Review Article

Mechanisms and characteristics of subcapsular sinus macrophages in tumor immunity: a narrative review

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Background and Objective: Lymph nodes constitute an integral component of the secondary lymphoid organs, housing a diverse population of macrophages. Macrophages exhibit heterogeneity in terms of localization, phenotype and ontogeny. Recent evidence has established that subcapsular sinus macrophages (SCSMs) are the initial cells exposed to antigens from afferent lymph vessels, playing a crucial role in the host immune response against invading pathogens and tumor cells. In order to summarize the role and mechanisms of SCSM in tumor immunity, this study systematically reviews research on SCSMs in tumor immunity.

Methods: A systematic search was conducted in PubMed and Web of Science to identify articles investigating clinical significance and mechanisms of SCSMs. Study eligibility was independently evaluated by two authors based on the assessment of titles, abstracts and full-texts.

Key Content and Findings: The narrative review included a total of 17 studies. Previous research consistently showed that a high level of SCSM in patients with various carcinomas is associated with a favorable long-term prognosis. SCSM acts as the front-line defender in antitumor activity, engaging in intricate communication with other immune cells. Moreover, SCSM could directly and indirectly modulate tumor immunity, and the integrity of SCSM layer is interrupted in disease status. Several studies explored the feasibility of targeting SCSM to activate immunity against tumors. However, the direct molecular interactions and alternation in signal pathway in the tumor immunity of SCSM are less well established in previous researches.

Conclusions: This narrative review underscores the critical role of SCSM in tumor immunity. Future studies should focus on the deeper mechanism underlying SCSMs and explore their clinical applications.

Keywords: Macrophages; subcapsular sinus; tumor; immunity

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Introduction

Composing of lymphatic vessels and lymph nodes (LNs), the lymphatic system plays pivotal a role in conferring immunity against diverse pathogens and malignant tumors. The broad lymphatic vessels collect and transport soluble antigens, peptides, metabolites, invasive pathogens, and immune cells to the draining LNs via afferent lymphatic vessels (1,2). Here, migrating antigen-presenting cells (APCs) and resident LN immune cells interact with antigens to initiate the immune activation cascade. After that, the lymph and activated immune cells traverse through circulations and enter the site of pathogen invasion to furnish immunological defense (3). Subcapsular sinus macrophages (SCSMs), a subgroup of macrophages in secondary lymph organs, undergo redistribution upon immune activation, contributing to antigen handling (4). However, compared to their role in anti-viral immunity, the understanding of SCSMs in tumor immunity is less well explored. Additionally, the clinical application of such crucial macrophage subtype has not been established as well. This article comprehensively reviews the features and antitumor function of subcapsular sinus SCSMs in the context of tumor challenges, aiming to provide insights for further studies on the mechanisms and practical applications of SCSMs. We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-2032/rc).

Methods

Searching strategy

The systematic search was conducted on PubMed and Web of Science up to 23th September 2023. The search keywords included "CD169" OR "Siglec-1" OR "sialoadhesin" and "cancer" OR "carcinoma" OR "neoplasm" OR "tumor" (*Table 1*). Articles exploring the clinical significance or the mechanisms of SCSMs in carcinoma were identified.

Screen process

All articles were screened by two authors (F.S. and Y.Z.) independently, with any disagreements resolved by a third author (Y.S.). Eligibility of studies was based on the assessment of title, abstract and full-text. Except for review, meta-analysis, case studies, conference abstracts and editorials, all study designs were included without limitations. Studies investigating extranodal CD169$^+$ macrophages, or the function of SCSM in viral immunity were excluded. Relevant data from included studies were extracted by two authors (F.S. and Y.Z.) independently.

A total of 558 studies were screened for eligibility based on titles, abstracts and full-texts, and 17 studies were included in this systematic review. The flow of identification, screening and inclusion processes is depicted in *Figure 1*.

Biological characteristics of SCSM

LNs could be anatomically divided into two primary regions: the cortex and the medulla. The cortex primarily consists of B cell follicles and T cell areas, while the medulla is composed of lymph-draining sinuses separated by medullary cords (5). The subcapsular sinus is a region located between the capsule and the cortex. Lymph is released by afferent lymphatics into subcapsular sinus, percolates through trabecular and cortical sinuses into medullary sinuses, and is ultimately collected by efferent lymph vessels to exit the LNs. SCSM and medullary macrophages are the two main cell types that populate the LN sinus (6).

SCSM, first discovered by Kraal and Janse in the 1980s via a panel of antibodies in mouse, constitute a class of sinus-lining macrophages that are directly exposed to lymph-borne antigens (7). Humans and mice demonstrate a high degree of conservation in CD169, a protein containing 17 immunoglobulin-like domains that belongs to the sialic acid-binding immunoglobulin-like lectin family and immunoglobulin superfamily. CD169 displays a wide range of molecular binding capabilities and may serve as a mediator of the cell-to-cell adhesion and antigens phagocytosis (4,8). SCSM in human also expresses CD163, CD204, Mac1 (CD11b/CD18), programmed cell death ligand 1 (PD-L1) and Fascin, while being negative for F4/80 and CD11c markers (9,10).

As the gatekeeper at the entry site of LNs, SCSM are the first cellular entity to bind antigens and function as a filter to prevent virus and bacteria from spreading through blood flow (11,12). Nonetheless, SCSM express low level of lysosomal enzyme and exhibit poor ability in the phagocytose and direct clearance of pathogens (9). Instead, SCSM could serve as a repository of viral antigen and enhance humoral and cellular immunity activation by supporting the reproduction of captured pathogens. The intensity of adaptive immune response correlates with viral replication within the SCSM in various viral infections

Table 1 The search strategy summary

Items	Specification
Date of search	23th September 2023
Databases and other sources searched	PubMed and Web of Science
Search terms used	(((CD169) OR (sialoadhesin)) OR (Siglec-1)) AND ((((cancer) OR (carcinoma)) OR (neoplasm)) OR (tumor))
Timeframe	From 2010 to 2023
Inclusion and exclusion criteria	Inclusion criteria: articles investigating the significance of SCSM in clinical study or basic research Exclusion criteria: review, meta-analysis, case studies, conference abstracts or editorials; studies investigating $CD169^+$ macrophages located in extranodal sites
Selection process	Screen title for identification; screen abstracts and full-texts for eligibility

SCSM, subcapsular sinus macrophages.

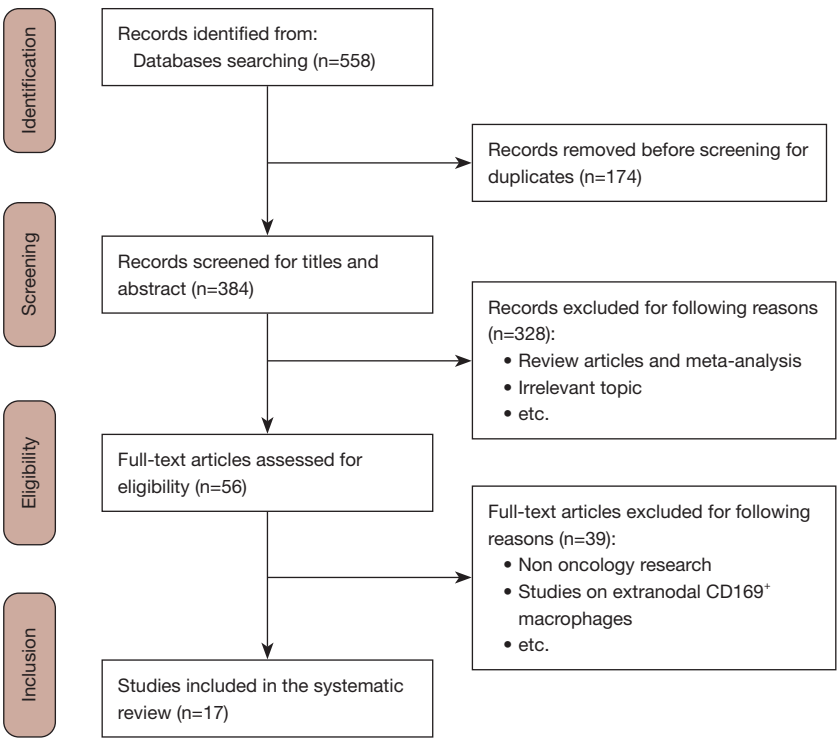

Figure 1 The flow diagram of identification, screening and inclusion.

(13,14). Several types of immune cells are recruited based on the type of microbes (15). Moreover, the production of IL-1, IL-18, and IFN-I by SCSM in the early stages of infection could stimulate innate and adaptive immune responses (16,17). Interestingly, an enforced replication is observed for virus within SCSM (11,18,19). Local intercellular communications between SCSM and dendritic cells (DCs), B cells, innate lymphoid cells, natural killer (NK) cells, or NK T cells are reported for antigen presentation and immune activation (17,20-22). Despite partial inhibition or postponement of adaptive immunity upon the depletion of SCSM, the intrinsic mechanism of such cellar interactions remains obscured. Nevertheless, SCSMs are essential for the maintenance of tolerance via

the elimination of dying cells and autoantigens as well (23). The depletion of SCSM leads to a failure to induce tolerance and an impaired immune activation *in vivo* model following autoantigen injection.

The origin and replenishment of SCSM

The developmental kinetics of SCSM is comparable to those of LNs (24). SCSM may originate from the hematopoiesis yolk sac during the embryonic stage and are subsequently replaced by bone marrow monocytes that populate the LNs after birth. After maturing, they could maintain the SCSM network in equilibrium by proliferating locally, rather than the supplement of bone marrow monocytes. The SCSM layer may be disrupted by the activation of inflammation, the natural course of tumor progression or anti-cancer treatments, leading to a reduction in SCSM density (25,26). After ablation, the replenishment of SCSM depends on the integration of blood-borne monocytes in several waves (27,28). The early recruited monocytes could aid in coping with inflammation, while macrophages recruited at later waves would differentiate into self-maintaining SCSMs.

The macrophage niche is essential for the genesis of SCSM in the embryonic stage and the replenishment of SCSM following ablation. This niche could foster the local macrophage population by secreting survival factors, acts as an anchoring scaffold, and imprints the macrophages with tissue-specific tasks (29,30). The effect of colony-stimulating factor (CSF)/CSF receptor signal is pivotal for the maturation and replacement of SCSM, and SCSM are depleted after the blocking or know-down of the CSF signal (31). Besides, B cells are an important component of macrophage niche through secreting lymphotoxin-α1β2, without which SCSM would display an aberrant phenotype and fail to protect mice from fatal infection (9,32). Moreover, lymphatic endothelial cells play a crucial role in the niche by secreting colony stimulating factor-1 (CSF-1), the principal regulator of macrophage survival and proliferation (33). On the other hand, the receptor activator of nuclear factor kappa-B and its ligand (RANK-RANKL) signal regulated by mesenchymal cells is also required for the differentiation of SCSM and functions of lymphatic endothelial cells (33). Transforming growth factor-β (TGF-β) downregulates the expression of CD169 on monocyte-derived macrophages in a dose-dependent manner, while interferons or lipopolysaccharides upregulate its expression (34). The cellular mechanisms that govern the development of SCSM are complicated, and due to the inherent technical challenges in isolating SCSM, specific mechanisms still warrant investigation (35).

Correlation between SCSM and carcinoma

The correlation between SCSM and several malignant diseases has been examined in several studies (*Table 2*). Colorectal carcinoma, bladder cancer, prostate cancer, breast cancer, endometrial carcinoma, oral cancer, esophageal cancer, gastric cancer, melanoma as well as head and neck squamous cell carcinoma were investigated in these studies (36-47). In these studies, the density of SCSM were evaluated with the CD169 or a CD169 to CD68 ratio in subcapsular sinus of LNs. Overall survival, cancer-specific survival, and disease-free survival (DFS) were assessed as long-term outcome. Different from the xenografts in murine models, the density of SCSM varied across cases. In nearly all of the aforementioned studies, a high density of SCSM in reginal LNs was demonstrated to be considerably associated with improved survival for patients with carcinomas, with the exception of a study by Shiota *et al.*, which reported no significant correlation (39). The impact of SCSM on DFS in esophageal cancer was marginally significant (P=0.056) (44). Even though the density of SCSM was not an independent risk factor for DFS in patients with gastric carcinoma, SCSM could potentially predict 5-year DFS in advanced-stage patients (45). It is worth noting that several studies also reported the associated clinical pathological features and tumor microenvironment. For instance, a high density of SCSM was observed in patients with smaller primary tumor size and less T stage in bladder cancer and breast cancer (37,39,40), while in patients with low N stage or without lymph metastases, the level of SCSM in reginal LNs was higher in breast cancer and endometrial carcinoma (39,41).

The level of SCSM is correlated with specific biological characteristics of tumors. Prostate-specific antigen (PSA)-relapse is independently linked with scan positivity and extrapelvic metastases in prostate cancer (48). Although SCSM is not related to PSA-relapse, it is the only factor that correlated with prostate cancer death in patients with PSA-relapse (38). In breast cancer, Ki-67, progesterone receptor and PD-L1 expression are excellent candidate biomarkers for prognosis and therapy. Ki-67 is a well-established cell proliferation marker and has a statistically significant positive association with the risk of cancer relapse and death (49). The high density of SCSM in patients with low Ki-67 index is basically in accordance

Table 2 Studies investigation the correlation of subcapsular sinus macrophages with malignant tumors

Author	Year	Cancer types	Number of patients	OS	CSS	DFS	Clinicopathological features	Immune cells
Ohnishi *et al.* (36)	2013	Colorectal carcinoma	83	↑ (P=0.0092)	–	–	–	High SCSM correlated with $CD8^+$ T cell in tumor (P<0.0001)
Asano *et al.* (37)	2018	Bladder cancer	44	–	↑ (P=0.0078)	–	High SCSM associated with low T stage (P=0.0046)	High SCSM correlated with $CD8^+$ T cell in tumor (P=0.0046)
Strömvall *et al.* (38)	2017	Prostate cancer	106	–	↑ (P=0.002)	–	High SCSM associated with low risk of dying in patients with PSA-relapse (P=0.0046)	–
Shiota *et al.* (39)	2016	Breast cancer	146	–	NS (P=0.301)	NS (P=0.777)	High SCSM associated with less LN metastasis, smaller tumor size, less clinical stage and low Ki-67 index	High SCSM correlated with $CD8^+$ T cell in tumor for in Ki-67-high cases (P=0.0481)
Björk Gunnarsdottir *et al.* (40)	2020	Breast cancer	286	–	–	↑ (P=0.011)	High SCSM associated with smaller tumor size (P=0.003), higher PR-positivity degree in LN (P=0.031) and higher PD-L1 expression (P<0.001)	–
Ohnishi *et al.* (41)	2016	Endometrial carcinoma	79	↑ (P=0.0139)	–	–	Fewer SCSM associated with advanced clinical stage (P=0.049) and more LN metastasis (P=0.029)	High SCSM correlated with increased $CD8^+$ T cell (P=0.0053) and $CD57^+$ NK cells (P<0.001) in tumor
Kawaguchi *et al.* (42)	2022	Oral cancer	89	↑ (P=0.002)	–	↑ (P=0.001)	–	High SCSM correlated with $CD8^+$ T cell in tumor (P<0.001)
Saito *et al.* (43)	2015	Malignant melanoma	93	↑ (P=0.001)	–	↑ (P=0.005)	–	High SCSM correlated with $CD8^+$ T cell in tumor (P=0.026); IFNα-secreting cells were close to SCSM in LNs
Takeya *et al.* (44)	2018	Esophageal cancer	182	–	↑ (P=0.0453)	NS (P=0.056)	–	–
Kumamoto *et al.* (45)	2021	Gastric cancer	294	–	↑ (P=0.004)	NS (P=0.112)	–	High SCSM correlated with $CD8^+$ T cell in tumor (P<0.001)
Topf *et al.* (46)	2019	Head and neck squamous cell carcinoma	22	–	↑ (P=0.693)	–	Fewer SCSMs were observed in metastatic LNs compared to tumor-free LNs (P<0.001)	–
Saito *et al.* (47)	2023	Colorectal cancer	83	↑ (P=0.009)	–	–	SCSM status did not significantly associated with mismatch-repair deficiency status	High SCSM correlated with $CD8^+$ T cell in tumor (P<0.001)

↑, favorable survival with high SCSM in regional lymph nodes; –, no detailed information. OS, overall survival; CSS, cancer specific survival; DFS, disease-free survival; SCSM, subcapsular sinus macrophages; PSA, prostate-specific antigen; NS, no significant difference; LN, lymph node; PR, progesterone receptor; NK, natural killer; IFN, interferon.

Table 3 Studies investigation possible mechanisms of subcapsular sinus macrophages

Author	Year	Study design	Cancer type	Mechanisms
Asano *et al.* (53)	2011	*In vitro* and *in vivo* experiments	Lymphoma	SCSMs could phagocytize tumor-derived extracellular vesicles and activate $CD8^+$ T cell under cross-presentation with dendritic cells
Ohnishi *et al.* (36)	2013	Clinical study and *in vitro* experiments	Colorectal cancer	SCSM has direct contact with $CD8^+$ $CD43^+$ double-positive T cells in reginal LNs; high SCSM correlated with $CD8^+$ T cell in tumor
Saito *et al.* (43)	2015	Clinical study and *in vitro* experiments	Malignant melanoma	High SCSM correlated with $CD8^+$ T cell in tumor; macrophages stimulated IFNα and IFNβ expressed high level of CD169; IFNα-secreting cells were close to SCSM in reginal LNs
Pucci *et al.* (26)	2016	*In vitro* and *in vivo* experiments	Malignant melanoma	SCSM block the spread of tumor-derived extracellular vesicles physically, prevent its interactions with B cells and activate tumor-enhancing B cell immunity
Takeya *et al.* (44)	2018	Clinical study and *in vitro* experiments	Esophageal cancer	The expression of Indoleamine 2,3-dioxygenase on SCSMs is similar to the expression of SC169 and linked to M1-like activation
Tacconi *et al.* (54)	2021	*In vitro* and *in vivo* experiments	Breast cancer	SCSMs mediate the anti-metastatic effect through the regulation of B cells
Virgilio *et al.* (55)	2022	*In vitro* and *in vivo* experiments	Malignant melanoma	SCSMs secrete IL-1α which could promote melanoma metastasis via STAT3 signal pathway
Anami *et al.* (56)	2023	*In vitro* and *in vivo* experiments	Several murine cancer cell lines	SCSMs contribute to the antitumor effect of anti-PD-L1 therapy through the activation of immunological responses to tumor cells

SCSM, subcapsular sinus macrophages; LN, lymph node; IFN, interferon; PD-L1, programmed cell death ligand 1; IL, interleukin.

with the fact that high level of SCSM indicates favorable prognosis (39). Progesterone receptor and PD-L1 are also valuable prognostic biomarkers, affecting the effectiveness of endocrine and immune therapies in breast carcinomas (50-52). The expression of these two biomarkers is considerably different in SCSM high and SCSM low subgroups. Given the crosstalk between SCSM and adaptive immune cells, it is not surprising to observe the activation of immune cells in patients with high SCSM levels. An increased $CD8^+$ lymphocyte and NK cells in the primary tumor are correlated with high level of SCSM in patients in various cancers.

Mechanisms of tumor immunity of SCSM

According to previous studies (26,53,54), SCSM mainly exert anti-cancer effects during tumor development, which is supported by clinical findings (36-47). Eight studies directly explored the potential mechanisms of SCSMs in tumor immunity, and the basic information of these studies is summarized in *Table 3* (26,36,43,44,53-56). Among them, 5 studies involved *in vitro* and *in vivo* experiments aiming at elucidating the signal pathways and molecular interaction of SCSMs. The tumor suppressive effect could mainly be divided into several aspects, as follows.

Extracellular vesicles, which could be categorized as exosomes and shed microvesicles, are lipid nanovesicles that express a high level of phosphatidylserine and play a crucial role in cell-cell communication by transporting contents to distant or proximal site of the body (57). A key source of extracellular vesicles is the fragmentation and packaging of cellular contents during cellar apoptosis (58). Previous studies have reported that tumor-derived extracellular vesicles (TEVs) could promote the formation of cancer-promoting environment by the transportation of proteins, nucleic acids, lipids, and small molecules (59,60). TEVs have complicated interactions with immune cells during the immunoediting phase (61). In the elimination phase, DCs phagocytize the proteins on the surface and are carried by TEV, thereby facilitating the activation and maturation of NK cells and $CD8^+$ lymphocytes (62). However, during the escape phase, TEVs modify and block the differentiation of DCs, lymphocytes and NKs, resulting in decreased antitumor immunity (63,64). A significant role of SCSM is the physical barrier against tumor cells and TEVs. In murine model, interactions between TEVs and SCSM were observed in the draining LNs (26). SCSM could phagocytize TEVs in a phosphatidylserine dependent

manner through the surface expressed α2,3-linked sialic acids on CD169 (53,65). After the specific depletion of SCSM, TEVs could reach B cell follicles at the early stage of cancer transplantation in murine model, foster the tumor-promoting humoral immunity and enhance pro-tumor IgG response (26). On the other hand, the phagocytosis of TEVs by SCSM could prevent the inhibitory effect of vesicles on antigens presentation to cytotoxic T cells (CTLs) by DCs, resulting the inhibition of antitumor immunity (66). Considering the extensive effect of TEVs on NK cells and T lymphocytes in escape phase, the cancer progression suppress mechanism of SCSM through TEV pathways still has great potential for elucidation. Additionally, the metastasis of tumor cells to local drainage LNs is an important approach to spread systemically (67). Similar to the interaction with lymph-borne pathogens, SCSM could directly bind with tumor cells in the draining LNs coming from afferent lymphatic vessels and prevent them from spreading through efferent lymphatic vessels (15). This is basically consistent with the observation that the high density of SCSM is correlated with less LNs metastasis reported in clinical studies.

Another crucial mechanism of SCSM in the progression of cancer is the presentation of antigens and activation of the immune system. Among tumor infiltrated lymphocytes, CD8 T cells, the key components antitumor immunity, are capable of detecting and eliminating tumorigenic cells directly and producing effector cytokines or cytotoxic molecules. Dysfunction or exhaustion of CTLs would lead to a pro-tumor microenvironments (68). Asano *et al.* observed co-localization of SCSM and CD8 T cells in the challenge with subcutaneous vaccination of irradiated tumor cells (53). Given that no direct evidence for the antigen presentation function of SCSM was observed, cross-presentation of DCs and SCSM might be necessary for the priming of CTLs. Studies have also reported severe impairment of CD8 T cell activation and antitumor immunity activity in the depletion of SCSM. Furthermore, SCSM, rather than DCs, are the resident APCs that are dominant the cross-presentation between DCs and SCSM in the priming of antigen-specific CD8 T cells (4,66). The positive association between density of SCSM and CD8 T lymphocytes in primary cancer, according to studies for clinical specimen, further confirmed this interaction. Interestingly, CTLs induced by DCs are biased towards strongly binding epitopes, while CTLs activated by SCSM could be specific for an extensive range of epitopes (69). Strikingly, although TEVs abundantly bound to CD169 on SCSM, considerably stronger CTL responses were raised with antigen-pulsed exosomes in CD169-deficient mice, indicating the complicated activation process underlying SCSM (65). In a mouse subcutaneous injection model, Tacconi demonstrated that the inhibitory ability of SCSM on tumor metastasis depended on the presence of B cells, and the increased metastatic tumor load was abolished after the depletion of B cells regardless the ablation of SCSM (54). A higher level of NK cells was reported in high SCSM patients with endometrial carcinoma. Although SCSM could act as the primary mediator of NK cell activation in response to lymph-borne virus, there is no evidence that SCSMs could directly prime NK cells in the tumor immunity as early sensors in the functional level yet (18,70). Besides, the activation of iNKT cells in LNs was induced under the stimulation of CD169-targeting liposomes with lipid antigen, demonstrating the ability of SCSM to activate a wide range of immune cells in the tumor immunity.

In the immunity activation response to pathogens, SCSM can exert protective effect by producing a series of cytokines, including IFN-I, IL-1, and IL-18 (16,71). IFN-I could induce intracellular response, innate and adaptive immunity to clear pathogens. In the immune response to tumors, exposure to IFN-I could enhance the expression of co-stimulatory molecules, prolong lifespan of DCs, and allow them to persist in keeping intracellular antigen particles, subsequent boosting activation of CLTs (72,73). Combining the fact that SCSMs can phagocytize tumor antigens at early-stage and secrete a high amount of IFN-I, they could provide an optimal stimulus for CD8 lymphocytes activation. Interestingly, while the role of cancer suppression has been verified in most studies, Virgilio found that the production of IL-1α by SCSM in the melanoma could promote tumor metastasis through STAT3 signal pathways, indicating that the functions and mechanisms of SCSM are not yet precisely understood (55).

Conversely, the phenotype of SCSM is greatly altered with the tumor progression. SCSM that come into contact with tumors would undergo cell death (55). In the challenge of a virus, a burst of inflammasome activation and cell death occur in SCSM, which broadens the CTL response (25). In mice with melanoma, there was area near the afferent lymphatic vessels free of SCSM in the metastatic LNs, indicating that cell deaths were induced for SCSM (55). It was proposed that the total number of SCSM remained constant in the tumor plantation model that was associated with the cell death happening to SCSM, which may offset cell recruitment and proliferation. Whereas macrophages

and immune cells were recruited and LNs were enlarged, resulting the density and frequency of SCSM being lower in the tumor plantation models than those in normal murine model. However, the molecular alternation of cell death in the challenge of tumor remains enigmatic and it is quite hard to investigate. Tacconi *et al.* evaluated the transcriptomics of SCSM under homeostatic and tumor-bearing conditions and observed an enrichment of 714 genes (54). Most of the enriched genes regulated cell-proliferation related processes including DNA replication, chromosome transformation. SCSM in LNs was surrounded by cells secreting IFN, by which the expression of CD169 on macrophages could be upregulated (43). These demonstrated dynamic change in the number of SCSM after capturing tumor cells and pathogens. However, whether these inflammation-induced SCSM exhibit similar characteristics as residential SCSM is not clear yet.

Furthermore, prior studies have highlighted additional pathways involving extranodal CD169$^+$ macrophages in response to tumor challenges. JAK2/STAT3 signal pathway is activated in residential CD169$^+$ macrophages, leading to the upregulation of PD-L1 and evasion of T cell-mediated immune surveillance in breast cancer (74). In liver cancer, IFNα could induce the expression of CD169 on tumor-infiltrating macrophages, polarizing the CD169$^+$ macrophage population and enhancing CD8$^+$ T cell activities (75). Additionally, Kim *et al.* demonstrated that blood monocyte-derived CD169$^+$ macrophages function as an antitumor subpopulation (76). Notably, these macrophage subpopulations share the expression of key molecule CD169 with SCSM. Given that the functions and mechanisms of SCSM are not yet precisely understood, investigating whether SCSMs have a direct or indirect temporal or spatial association with these cell subpopulations, or share a common molecular pathway mechanism is warranted.

Discussion

In this study, a systematic review of SCSM in tumor immunity was conducted with the aim of providing a comprehensive overview of the current literature. The review encompasses findings of clinical studies as well as *in vitro* and *in vivo* experiments, exploring the role and underlying pathways of SCSMs.

SCSMs represent a group of sinus-lining macrophages directly exposed to lymph-borne antigens in the LNs. They could potentially function as cell subpopulations that first receive molecules from the primary tumor in tumorigenesis. The macrophage niche is crucial for the development and replenishment of SCSM, and the SCSM layer may be disrupted under pathological conditions. While the depletion of SCSM *in vitro* experiments results in immune surveillance failure and impaired immune activation, the consequences of SCSM disruption in terms of immune exhaustion or other immunological outcomes remain undetermined.

Synthesizing the included studies revealed that SCSM generally plays an antitumor role in most carcinomas. Higher density of SCSM in LNs is consistently correlated with favorable long-term outcomes, and increased SCSM in regional LNs is usually associated with greater infiltration of tumor-infiltrating immune cells, especially CD8$^+$ T cells.

Previous studies have explored potential mechanisms of SCSMs in tumor immunity, highlighting their role as a physical barrier that phagocytize TEVs and cell debris, preventing the immune suppression of B cells induced by primary tumor molecules (26). Besides, phagocytized tumor-associated antigen are cross-presented with DCs to stimulate immunity against tumor (53). While the regulation of B cells is imperative for the antitumor effect of SCSMs, the intricate signal pathways and molecular interplays underpinning this effect are often not explored (54). Interestingly, it was observed that tumor models characterized by an augmented density of SCSM exhibit heightened immunological responses to tumor cells under PD-L1 therapy (56). However, Virgilio *et al.* demonstrated that an SCSM-related IL1α-STAT signal pathway could facilitate melanoma metastasis (55). Notably, despite the demonstrated correlation between the elevated density of SCSMs and increased immune cell infiltration and activated tumor immunity, the majority of studies did not explore the detailed signal pathways and molecular interactions governing the antitumor effect of SCSMs.

In the majority of studies, the density of SCSM is considered an indicator for long-term prognosis due to its significant correlation with survival. Some studies have explored the potential clinical application of SCSM, indicating that substances like naringin, an inducer of CD169-expression for SCSM (77), could bolster immunity and improve the effect of PD-L1 therapy. Similarly, naringenin, the major active compound of naringin with oral administration *in vivo*, could activate SCSM and further promote T cell-mediated anti-tumor immunity (42).

These findings suggest that, besides serving as prognostic biomarkers, SCSM could serve as crucial therapeutic targets in cancer treatments.

Extensive clinical and fundamental literatures have concentrated on the role of SCSM in cancer. The current and further studies in this field of research mainly focus on four key aspects. Firstly, the mechanism of SCSM in pathogens immunity has been demonstrated to be more specific than tumor immunity. It is worthwhile to investigate the comprehensive molecular mechanism that underlies the alternation of SCSM in cancer microenvironment, including the process and presentation of phagocytosed TEVs and tumors cells in SCSMs, the direct and indirect activation of effector cells by SCSM through cross-presentation of tumor antigen and cytokines, as well as SCSM apoptosis during tumor progression and cytotoxic therapy. Secondly, while most studies have demonstrated the anti-tumor role of SCSM through the depletion of TEVs and priming of CTLs, the protumor effect of SCSM has also been established. Therefore, it is worth investigating how the microenvironment regulates the two different roles of SCSM in tumor development. Third, the low abundance and sensitivity to manipulation are two challenges that model systems face in the study of SCSM. During the preparation and extraction, SCSM could easily undergo fragmentation, and released blebs could be captured by associated cells, resulting in a CD169 positive stain for lymphocytes that have acquired SCSM-derived membrane blebs (23,78). The *in vitro* purification of SCSM with the fluorescence-activated cell sorting (FACS) could be greatly hampered. Additionally, the existing models that explore the role of SCSM in tumors are primary based on cell-derived xenograft or involving exposing murine to tumor-related components. However, it is plausible that SCSM could have a more practical clinical application in tumor induced animal models. Therefore, the development of novel models to investigate SCSM could directly promote research on the mechanisms between SCSM and microenvironment. Moreover, the exploration of the clinical applications of SCSMs is meritorious. Recent studies have elucidated a profound association between the density of SCSM and the long-term prognosis of patients with carcinomas. The clinical utility of SCSM as a prognosis factor necessitates establishment across a broad spectrum of malignant diseases in further studies. Nevertheless, the density of SCSM is closely correlated with nodal stage in several cancers. Given the pivotal role of SCSMs as the gatekeeper of LNs, their function could be altered at the early stage of regional LNs metastasis. Further studies are required to determine whether SCSM can serve as an indicator in micrometastasis and help the guidance of clinical decision. Additionally, while naringin and naringenin exhibit potential in activating SCSMs for clinical therapy, recognizing SCSM as a therapeutic target in cancer treatment necessitates further investigations (42,56).

Conclusions

In recent years, a multitude of studies have substantiated the correlation between SCSMs and favorable prognosis in patients with malignant diseases and delved into the mechanisms underlying the role of SCSM in tumor immunity and progression. SCSM could capture TEVs and tumor cells, cross-prime effector cells, and secrete crucial cytokines at the early stage of tumor progression. The exploration of SCSMs not only contributes to a deeper understanding of tumor immunity but also holds promise for the innovation of novel therapeutic modalities. In future studies, the detailed mechanisms, models to explore SCSMs and their clinical value could be expected to be validated.

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Footnote

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