News Release

An unexpected role for the ancient, evolutionarily conserved complement system

— Complement C3 produced locally within the tumor, not that circulating in the blood, governs the efficacy of cancer immunotherapy —

Key Points

- Complement proteins are produced mainly in the liver and circulate in the blood to protect the body against infection; however, the role of complement produced locally within each organ has remained largely unknown.
- In cancer, fibroblasts — one of normal cell types that surround cancer cells — produce complement C3.
- This locally produced complement C3 suppresses the accumulation of immunosuppressive myeloid cells within the tumor, creating an environment in which cancer immunotherapy is more likely to be effective.

Summary

The research group led by Assistant Clinical Professor Yuki Miyai and Professor Yuichi Ando (Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital), Lecturer Shintaro Iwama and Professor Hiroshi Arima (Department of Endocrinology and Diabetes), and Professor Atsushi Enomoto (Department of Pathology), Nagoya University Graduate School of Medicine, in collaboration with Lecturer Tetsunari Hase (Department of Respiratory Medicine) and Specially Appointed Professor Masahide Takahashi (International Center for Cell and Gene Therapy; Professor Emeritus of Nagoya University), Fujita Health University, has discovered a previously undefined role for complement C3 (hereafter termed C3) produced by cancer-associated fibroblasts (CAFs) within tumor tissue, identifying it as a new factor that regulates the efficacy of cancer immunotherapy.

C3, the central molecule of the complement system, is mostly produced in the liver and travels through the blood. Using cancer mouse models, the group separated the roles of C3 according to its source. Even when liver-derived circulating C3 was greatly reduced, immunotherapy (an anti-PD-1 antibody) remained effective. In contrast, when the “local C3” produced by CAFs within the tumor was lost, immunotherapy became less effective, even though circulating C3 was barely changed. In other words, what determined the

efficacy was not the C3 in the blood, but the local C3 produced at the tumor site.

This local C3, through its degradation product iC3b, suppressed the accumulation of immunosuppressive myeloid cells (monocytes and macrophages) in the tumor and created an environment conducive to immunotherapy. Indeed, combining a drug that targets this pathway restored efficacy even in tumors that were intrinsically resistant to immunotherapy. In human cancers such as lung cancer, the higher C3 in the tumor stroma, the better the treatment outcomes and prognosis, whereas the amount of C3 in the blood was not associated with efficacy.

C3 is a very ancient molecule that existed long before the blood circulatory system evolved, and it is found in evolutionarily primitive organisms such as sponges. This study reveals that, by acting “locally,” this ancient C3 governs the efficacy of modern cancer immunotherapy. The findings are expected to contribute to the development of biomarkers that predict which patients are likely to benefit from immunotherapy, and of new therapies that render resistant cancers responsive.

These findings were published in the British scientific journal *Nature Communications* on July 15, 2026.

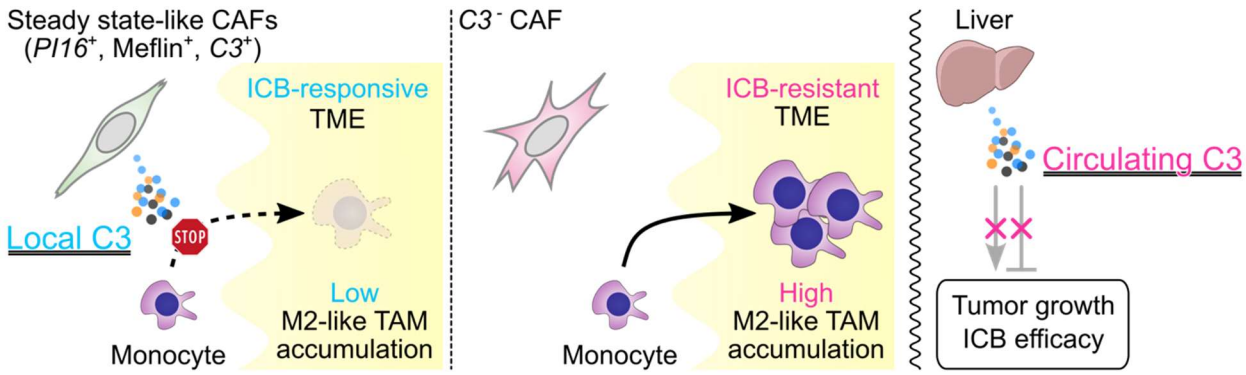

Figure. Locally produced complement C3 in the tumor shapes the efficacy of cancer immunotherapy

(Left) Steady state-like CAFs (PI16$^+$, Meflin$^+$, C3$^+$) supply local C3 in the tumor. Its degradation product iC3b suppresses the infiltration of monocytes, limiting the accumulation of immunosuppressive M2-like tumor-associated macrophages (TAMs) and creating an immune checkpoint blockade (ICB)-responsive tumor microenvironment (TME). (Middle) When CAFs lack C3 (C3$^-$ CAF), monocyte infiltration and M2-like TAM accumulation increase, producing an ICB-resistant TME. (Right) C3 circulating in the blood derived from the liver does not contribute to tumor growth or ICB efficacy.

Research Background

Complement is a central mechanism of innate immunity, and C3 is the key molecule at which all of its activation pathways converge. Most C3 is produced in the liver and is abundant in the blood, where it contributes to defense against infection and other immune processes. At the same time, C3 is a very ancient molecule that existed long before the blood circulatory system evolved, and it is present even in evolutionarily primitive organisms such as sponges. Nevertheless, what C3 produced “locally” within tissues actually does has remained poorly understood.

In recent years, innate immunity has emerged as an important factor in the efficacy of cancer immunotherapy (immune checkpoint inhibitors, such as anti-PD-1 antibodies). Tumor tissue contains abundant CAFs in the stroma surrounding cancer cells, and some CAFs had been reported to produce C3. The group has previously shown that Meflin, a protein expressed on CAFs, is a marker of “good,” cancer-restraining CAFs and that it enhances the efficacy of immunotherapy. In the present study, the team therefore investigated how anti-tumor immunity and the efficacy of immunotherapy differ depending on whether C3 is “blood-derived (systemic)” or “locally derived.”

Research Results

In colorectal and lung cancer mouse models, the researchers selectively deleted systemic C3, liver C3, or CAF C3 and compared the outcomes. Even when circulating C3 reduced by about 90% by the deletion of liver C3, immunotherapy (an anti-PD-1 antibody) remained effective. In contrast, deleting C3 in Meflin-positive CAFs made immunotherapy less effective, even though circulating C3 was barely reduced (a decrease of only about 9%). This showed that the determinant of efficacy was not C3 in the blood but “local C3.”

The degradation product of local C3, iC3b, acts on the receptor CR3 (CD11b/CD18) on the surface of myeloid cells such as monocytes, suppressing their infiltration into the tumor. As a result, the accumulation of immunosuppressive M2-like tumor-associated macrophages (TAMs) was reduced, creating a tumor microenvironment (TME) in which immunotherapy works more readily.

Using both human and mouse data, the team showed that the main source of this local C3 is a population of “steady state-like” CAFs, which are positive for PI16, Meflin, and C3, that resembles the fibroblasts found in normal tissues.

When an antibody or an agonist targeting CD11b that suppresses myeloid cell infiltration was combined with immunotherapy, the effect of the anti-PD-1 antibody was restored even in mouse tumors that had originally been resistant to the immunotherapy.

In clinical specimens from human cancers such as lung cancer, patients with higher stromal C3 expression had fewer M2-like macrophages and better response rates, progression-free survival, and overall survival with immunotherapy. By contrast, the amount of C3 in the blood was not associated with treatment efficacy.

Research Summary and Future Perspective

The local C3 → iC3b → CR3 pathway may serve both as a predictive biomarker for the clinical benefit of immunotherapy (stromal C3 within the tumor) and as a new therapeutic target for rendering resistant cancers responsive. Going forward, the group will advance translational validation toward clinical application, including methods to increase or activate local C3 and the optimal timing of therapeutic intervention. Elucidating the significance of local C3 produced by fibroblasts is also expected to deepen our understanding of a broad range of biological phenomena beyond cancer, such as inflammation and tissue repair.

Publication

Journal: *Nature Communications*

Title: Local, but not circulating, complement C3 shapes immune checkpoint blockade efficacy by controlling myeloid cell infiltration

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DOI: 10.1038/s41467-026-75542-3