further investigate the interactions between tumor cells and the host, especially in terms of cytokine production, we established an in vitro model in which cancer cells and PBMCs were cocultured. Two pancreatic cancer cell lines, one of which was not producing IL-6 (Panc-1, IL-6 mRNA negative) and one which was producing IL-6 (T3M4, IL-6 mRNA positive), were selected for coculture experiments. These experiments had two striking results. First, we could show that T3M4 as an IL-6-positive cell line but not Panc1 as an IL-6-negative cell line triggered the production of IL-6 in PBMCs of patients with cachexia, and this activation was reduced in the presence of neutralizing IL-6 antibodies. Second, PBMCs of cachetic patients reacted to the T3M4 triggering up to 14 times stronger than PBMCs of normal controls or noncachectic patients. Therefore, cachetic PBMCs might be sensitized by the tumor in vivo and triggered to further IL-6 overexpression without having any direct physical contact to tumor cells. The observation that the IL-6 mRNA expression of PBMCs from cachetic patients is low after 24 hours of culturing the PBMCs in the absence of tumor cells (Fig. 3A), contributes to the hypothesis that there has to be a constant tumor-derived stimulus to the sensitized PBMCs to maintain high IL-6 mRNA expression. O’Riordain et al. could show an accumulation of IL-6 protein in 24 hours culture of PBMCs derived from cachectic pancreatic cancer patients (45). Therefore, it is most likely that our measurement of end point IL-6 mRNA expression reflects the consequence of the in vitro stimulus withdrawal, whereas the high amount of IL-6 in supernatants from the O’Riordain study represents the accumulation of the early IL-6 production from sensitized PBMCs and its later decline.

Whether the sensitizing/triggering factor is IL-6 itself, produced by the cancer cells, or whether additional, not-yet-defined factors are involved, has to be further evaluated. In our study, the expression of IL-6 was not changed in tumor cells

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during their exposure to different PBMCs, although expression profile of the PBMCs changed dramatically. Similarly, Wigmore et al. showed that neither TNF-α nor IL-1 could influence an IL-6 status of pancreatic tumor cells (21). Thus, it is possible that certain tumors have an intrinsic potential to sensitize PBMCs in a procachectic way. Because a neutralizing IL-6 antibody could reduce T3M4-induced IL-6 expression of PBMCs from cachectic patients up to 60%, we further hypothesized that IL-6-dependent mechanism is at least a part of the pathway leading to the IL-6 overexpression in cachectic PBMCs. In view of the fact that the level of IL-6 mRNA expression in the T3M4-activated PBMCs correlates with the systemic cyclic AMP receptor protein levels and considering data of O’Riordain et al., who could show that PBMCs of cachectic patients with pancreatic cancer can induce the acute-phase protein response in liver cells in vitro, we conclude that tumor-primed PBMCs of cachectic patients may induce the acute-phase response in the liver (45).

In summary, our results show that in pancreatic cancer the tumor itself is a source of cachexia-mediating cytokines and that IL-6 seems to be a key player in cachexia development in pancreatic cancer patients. Additionally, PBMCs of pancreatic cancer patients with cachexia are sensitized and are stimulated to produce IL-6 in large amounts by IL-6-positive pancreatic cancer cells. Therefore, we expect that the development of cachexia in pancreatic cancer is at least in part dependent on triggering by the tumor and subsequent cytokine release (particularly IL-6) by activated PBMCs of the host.

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