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Cancer-Associated Immune Deficiency: 
A Form of Accelerated Immunosenescence? 

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1. Introduction

Cancer (medical term: malignant tumor) is a major global health problem and a life-threatening disease that accounts for ~13% of all deaths annually. The number of cancer deaths gradually increases year by year, and it is estimated that more than 11 million people will die from malignances in 2030. Various definitions of cancer have been proposed over the last few decades. In general, cancer displays several malignant features including the uncontrolled proliferation of abnormal cells, local invasion of normal tissue, and metastasis to a distant organ via the circulatory or lymphatic system. Environmental and genetic factors are considered to be the major causes of cancer. Cancer is believed to originate from a single normal cell through a multistage transformation that is assumed to take decades of development. Continuous exposure to some environmental factors (e.g., tobacco, unhealthy diet, radiation, chemical toxins, viruses, etc.) can potentially interact with gene changes in our bodies to enhance the formation of cancer (see http://www.who.int/mediacentre/factsheets/fs297/en/index.html).

Conventional treatments include surgical resection, chemotherapy, and radiotherapy. Although these series of interventions can effectively control localized or disseminated tumors, there is still a high rate of metastatic recurrence, thus limiting a patient’s survival. Other strategies, such as immunotherapy, cytokine therapy, and adoptive cell therapy, have shown some promising results for malignances in animal models. Unfortunately, several phase I/II clinical trials have shown that most patients still fail to completely eliminate cancer (Aldrich et al., 2010). It is becoming increasingly clear that cancer cells express immunogenic antigens that can induce an effective immune response against tumor formation (Lowe et al., 2007); therefore, during the initial stages of disease, cancer cells could essentially be recognized and rejected by the immune system, which exerts host-protective and tumor-modeling actions on developing tumors. Nonetheless, cancer cells also have numerous mechanisms to evade immunosurveillance (Burnet, 1970; Dunn et al., 2002), such as the downregulation of major histocompatibility complex (MHC) molecules or the antigen processing and presentation machineries, increasing the secretion of inhibitory cytokines, and the expression of inhibitory molecules to induce apoptosis in tumor-specific T cells (Dunn et al., 2004; Ferrara et al., 2003; Gabrilovich et al., 1996). On the basis of these phenomena, countless studies have confirmed the hypothesis that breaking self-tolerance and priming T lymphocytes are essential to treat cancer. Here, we discuss another possible
immunosurveillance evasion mechanism in which the immune system fails to eliminate tumors not because tumor antigens are absent, but rather that an inappropriate proportion of T lymphocytes with an “accelerated immunosenescence” status are present in cancer patients (Chen et al., 2010). Although cancer patients are often considered to have poor immunity, very few attempts have been made to examine the dysfunctional immune profile of these patients in detail. Thus, it is not surprising that there is a vast discrepancy in the responses of cancer patients to immunotherapy. This chapter will cover selected aspects of cancer-associated immune deficiency, emphasizing the cause and effect of accelerated immunosenescence in cancer patients. A better understanding of the immune profiles of cancer patients may inform more successful therapeutic strategies for the treatment of malignancies.

2. Cancer-related immune deficiency

When patients are diagnosed with cancer, a phenotypic classification might be very useful to evaluate their immune status and track the progression of the disease. The immune system exhibits characteristic changes during cancer growth and progression, and these changes are significant in some specific T-cell populations. Compared with normal individuals, the immune profiles of cancer patients include the following characteristics (Fig. 1):

![Diagram showing immune profiles over cancer progression.](www.intechopen.com)
2.1 Inverted CD4/CD8 ratio
The antitumor immune responses are predominantly governed by the cell-mediated immunity. CD4 and CD8 T cells are the main types of lymphocytes in cell-mediated immunity and play a central role in the induction of efficient immune responses against tumors (Ho et al., 2002; Pardoll & Topalian, 1998; Toes et al., 1999). There are 2 different subsets of CD4 T cells, helper T cells (T\textsubscript{H} cells) and regulatory T cells (T\textsubscript{reg} cells), each with a different function. Once activated, T\textsubscript{H} cells mediate the activation of CD8 T cells. Conversely, T\textsubscript{reg} cells attenuate the immune reaction to maintain immunotolerance and suppress autoreactive T cells (Buckner, 2010). CD8 T cells, which are also called cytotoxic T cells (T\textsubscript{c} cells), directly kill cancer and infected cells. Since CD4 T\textsubscript{H} cells play an important role in optimizing CD8 T cells activation, an adequate number of CD4 T\textsubscript{H} cells is therefore required to sustain the effector function against tumor cells by CD8 T cells.
In normal adults, CD4 and CD8 T cells each constitute well over 20% of the total lymphocyte population, whereas the proportion of these cells in cancer patients is lower and appears to decline according to the cancer stage (Chen et al., 2010; Mozaffari et al., 2007). An inadequate amount of T cells indicates that cancer patients cannot generate a sufficient immune response, resulting in an increase in the frequency and severity of infectious diseases. The ratio of CD4/CD8 T cells has indeed been used as an indicator for evaluating an individual’s immune function. In general, the CD4/CD8 ratio in healthy people is often >1; nonetheless, in patients with terminal cancer, this ratio drops significantly. Thus, an inverted CD4/CD8 ratio in cancer patients is one of the T-cell immune risk phenotypes (IRP) that is associated with increased morbidity and mortality (Wikby et al., 1998).

2.2 Subpopulation shifts in the T cells
The pattern of T cells differentiation may also serve as an important indicator for evaluating immune status in cancer patients. Naïve T cells are thought to be quiescent and capable of recognizing novel antigens (from tumor cells or pathogens) presented by antigen-presenting cells (APCs) to initiate the so-called adaptive immune response. Upon additional antigenic stimulation, primed T cells may start further differentiation leading to the clonal expansion of antigen-specific cells capable of executing immune response. Most of the activated T cells die rapidly through apoptosis; however, some may differentiate into memory T cells and survive for a long period of time. Once memory T cells encounter the same antigen, they will restart a faster and stronger immune response than the naïve T cells. Thus, it is of crucial importance for the immune system to have sufficient amounts of naïve T cells to respond to a variety of novel antigens.
In humans, the expression patterns of C-C chemokine receptor 7 (CCR7) and leukocyte common antigen isoform (CD45RA) are associated with the naïve, memory, and effector function of human T cells (Fig. 2, upper panel) (Sallusto et al., 1999). In general, naïve T cells express CCR7\textsuperscript{+} and CD45RA\textsuperscript{+}. Effector T cells, in contrast, have a CCR7\textsuperscript{−} and CD45RA\textsuperscript{+} phenotype. Memory T cells can be further divided into 2 sub-populations according to the differential expression of CCR7. CCR7\textsuperscript{+} T cells can be considered as precursors of the CCR7 subgroup. CCR7\textsuperscript{+} T cells are identified as central memory (CM) cells that secrete the cytokine interleukin 2 (IL-2), while the CCR7\textsuperscript{−} population has been referred to as effector memory (EM) cells that predominately express interferon-\gamma (IFN-\gamma) and interleukin-4 (IL-4). Both subgroups provide immunologic memory. T\textsubscript{CM} cells generally localize in lymphoid tissues and generate a rapid and vigorous immune response when an identical antigen is
encountered, whereas T_{EM} cells patrol peripheral organs where they may also reach local lymph nodes through afferent lymph vessels (Mackay et al., 1990). It has been shown that T_{CM} cells have a superior anti-cancer killing function than T_{EM} cells. (Klebanoff et al., 2005)

The distribution of T-cell subpopulations varies substantially in patients with cancer, from being normal in some early-stage to being increasingly disturbed at more advanced disease and in those whom have undergone chemotherapy. Typically, patients have a relative shrinkage of early T cells populations including the naïve and T_{CM} cell, but an increased proliferation and differentiation toward T_{EM} and effector T cells, one of the characteristic features of T-cell exhaustion (Klebanoff et al., 2006) (Fig. 2, lower panel). The distribution of T-cell subsets in cancer patients may explain the abnormal immune status that they suffer from: inadequate naïve and T_{CM} cells cause a shortage in the source of T cells with higher plasticity, while the accumulation of T_{EM} cells without appropriate T_{H} cells to prime an efficient immune response causes immune exhaustion. Another possible explanation has been advanced in which the T-cell pool shrinks as dysfunctional T cells accumulate and compete for survival with naïve and T_{CM} cells. While the total size of the T-cell pool remains

Fig. 2. Alteration of T-cell subpopulations in advanced cancer patients. The expression of the phenotypic markers CD45RA and CCR7 was used to define naïve, central memory, effector memory, and effector subpopulations (upper panel). The relative proportions of T-cell subpopulations in normal individuals and advanced cancer patients (lower panel). N, naïve T cells; CM, central memory T cells; EM, effector memory T cells; E, effector T cells.
unchanged, some memory T-cell subsets that are present at a low frequency may be lost (Akbar et al., 2004). These phenomena indicate that a patient’s immune status is unfavorable against cancer. This is especially evident in advanced disease, particularly in patients extensively treated with chemotherapy. The immune system of such patients would suffer from chronic stimulation by relentless release of tumor or viral antigens resulted from disease progression and treatment. In time, this may lead to the impairment of naïve T-cell differentiation and a failure of adequate effector and proliferative capacity. Similar phenomena are observed in some chronic virus infection systems in humans (e.g., human immunodeficiency virus, and hepatitis C virus, etc.). Despite a vigorous immune response and subsequent generation of memory T cells in the early stages of viral infections, continue virus stimulation may serve as a driving force for the generation of virus specific T-cells. However, the activity of such T-cells is gradually lost during the persistent virus infection, eventually leading to the accumulation of exhausted T cells (Letvin & Walker, 2003; Pantaleo & Koup, 2004; Rehermann & Nascimbeni, 2005).

2.3 Down-regulation of CD28 on T cells

In general, the initiation of T-cell activation requires at least 2 signals. Antigen presenting cells (APCs) uptake foreign antigens (from tumor cells or infectious materials) and then present antigenic peptides that are bound to class I or class II MHC molecules to form the peptide-MHC complex. This complex and specific T-cell receptor (TCR) engagement provide a recognition signal (signal 1) for the activation of naïve T cells. However, signal 1 is not sufficient to fully activate an immune response on its own. Having received signal 1, the interaction of a co-stimulatory molecule with its ligand provides the verification signal (signal 2) (Allison, 1994; Liu & Linsley, 1992). Without signal 2, T cells will enter the anergy state (Harding et al., 1992; Mueller et al., 1989). CD28 is one of the co-stimulatory molecules on the surface of T cells and a critical component of the adaptive immune response against infections and tumors. Furthermore, naïve and T

CM

 cells express CD28 on their cell surface, whereas T

EM

 and effector T cells are predominantly CD28

- 

(Pawelec et al., 2009). CD28 provides a co-stimulatory signal to interact with B7 molecules expressed on APCs and amplifies the signals delivered via the TCR, including increased cytokine expression, promotion of T-cell proliferation, and survival (Okkenhaug et al., 2001; Viola et al., 1999). With cancer progression, the surface expression of CD28 on T cells is gradually downregulated, resulting in the accumulation of CD28

- 

 CD28

+ 

 T cells 
left to mount an adequate response to the antigen introduced by the vaccine.
2.4 Lower interleukin-7 receptor α chain (IL-7Rα) expression
Interleukin-7 (IL-7) is a pleiotropic cytokine that preferentially maintains B, natural killer, and T-cell survival and homeostasis (Kim et al., 2008; Kittipatarin & Khaled, 2007; Surh & Sprent, 2008). It shares the use of the interleukin-2 receptor γ chain (IL-2Rγ) with interleukin 2 (IL-2), but has its own IL-7Rα. IL-7Rα is mainly expressed by all naïve T cells (Fry & Mackall, 2005). IL-7Rα+ T cells enhance their proliferation in response to homeostatic signals compared with IL-7Rα− cells. In cancer patients, the decrease in the naïve T-cell population has been found to be associated with the down-regulation of IL-7Rα, but not the plasma IL-7 level. Furthermore, the expression of IL-7Rα in naïve CD4 T cells is significantly lower than in naïve CD8 T cells. This may partly explain why CD4 is also at a lower level than CD8 in cancer patients. The mechanism underlying the down-regulation of IL-7Rα remains poorly understood. Some investigators suggested that the accumulation of TEM cells and prosurvival cytokines, such as interleukin-6 (IL-6), may suppress the expression of IL-7Rα (Park et al., 2004; van Leeuwen et al., 2005). Indeed, plasma IL-6 levels are higher in cancer patients than in healthy individuals, suggesting a possible association with the down-regulation of IL-7Rα. Another possible explanation is that the down-regulation of IL-7Rα might be caused by a persistent viral infection as many persistent virus-specific T cells lack IL-7Rα (Wherry et al., 2004). In an in vitro study, van Leeuwen and colleagues showed that IL-7Rα− T cells fail to respond to IL-7, but survived and expanded after TCR stimulation. Therefore, it is suggested that IL-7Rα− T cells specific for persisting viruses are maintained via their intermittent contact with antigens derived from the latent virus (van Leeuwen et al., 2005). IL-7Rα− T cells may thus survive and accumulate in cancer patients because they are regularly triggered by antigens released during chemotherapy or due to the reduced immune status and, therefore, do not depend on IL-7 for their survival. Consequently, antigen-experienced effector and memory T subsets are replaced by expanded clones of cells that display a late differentiation phenotype, especially the CD8 subset. Likewise, the repertoire of cells available to respond to novel antigenic challenges shrinks.

2.5 Higher IL-6 production
IL-6 is one of the pro-inflammatory cytokines, e.g., interleukin-1 β (IL-1β), tumor necrosis factor-α (TNF-α), and IFN-γ, which regulate immune reactions to tissue damage and lead to inflammation (Kishimoto, 2010). IL-6 has been found to be a “two-edged sword” in a variety of human tumors, in that it can switch from behaving as a paracrine growth inhibitor to behaving as an autocrine growth stimulator with the same cells during malignant tumor cell proliferation (Knupfer & Preiss, 2007). Cancer patients often have prominent circulating levels of IL-6, but not TNF-α and IFN-γ, compared with the levels in healthy individuals. However, the source of the circulating IL-6 in patients is not clear, but it may be produced by macrophages and T cells reacting to the tumor or by the tumor itself (Ebrahimi et al., 2004). Recent reports showed a correlation between increased serum levels of IL-6 and advanced stage metastatic disease and poor outcomes in other types of cancer (Bellone et al., 2006). On the other hand, IL-6 is considered a crucial pro-inflammatory cytokine in immunosenescence and involved in induction acute-phase of C-reactive protein (CRP) in the liver that is associated with the increased morbidity of elderly (Krabbe et al., 2004; Wikby et al., 2006).
2.6 Human cytomegalovirus (CMV) reactivation and CMV-specific CTLs

CMV is a highly prevalent herpes virus that is chronically carried by more than 70% of the world’s population (Rawlinson, 1999). It appears to be the most immunodominant antigen confronted by a carrier’s immune system throughout life. The primary CMV infection usually occurs early in childhood, but seldom causes severe disease, and was long thought not to be a major human pathogen. However, the virus has mechanisms to evade immune surveillance and survive in an immunocompetent host. Once infected, the virus hides in the human body and the immune system is unable to eliminate it completely. A hallmark of latent CMV infection is its capacity to induce recurrent disease, mainly in immunocompromised individuals. Patients at high risk for reactivation of latent CMV include those with a human immunodeficiency virus infection, malignancies, organ transplant, or on immunosuppressive therapy (Alberola et al., 2001; Chemaly et al., 2004; Limaye et al., 2001). It has been suggested that CMV-specific effector T cells accumulate with aging in such large numbers that they may be the dominant T-cell population in the peripheral blood of healthy elderly individuals. In fact, CMV-specific CD8 T cells in such individuals may constitute as much as 50% of the entire CD8 T-cell repertoire (Khan et al., 2002).

In cancer patients, over 50% of patients on cancer chemotherapy experience CMV reactivation during the course of chemotherapy (Han, 2007; Kuo et al., 2008; Ogata et al., 2011), with the average viral load peaking after the third course of treatment (Kuo et al., 2008). Furthermore, CMV-specific IgG titers are simultaneously elevated with the increase in virus load. In addition, the clonal expansion of CMV-specific CD8 T cells is also observed in cancer patients; however, these cells are predominantly CD28–, indicating that the expanded CMV-specific T-cell clones are terminally differentiated cells, i.e., essentially hyporesponsive to CMV (Chen et al., 2010). These T cells not only suppress other memory T-cell populations through competition for space or growth factors but also reduce the overall T-cell diversity and function (Effros et al., 2005; Messaoudi et al., 2004). The adverse impact of CMV on the immune status of cancer patients, thus, may be due to the presence of clonally expanded, highly differentiated, dysfunctional CMV-specific T cells that inhibit the diversity and ability of the immune system to respond to other antigens (Wherry et al., 2007). In extensively treated patients with terminal cancer, a decrease in the population of early-differentiated T cells, such as naïve and TCM cells, is associated with the expansion of a CMV-specific T-cell clone. In addition, IL-7Ra expression of the immune cells was inversely correlated to the intracellular viral load of CMV. Following chemotherapy, CMV reactivation left a fingerprint on the T-cell population, i.e., a significantly enhanced number of circulating cytolytic T cells in CMV carriers. The clonal expansion of CMV-specific T cells may thus shrink the repertoire of immune cells available for other antigens. In fact, this may be a contributory factor to the disease progression frequently seen in cancer patients. Therefore, CMV drives the expansion of T-cell subsets that are linked with immunosenescence, which may add to the chemotherapy-associated deterioration of immune function (Messaoudi et al., 2004; Wherry et al., 2007).

3. Accelerated immunosenescence

“Immunosenescence” has often been described as age-associated deterioration of the immune system in the elderly. The Swedish OCTO/NONA longitudinal studies of the very elderly (>85 years) identified some immune parameters, the so-called “immune risk profile,”
which predict the 2, 4, and 6 year mortality rates. Immune risk profiles (IRP) mainly include (Ferguson et al., 1995; Pawelec et al., 2004; Pawelec et al., 2006; Wikby et al., 1998):

i. inverted CD4/CD8 ratio,
ii. poor T-cell proliferative activity,
iii. increased CD28-CD8 T cells,
iv. persistent CMV infection,
v. clonal expansion of dysfunctional CMV-specific CD8 T cells.

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<th>Age-associated immunosenescence (&gt;85 years)</th>
<th>Aggressively treated cancer patients (45–75 years)</th>
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<td>CMV viral load</td>
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Table 1. Comparison of the immune profiles in age-associated immunosenescence and aggressively treated cancer patients. +, increase; -, decrease. *Patients with various types of cancer were enrolled in the Mackay Memorial Hospital. None of the patients had received immunotherapy when the blood samples were collected, but all had received chemotherapy according to the standard treatment regimen for their specific cancer (Chen et al., 2010).

It has been suggested that age-related dysfunction may not be the sole cause of immunosenescence, but the presence of an infectious component appears to be the force driving T cells towards senescence. Pawelec et al. has proposed that CMV infection is responsible for the development of immunosenescence in the elderly, not aging per se (Pawelec et al., 2006). The inflame-aging hypothesis in human ageing proposed by Franceschi et al. also suggests that immunosenescence is mainly driven by the chronic viral antigen stimulation (Franceschi et al., 2000). Repeated CMV infection induces significant expansion of late differentiated-stage of CD28-CD8 effector cells, leading to alteration of homeostatic T-cell (i.e., inverted CD4/CD8 ratio and T-cell subpopulations, etc.). An analysis of immunosenescence data revealed that elderly individuals had a decreased number of naïve T cells and an increased number of effector/memory and effector CD8 T cells compared to young individuals; however, both had a similar amount of T_{CM} cells. Such large expansion would not only limit the number of clonal expansions of CMV-specific T cells but also result in shrinkage of clonal diversity (Hadrup et al., 2006; Pawelec et al., 2004). Thus, it is not surprising that old people have increased susceptibility to pathogens. The CMV-specific CD28-CD8 effector cells can secrete IL-6 cytokine that prolong inflammatory activity during pathogen infections (OMahony et al., 1998). The increased levels of circulating IL-6 would potentially induce CRP that is significantly correlated with mortality of elderly (Krabbe et al., 2004; Wikby et al., 2006). Patients with cancer are more vulnerable than healthy individuals to have CMV reactivation. In fact, the immune status of cancer patients is very similar to IRP seen in the elderly. Our previous data have shown that
patients with cancer may suffer from a very high rate of CMV reactivation during chemotherapy (Kuo et al., 2008) that the pattern of IRP in age-associated immunosenescence can develop in a short period of time. Therefore, down-regulation of early differentiated subpopulations (naïve and $T_{CM}$ cells), accumulation of the CD28- population and CMV-specific T cells, and high levels of CMV viral load and IL-6 secretion were observed in cancer patients who were extensively treated (Table 1). We propose that CMV reactivation (viral antigens) combined with cancer progression (tumor antigens) and treatment schedule may drive T cells toward senescence in cancer patients (Chen et al., 2010). These data refer a similar phenomenon of “accelerated immunosenescence”. Thus, it is not surprising that several clinical trials of immunotherapy still fail to completely eliminate cancer. The immune exhaustion of advanced cancer patients could be one of the reasons for the poor clinical outcome of immunotherapy.

4. Conclusions

In summary, we propose that patients with advanced cancer who received extensive treatment have an accelerated immunosenescence that may be clinically relevant for cancer treatment. Typically, there is a decrease in naïve and $T_{CM}$ cells, but an increase in the proliferation and differentiation of the $T_{EM}$ population. The immune impairment in these patients is associated with multiple factors such as the stage of cancer, impact of treatment schedules, and consequence of CMV reactivation. It has been suggested that, with aging, CMV-specific effector T cells accumulate in such large numbers that they may be the dominant T-cell population in the peripheral blood of healthy elderly individuals. These $T_{EM}$ cells are found to be specific for fewer epitope of CMV (Pawelec et al., 2005).

In addition, CMV infection may induce a decrease in T-cell telomere length and lead to a shift in the composition of the T-cell pool (van de Berg et al., 2010). The deleterious effect of CMV persistence on the human immune system is usually insidious and requires decades to be recognized. By contrast, the immune systems of cancer patients are somehow rapidly driven to an analogous state of immunosenescence. Therefore, it is conceivable that patients who receive extensive chemotherapy would have a greater risk of repeated CMV exposure, leading to the accumulation of CMV-specific immune cells. The clonal expansion of CMV-specific T cells may thus shrink the repertoire of immune cells available for other antigens and result in the chemotherapy-associated deterioration of immune function.

With a more complete understanding of the immune profile of cancer patients, clinical investigators will be able to provide strategies to restore a robust immune response in the tumor-bearing host (active tumor immunity) or, alternatively, promote immunity by the adoptive transfer of activated effector cells or tumor-specific antibodies into the tumor-bearing host (passive tumor immunity). In addition, certain biomarkers, such as the T-cell subpopulations, IL-7Rα, CD28, IL-6, CMV-specific T cells, CMV-specific IgG, and CMV viral load, may be useful for monitoring the immune status of patients during, or more importantly, before cancer treatment. Since CMV reactivation may in turn serve as the driving force for generating virus-specific T cells rather than tumor-specific T cells, we propose that even latent CMV infection may contribute to the immune tolerance of tumors. This raises the intriguing possibility that preemptive anti-CMV treatment could be an important adjunct in cancer treatment, especially during chemotherapy. Without consistent antigenic stimulation, $T_{EM}$ cells undergo apoptosis, resulting in a decrease in this cell population and an increase in committed effector cells. Prevention of CMV reactivation
before the initiation of conventional therapy or immunotherapy could promote immune reconstitution and therefore contribute to a better response once specific anti-cancer treatment is given. We believe that this strategy is worthy of further investigation.

5. References


Cancer is now the leading cause of death in the world. In the U.S., one in two men and one in three women will be diagnosed with a non-skin cancer in their lifetime. Cancer patients are living longer than ever before. For instance, when detected early, the five-year survival for breast cancer is 98%, and it is about 84% in patients with regional disease. However, the diagnosis and treatment of cancer is very distressing. Cancer patients frequently suffer from pain, disfigurement, depression, fatigue, physical dysfunctions, frequent visits to doctors and hospitals, multiple tests and procedures with the possibility of treatment complications, and the financial impact of the diagnosis on their life. This book presents a number of ways that can help cancer patients to look, feel and become healthier, take care of specific symptoms such as hair loss, arm swelling, and shortness of breath, and improve their intimacy, sexuality, and fertility.

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