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REVIEW ARTICLE

Advances in the diagnosis and treatment of patients with cancer cachexia

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Abstract

Cachexia is a common complication with an incidence rate of 50%–80% in cancer patients. It is also responsible for 20% of mortality among these patients. Cachexia can significantly reduce the efficacy of antitumor therapies and increase treatment-related toxicity and adverse effects in cancer patients. This increases the symptom burden in patients, affects their quality of life, and ultimately shortens their survival time. The mechanism underlying the development of cachexia is complex and diverse and involves various factors and pathways, each playing an important role. Treatment approaches for cachexia are multimodal, including nutrition support therapy, appetite stimulants, and therapeutic drugs that specifically target the mechanism behind the disease. In recent years, we have gradually gained a better understanding of cachexia, and significant progress has been made in delineating molecular mechanisms, staging and diagnosis, and therapeutic drug treatment of cancer cachexia. This article reviews the research progress of cancer cachexia based on these contexts.

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Definition and diagnosis of cachexia

Cachexia is a complex metabolic syndrome that threatens patients' lives. It is characterized by weight loss and muscle wasting with or without fat loss. The pathophysiological characteristics of cachexia include weight loss, anorexia, inflammation, insulin resistance, muscle protein breakdown, and fat decomposition [1–2]. Cachexia is most commonly seen in various chronic consumptive diseases, such as chronic obstructive pulmonary disease, rheumatoid arthritis, chronic kidney disease, chronic heart failure, AIDS, and malignant tumors [3–8]. Cancer cachexia, also known as cancer anorexia cachexia syndrome (CACS), has an incidence rate of approximately 50%–80% in patients with various types of cancer. Of all cancer types, the incidence rate of cachexia is the highest in pancreatic cancer and upper gastrointestinal cancer patients (> 80%), followed by lung and colon cancers, wherein approximately 50%–60% of patients develop cachexia [9–10]. Among the different causes of death, cachexia is responsible for 20%–40% of deaths in cancer patients [11–12]. Many previous studies have shown that cachexia not only reduces the efficacy of antitumor therapies and increases treatment-related toxicity and adverse effects but also increases the symptom burden in patients, reduces their quality of life, and ultimately shortens their survival time [13–17].

Despite the complex and diverse mechanisms involved in the development of cachexia, a precise and standardized definition for cachexia is still lacking. Moreover, the identification, diagnosis, and treatment of cachexia are often neglected in the clinical setting [18–19]. In a consensus meeting held in Washington D.C. in 2006, experts unified the definition of cachexia: a complex metabolic syndrome associated with underlying illness and characterized by loss of muscle with or without loss of fat mass [20]. In 2011, the international expert consensus set the diagnostic criteria for cachexia: a patient is diagnosed with cachexia if in the past 6 months, weight loss was greater than 5% or 2% in individuals with body mass index (BMI) of less than 20 kg/m^2 or those with sarcopenia [21]. This definition has since become widely accepted and adopted by a

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number of clinical studies on cachexia [22–24].

Molecular mechanism of cachexia

Muscle wasting is one of the important features of cancer cachexia, and its pathophysiology is characterized by an imbalance in the synthesis and degradation of muscle proteins. Currently known cytokines and molecular mechanisms involved in cachexia-induced muscle wasting are summarized below.

Systemic inflammation

Systemic inflammation is the main mechanism leading to muscle wasting and fatigue in patients with cachexia [25]. Early studies on the mechanism of cachexia have principally focused on inflammation. The pro-inflammatory factors produced by the body or the tumor, including TNF-α, IL-1, and IL-6, are closely related to muscle wasting in cancer cachexia [26–28]. Many studies have shown significantly increased inflammatory markers in the blood of cachectic animal models and patients [29–32]. Earlier studies have considered TNF-α as a major factor that induces cachexia. It has been shown to cause muscle protein breakdown and muscle atrophy in animal experiments [33–34]. TNF-α and IL-1 induce cachexia through the activation of IKK complexes, which leads to the phosphorylation of the IκBa protein and the release of NF-κB. This activates the muscle-degrading factors MuRF1 and Atrogin-1, resulting in protein loss and muscle atrophy [35–36]. IL-6 induces cachexia through binding to IL-6 receptors, which activate the downstream JAK-STAT pathway. Animal experiments have shown that STAT3 can cause muscle fiber atrophy and that the IL-6/JAK-STAT3 pathway is closely related to skeletal muscle atrophy [37].

Ubiquitin proteasome pathway (UPP)

The UPP is an important pathway for muscle degradation in cachexia [38–39]. The majority of muscle proteins, particularly muscle fibers, are degraded by the UPP. The degradation is generally divided into two steps: the substrate protein is first covalently bound to different types of ubiquitin molecules and is then degraded by the 26S protease. The process of protein ubiquitination is usually regulated by three enzymes: ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin ligase (E3) [40]. Atrogin-1 and MuRF-1 are two important E3 ubiquitin ligases. A marked increase in the expression of Atrogin-1 and MuRF-1 has been observed in cachexia, and their expression is correlated with muscle atrophy [41–42]. Many animal experiments have shown that cancer cachexia can significantly increase the activity of the ubiquitin proteasome system (UPS), resulting in increased expression of Atrogin-1 and MuRF-1 [43–45].

PI3-K/Akt/mTOR pathway

The IGF-1 signaling pathway is an important pathway involved in muscle anabolism. Studies have shown that the IGF1/Akt pathway can inhibit protein degradation and promote muscle growth [46–47]. In addition, binding of IGF1 to the receptor can activate the PI3K/Akt signaling pathway. This activates mTOR and phosphorylates its effector targets S6K1 and 4E-BP, which in turn promote muscle formation [48–49]. Akt can also translocate FoxO proteins (FoxO1, FoxO3, and FoxO4) from the nucleus to the cytoplasm, leading to their phosphorylation and inactivation. Activated FoxO proteins can act as transcription factors and regulate autophagy, which promotes the ubiquitin-mediated degradation of muscle cells [50–52]. IGF-1 expression is significantly reduced in animal models of cancer cachexia, and supplementation with low-dose IGF-1 can reduce muscle atrophy and weight loss. However, anti-IGF-1 treatment has not been shown to exacerbate muscle atrophy in cancer patients [45, 53–54].

TGF-β/SMAD pathway

The TGF-β superfamily is another factor that has been recently found to be associated with muscle atrophy in cachexia. The most representative family members are activin A and myostatin [55]. Activin A is implicated in many physiological functions, including erythrocyte formation, cell growth, differentiation, and immune response [56]. Myostatin, also known as GDF8, is an important negative regulator of muscle growth and is secreted by muscle cells. Its deletion and mutation are associated with the pathological condition of muscle hypertrophy [57–58]. Both activin A and myostatin activate type I receptors by binding to the ActRIIB receptor on the surface of muscle cell membranes (ALK4 or ALK7 is an activin A type I receptor, while ALK5 or ALK7 is a myostatin type I receptor). The activated type I receptors, in turn, phosphorylate the SMAD complexes (SMAD2, SMAD3, and SMAD4) and cause muscle atrophy by regulating transcriptional responses [59–60]. Myostatin and activin A can also activate FoxO3 by suppressing Akt activity, which in turn upregulates MuRF-1, Atrogin-1, and autophagy-related genes, leading to the breakdown of muscle protein [61]. It has been observed in animal experiments that elevated activin A expression is associated with muscle wasting in cachexia. In addition, the inhibition of activin A can reduce muscle wasting and improve muscle function. The levels of activin A in the blood of patients with cancer cachexia have also been shown to be significantly elevated [62–64]. The myostatin/activin A/SMAD pathway may be present early in cachexia. A study on patients with early stage gastric cancer detected increased expression of myostatin in patients' muscles prior to their significant weight loss.

This suggested that myostatin might be a marker for early-stage cachexia [65]. However, studies on myostatin and muscle atrophy have reported inconsistent results. Some studies have shown that the increased expression of myostatin in muscles is associated with cancer cachexia-induced muscle atrophy, and the inactivation of the myostatin gene can inhibit muscle atrophy and tumor growth. By contrast, some studies have shown that the expression of myostatin in the serum is not associated with muscle loss [66–70].

GDF-15, also known as macrophage migration inhibitory factor 1, is another member of the TGF-β superfamily. Its hematologic level is significantly elevated in inflammation, cancers, and cardiovascular diseases [71]. Many studies have shown the increased expression of plasma GDF-15 in cancer patients, which is associated with their poor prognosis [72–74]. At the same time, GDF-15 levels are correlated with appetite. An increase in GDF-15 levels in the blood leads to a decreased appetite, which in turn causes weight loss [75]. The overexpression of GDF-15 in the muscles of experimental animals causes muscle atrophy; therefore, GDF-15 may directly promote skeletal muscle atrophy. In cancer patients, the high expression of GDF-15 is associated with weight loss and muscle loss; however, no correlation between GDF-15 and the appetite of patients has been observed [76].

Autophagy-lysosome pathway

Autophagy is a normal, ubiquitous catabolic process that degrades cytoplasmic components through lysosomes, and this process also occurs in skeletal muscles. When occurring properly, autophagy can help regulate the function of skeletal muscles and control skeletal movement and muscle metabolism. However, excessive activation of or deficiency in the autophagy function can result in muscle wasting and reduced muscle function [77–80]. Some studies using animal models of cachexia have shown that autophagy is significantly activated in the muscles of mice with cachexia [81]. The activation of the autophagy pathway has also been observed in the muscle or blood of patients with cancer cachexia, and autophagy is found to be significantly associated with muscle wasting and weight loss [82–84]. It is speculated that aerobic exercise and megestrol acetate may relieve the symptoms of cachexia-induced muscle atrophy by suppressing the excessive activation of autophagy and restoring the balance of muscle metabolism [85–86].

Staging and diagnosis of cachexia

The international expert consensus of cachexia [21] has divided the development and progression of cachexia into three consecutive phases: precachexia, cachexia, and refractory cachexia. Patients with precachexia usually present with clinical or metabolic symptoms, including anorexia and impaired glucose tolerance, accompanied by weight loss of ≤ 5%. A patient enters the cachexia phase if weight loss exceeds 5% or 2% for patients with BMI of less than 20 kg/m^2 or those with sarcopenia. Weight loss may occur under the influence of factors such as tumor type and stage, systemic inflammation, reduced food intake, and ineffective antitumor therapy. In refractory cachexia, the patient is usually at the end stage of cancer, with a performance status score of 3–4. The tumor progresses rapidly and is unresponsive to antitumor therapy, and the patient has an expected survival time of less than 3 months. Although the international expert consensus has set the definitions and descriptions for cachexia stages, to date, widely accepted criteria for staging cachexia are still lacking. In addition, staging of cachexia is crucial for treatment selection and prognosis of patients.

In 2009, Bozzetti F *et al* [87] classified cachexia into precachexia and cachexia based on the presence of 10% weight loss. They further classified the disease into asymptomatic precachexia (stage I), symptomatic precachexia (stage II), asymptomatic cachexia (stage III), and symptomatic cachexia (stage IV) based on the presence of anorexia, fatigue, or early satiation. This staging methodology preceded the development of the diagnostic criteria for cachexia by the international expert consensus and hence adopted a 10% weight loss as a diagnostic criterion. Furthermore, it lacks a diagnostic criterion for refractory cachexia. In 2011, Argiles JM *et al* developed a new tool for staging cachexia (CASCO) [88]. It included five major diagnostic indicators: body weight and muscle changes, inflammation/metabolic disturbances/immunosuppression and related parameters, physical performance, nutritional status, and quality of life. The total score of the scale is 100 points. It divides cachexia into mild (0–25 points), moderate (26–50 points), severe (51–75 points), and terminal phase (76–100 points). However, the scoring table contains a large number of questionnaires and metabolic and immunologic parameters. Its complexity and high cost limit its widespread use in clinical settings. Vigano A *et al* subsequently introduced a novel definition for staging cancer cachexia (CCS) [89] that comprehensively determined cachexia stages based on parameters such as inflammatory indicators, anorexia, weight loss, physical performance, and grip strength. However, their staging criteria failed to properly distinguish patients with precachexia and cachexia. In 2014, Blum D *et al* conducted a validation study on the international expert consensus on cachexia [90], in which patients were classified into different cachexia stages according to the degree of weight loss: patients with weight change (± 1 kg) or weight gain were classified as no cachexia; patients with weight loss > 1 kg but < 5% were classified as precachexia; patients

with weight loss > 5% or patients with a BMI < 20 kg/m^2 and weight loss > 2% were classified as cachexia; and patients with a BMI < 23 kg/m^2 with weight loss > 15% or those with a BMI < 27 kg/m^2 and weight loss > 20% were classified as refractory cachexia. However, weight loss alone cannot properly reflect the status of cachexia in patients. In addition, it cannot distinguish between patients without cachexia and those with precachexia. In 2016, Vigano AA *et al* optimized previous CCS criteria and developed a simple, clinically applicable system for staging of cachexia. Five indicators were used for staging and diagnosing cachexia, including abnormal biochemical parameters, reduced food intake, moderate weight loss, severe weight loss, and reduced performance status [91]. Although this staging system is simpler to use than the previous CCS criteria, as it eliminates the need to fill out questionnaires and measure grip strengths, it still cannot effectively distinguish between patients with precachexia and those with cachexia. Similarly, in 2017, Argiles JM *et al* validated and simplified the previously developed CASCO cachexia staging criteria into a new set of cachexia staging criteria (miniCASCO) [92]. Although miniCASCO is more convenient than CASCO, it still requires a large number of questionnaires and parameter testing such as that for IL-6 and ROS. Therefore, it is not suitable for rapid clinical diagnosis. Furthermore, its effectiveness has not been verified in clinical settings. Our research group recently developed a cachexia staging score (CSS) [93], which included five components for evaluation: weight loss, a questionnaire for sarcopenia SARC-F, performance status, appetite loss, and abnormal hematologic parameters. The total score was 12 points, of which 0–2 points were classified as non-cachexia, 3–4 points as precachexia, 5–8 points as cachexia, and 9–12 points as refractory cachexia. The simple design and low cost of this scoring tool facilitate its rapid clinical application. Its effectiveness has also been verified using various clinical parameters, including patients' body weight loss, BMI, muscle mass and function, proportion of sarcopenia cases, symptom burden, quality of life, and survival time. These results indicate that the scoring tool performs well in distinguishing patients with different stages of cachexia.

Advances in the treatment of cachexia

With the extensive research on the molecular mechanism of cachexia in recent years, significant progress has been made in the treatment of cachexia. Many novel drugs have shown therapeutic prospects for cachexia. As the mechanism underlying the development of cachexia is complex and diverse, a single treatment approach can hardly achieve satisfactory results. Therefore, cancer cachexia is best treated with comprehensive multimodal therapies. This section provides a summary of the main treatment approaches for cancer cachexia.

Nutrition support therapy

Weight loss and malnutrition are the most common signs of cancer cachexia that can adversely affect patients' clinical outcomes. Therefore, it is necessary to perform appropriate nutritional screening for cancer patients. Additionally, the advantages and disadvantages of nutritional intervention need to be weighed and properly balanced [94]. In clinical practice, nutrition support therapy is usually the most considered treatment for patients with cachexia. However, with deeper understanding of cachexia, we now realize that nutrition support therapy may not be applicable to all patients with cachexia. In addition, nutrition support therapy alone cannot completely alleviate patients' symptoms of cachexia. The international expert consensus on cachexia has pointed out that nutrition support therapy may not be beneficial to patients with refractory cachexia [21]. Therefore, guidelines in the United States do not recommend the routine use of nutrition support therapy in cancer patients receiving chemotherapy or minor surgery. According to the guidelines, nutrition support therapy should only be considered in patients who are unable to absorb adequate nutrients due to functional impairment [95]. Among the various nutritional supplements, n-3 polyunsaturated fatty acids have been shown by many studies to be beneficial to cancer patients, and they can increase their weight and improve their quality of life [96–98]. In addition, L-carnitine has been shown to alleviate fatigue while improving the nutritional status of cancer patients. However, other studies have obtained contrasting results [99–102]. Therefore, the use of nutritional supplements in patients with cachexia remains inconclusive.

Appetite stimulants

Appetite stimulants commonly used in patients with cancer cachexia include hormones and progesterone [2]. A systematic review has revealed that while hormones and progesterone drugs are recommended for the treatment of anorexia in cancer patients, there are uncertainties regarding their appropriate dose, timing, and treatment duration [103]. Hormonal drugs are often used as appetite stimulants to improve appetite, increase caloric intake, control pain, alleviate fatigue, and reduce nausea and vomiting of cancer patients [104–105]. Various hormonal drugs exert similar appetite-stimulating effects. The commonly used hormonal drugs include prednisone and dexamethasone. Studies have shown that 5 mg of prednisone administered orally three times per day and 3–6 mg of dexamethasone administered orally per day

can significantly increase patients' appetite compared with placebo [106]. However, hormonal drugs can only increase the appetite of patients for a short period of time; they cannot truly increase the weight of patients [107–108]. In addition, as hormone therapy is associated with many adverse effects that can negatively affect the patient's quality of life, the dosing and timing of hormonal drugs require careful monitoring [109].

The most common progesterone used clinically as appetite stimulants include megestrol acetate and medroxyprogesterone acetate. The appetite-stimulating effects of megestrol acetate are similar to those of dexamethasone. Several clinical studies have shown that megestrol acetate can significantly improve the appetite of cancer patients while having milder adverse effects compared with dexamethasone [110–112]. Medroxyprogesterone can also increase the appetite of cancer patients and increase their body weights. However, the increase is limited to adipose tissue, not muscle tissue [113–116].

Thalidomide

Thalidomide possesses immunomodulatory and anti-inflammatory effects. Hence, it can reduce the level of inflammatory factors (TNF-α and IL-6) in the blood, thereby inhibiting the NF-κB pathway and reducing cachexia [117–118]. Studies have shown that thalidomide has a positive therapeutic effect on cancer cachexia. However, some studies have reported that patients treated with thalidomide do not show a significant decrease in symptom severity and inflammatory parameters compared with the placebo groups. Therefore, the effectiveness of thalidomide for treating cancer cachexia will need to be confirmed by data collected from large-cohort randomized controlled trials [119–123].

Selective COX-2 inhibitors

Selective COX-2 inhibitors are anti-inflammatory drugs that can be used for the treatment of cachexia [124]. Phase II clinical studies have shown that when used in combination with other drugs, celecoxib can significantly increase the lean body mass, grip strength, quality of life, and performance status of cancer patients. It can also reduce the level of TNF-α in the blood and does not cause grade 3–4 adverse reactions [125–126]. However, the latest research shows that when used in combination with megestrol acetate, celecoxib cannot further enhance its efficacy in the treatment of cachexia [127].

TNF-α inhibitors

As TNF-α plays an important role in the development and progression of cachexia, therapeutic drugs that inhibit TNF-α may be beneficial for the treatment of cachexia [128–129]. It has been shown in animal experiments that TNF-α inhibitors significantly increase the appetite and body weight of tumor-bearing mice. Infliximab is a human and mouse chimeric monoclonal antibody that specifically blocks TNF-α. However, multiple phase II clinical studies have shown that infliximab fails to alleviate muscle atrophy or improve the quality of life of patients compared with the controls [130–133]. The above findings suggest that the mechanism underlying the development of cachexia can be diverse. Therefore, a single treatment modality can hardly produce satisfactory results, and the treatment of cachexia requires comprehensive multimodal therapies. Moreover, a phase II/III randomized controlled study on infliximab in lung cancer patients was prematurely terminated due to a significant reduction in quality of life in the treatment group.

In addition to TNF-α receptors, fibroblast growth factor-inducible 14 (Fn14), a receptor for TWEAK, is also a member of the TNF receptor superfamily. Fn14 has been shown to be related to the mechanism of cancer cachexia development [134–136]. Monoclonal antibodies against Fn14 have been shown to alleviate symptoms of cachexia and prolong survival in mice, whereas anti-TWEAK antibodies have no therapeutic effects on the Fn14-induced cachexia, suggesting that there may be another unknown ligand for Fn14 [137].

IL-6 receptor inhibitor

ALD518 is a humanized monoclonal antibody with high affinity toward IL-6. It is used in the treatment of anemia, cachexia, and asthenia [26, 138]. In a phase I clinical study, ALD518 has been shown to improve grip strength and fatigue in patients with advanced tumors [139]. A subsequent phase II randomized controlled trial in patients with advanced non-small-cell lung cancer (NSCLC) showed that compared with the control group, ALD518 significantly reduced body weight loss, alleviated lung symptoms, and improved fatigue and anemia in the treatment group [140–142]. These results indicate that ALD518 is safe and well tolerated. It may serve as a potential therapeutic drug to improve anemia, fatigue, and cancer-associated cachexia. However, its efficacy needs to be further confirmed in large cohorts and phase III randomized controlled clinical trials.

Ghrelin receptor agonist

Ghrelin is a newly discovered growth hormone-releasing peptide that is primarily synthesized in the stomach. It can regulate the release of growth hormone, stimulate appetite, inhibit the production of pro-inflammatory factors, and regulate energy fluxes in an organism [143–144]. Studies in animal models of cachexia and human patients with cancer cachexia have shown that ghrelin can significantly increase food intake and body weight in mice or patients with cancer cachexia [145–146]. The recently developed anamorelin is an oral ghrelin receptor agonist. It has been shown in preclinical studies that the administration of 10 or 30 mg/kg of anamorelin in mice can significantly stimulate appetite and increase food intake and body weight [147]. Two subsequent phase II clinical studies showed that continuous administration of anamorelin for 12 weeks significantly increased the lean body mass of patients with cachexia [148]. The results of two phase III randomized controlled clinical trials in patients with NSCLC (ROMANA1 and ROMANA2) showed that anamorelin significantly increased the lean body mass of patients with cancer cachexia, but not their grip strength and muscle function [149]. In a related phase III safety extension study, the use of anamorelin was extended to 24 weeks. The results showed that anamorelin was well tolerated. Additionally, anamorelin significantly increased the patients' body weights and reduced their symptom burden [150]. A recently completed randomized controlled clinical study of anamorelin in Japan also showed that it could increase the lean body mass in patients and alleviate symptoms such as anorexia; however, muscle function was not enhanced [151]. Many meta-analyses and systematic reviews also showed that anamorelin significantly improved the appetite and lean body mass of patients with cancer cachexia, but did not affect their grip strength and overall survival [152–153]. Despite these findings, anamorelin is still currently considered a new option for the treatment of cancer cachexia. Phase III clinical studies of anamorelin in Chinese patients with cancer cachexia are currently ongoing.

ActRIIB antagonists

Many studies have shown that levels of activin A and myostatin are significantly elevated in patients with cancer cachexia [55, 154]. The inhibition of the myostatin/activin A signaling pathway in mouse models of cancer cachexia can increase muscle volume and improve physical performance and muscle function [63, 155–156]. ActRIIB antagonists are inhibitors of the SMAD2/3 pathway, which is mediated by both myostatin and activin A. They can significantly reduce muscle atrophy and prolong survival in animal experiments, but have no effect on the levels of inflammatory factors in the blood [29]. Another myostatin-specific antibody, PF-134, has also been confirmed to reduce tumor-induced muscle atrophy and impaired muscle function in animal experiments. However, a clinical study on PF-134 was terminated due to oral bleeding and epistaxis that occurred during the trial [157]. LY2495655 is another myostatin-specific antibody that has been shown in clinical studies to alleviate muscle atrophy and improve grip strength and muscle function in patients with cancer cachexia. Phase II/III clinical studies on LY2495655 are ongoing [158].

Summary

With our increasing understanding of cancer cachexia in recent years, significant progress has been made in the diagnosis and treatment of cachexia. The international expert consensus has set clear definitions for cancer cachexia that are gradually becoming the accepted diagnostic standards. The staging criteria for cachexia are also continually being refined. Additionally, with the extensive research on the molecular mechanism of cachexia, there have been more promising targeted therapeutic drugs for cachexia. However, the mechanism underlying the development of cachexia is complex and diverse, and a single treatment modality will hardly produce satisfactory results. Many challenges remain in the diagnosis and treatment of cancer cachexia: How can we improve the screening of patients with cancer cachexia in clinics? What are the markers of the development and progression of cachexia? How can we optimize the staging and diagnosis of patients with cachexia? What are the appropriate multimodal treatment plans for cancer patients with different stages of cachexia? Future research should focus on finding solutions to these issues.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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