Alteration of Macrophage Infiltrating Compartment: A Novel View on Oral Carcinogenesis

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Keywords
Oral carcinogenesis · Macrophage · Infiltrating compartment

Abstract

Background: The mortality of oral squamous cell carcinoma (OSCC) has remained high for decades; therefore, methods for early detection of OSCC are warranted. However, in the oral cavity, various mucosal diseases may be encountered, including reactive lesions and oral potentially malignant disorders, and it is difficult to differentiate OSCC from these lesions based on both clinical and histopathological findings. It is well known that chronic inflammation contributes to oral cancer development. Macrophages are among the most common inflammatory cells in cancer stromal tissue and have various roles in cancer aggressiveness. Although the roles of macrophages in cancer development have attracted attention, only a few studies have linked macrophages to carcinogenesis, particularly, oral precancerous lesions. Summary: This review article consists of 3 parts: first, we summarize current knowledge on macrophages in human various epithelial precancerous lesions, excluding the oral cavity, to show the importance and gaps in knowledge regarding macrophages in carcinogenesis; second, we review published data related to the role of macrophages in oral carcinogenesis; finally, we present a novel view on oral carcinogenesis, focusing on crosstalk between epithelial cells and macrophages. Key Messages: The biological features of macrophages in oral carcinogenesis differ drastically depending on the anatomical compartment that they infiltrate. Focusing on the alteration of macrophage infiltrating compartment may serve as a useful novel approach for studying the role of the macrophages in oral carcinogenesis and for gaining further insight into cancer prevention and early detection.

Introduction

Histologically, most malignant tumors in the oral cavity are diagnosed as oral squamous cell carcinoma (OSCC). The mortality rate of OSCC is high, and it has remained largely unchanged for the past several decades [1]. Therefore, steps toward prevention and efficient methods for early detection are desired. Moreover, the precise mechanism of oral early carcinogenesis should be clarified. Oral leukoplakia (OL) is a common precancerous lesion, and it has been reported that 0.13–34.0% of
these develop into OSCC [2]. The malignant potential of OL is associated with the degree of epithelial dysplasia, and this observation has resulted in improved prognosis in patients with OSCC. Therefore, many research groups have investigated oral carcinogenesis, focusing on epithelial dysplasia in OL; however, the underlying mechanism has not been fully elucidated. The main reason for this is that the conventional method for histological evaluation of OL is challenging compared with that of other precancerous lesions. In fact, several researchers proposed that local biopsy of OL is likely to underdiagnose the condition [3, 4], and oral epithelial dysplasia is distinct from other types of epithelial dysplasia found in the head and neck region according to the World Health Organization classification [5].

OSCC is a cancer closely associated with chronic inflammation. Risk factors include not only cigarette smoking and alcohol use but also oral specific factors, such as dental trauma and the presence of periodontopathogenic bacteria [6–11]. In addition, chronic inflammatory-like oral diseases, including OL and oral lichen planus, exhibit malignant potential in association with OSCC [12]. Based on this knowledge, independent carcinogenic mechanisms in association with chronic inflammation in the oral epithelium should be considered, when establishing the diagnosis and designing efficacious treatment strategies for patients with oral precancerous lesion.

**Macrophages in Cancer Microenvironments**

Chronic inflammation is considered a major pathological feature of tumor development. Inadequate elimination of the inflammatory response leads to various cancer-associated disorders [13]. Moreover, Dvorak [14] proposed that tumors are wounds that do not heal, and accumulating investigations have added support to this hypothesis [15–19]. Therefore, in cancer tissue, infiltration and activation of inflammatory cells are observed in the same manner as in the wound healing process, and it could be considered that the cancer microenvironment, in which such biological responses occur, enhances the malignant phenotype of cancer cells.

Inflammation can either prevent/restrain or shape/promote tumor development, and tumorigenesis-associated inflammation is referred to as “cancer immunoediting,” which proceeds through the 3 phases known as “elimination,” “equilibrium,” and “escape” [20–22]. However, it has not been entirely elucidated how oral carcinogenesis is interpreted in this context.

It is well known that macrophages infiltrate various types of human cancer tissue, a pathological manifestation associated with a poor prognosis [23–25]. The dual role of macrophages has been explained by their functional plasticity. M1 (classically activated) macrophages produce type I proinflammatory cytokines such as interleukin (IL)-1β, IL-1α, IL-12, tumor necrosis factor-α, and glial fibrillary acidic protein [26, 27]. Conversely, M2 (alternatively activated) macrophages produce type II cytokines, such as IL-4, IL-6, and IL-10, promoting anti-inflammatory responses [27, 28]. Phenotypically, inducible nitric oxide synthase, human leukocyte antigen-DR, CD80, CD86, CD169, and TLRs 2 and 4 are induced by M1 macrophages, whereas M2 macrophages upregulate CD163, CD204, CD206, and arginase-1 [29].

From an oncological viewpoint, the concept is widely accepted that M1 macrophages are tumor suppressive, whereas M2 macrophages have tumorigenic functions [30–33]. M1 macrophages facilitate tumor-specific antigen presentation [34]. Moreover, M1 macrophages reportedly kill cancer cells by tumor-killing molecules (such as reactive oxygen species or nitric oxide) or antibody-dependent cellular cytotoxicity [35]. Conversely, M2 macrophages are widely known to promote tumorigenesis, angiogenesis, matrix remodeling, and metastasis [36]. Cancer metastasis is a critical cause for the lower survival rate of patients with malignancies. It has been revealed that several macrophage-derived humoral factors contribute to the migration of cancer cells [37–42]. In addition, the relationship between macrophages and epithelial-to-mesenchymal transition, which is a basic process in metastasis, has also been shown [43–45].

A therapeutic strategy that can target macrophage polarization has been proposed. Corosolic acid and oleanolic acid inhibited the proliferation of glioblastoma cells by suppression of M2 skewing of macrophages [46, 47]. The repolarization of the M2 macrophage to an M1 phenotype normalized the structure of the tumor blood vessels, whereas M2 macrophages were involved in the formation of abnormal dysfunctional blood vessels [48–52]. As described above, the M1/M2 balance of macrophage polarization has been considered an important concept in the tumor microenvironment.

**Tumor-Associated Macrophages in OSCC**

Macrophages infiltrating cancer tissue are named tumor-associated macrophages (TAMs), and a considerable proportion of these are skewed toward the M2 phe-
notype [53, 54]. Many studies of OSCC reported the significance of TAMs. Levels of CD11b-positive myeloid cells and CD206-positive TAMs are increased in human OSCC specimens during postradiotherapy recurrence [55]. On the other hand, most of human OSCC studies have used CD163 as an M2 macrophage marker. TAMs expressing CD163 significantly correlated with a poor prognosis in OSCC patients [56–60]. Currently, CD163 might be considered a more suitable M2 marker in OSCC patients. However, Xiao et al. [61] demonstrated that migration of OSCC cells was promoted by M1-like macrophages activated by exosome-transferred THBS1. Moreover, TAMs in oral premalignant lesions coexpress CD163 and STAT1, suggesting that the TAMs involved in oral precancerous lesions exhibit the M1 phenotype in a Th1-dominated microenvironment [62]. These studies introduced the hypothesis that macrophages might exhibit not only the M2 but also the M1 phenotype in oral carcinogenesis.

### Table 1. The oncogenic roles of macrophages in human epithelial tumors excluding those of the oral cavity

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Human-macrophage marker</th>
<th>Roles of macrophages (references)</th>
</tr>
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<tbody>
<tr>
<td>Laryngeal carcinogenesis</td>
<td>CD68</td>
<td>Progression from premalignant lesions to malignancy [63]</td>
</tr>
<tr>
<td></td>
<td>CD163</td>
<td>Positive correlation between the number of intraepithelial CD163+ macrophages and the histological grade of dysplasia [64]</td>
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<tr>
<td>Gastric carcinogenesis</td>
<td>CD204</td>
<td>Proliferative activity in gastric adenoma [65]</td>
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<tr>
<td>Colorectal carcinogenesis</td>
<td>CD204</td>
<td>Micro vessel density, proliferation, and p53 expression of colorectal adenoma [66]</td>
</tr>
<tr>
<td></td>
<td>CD68 and CD163</td>
<td>Morphology and size of polyploid and nonpolyploid precancerous lesions in colorectal adenoma [67]</td>
</tr>
<tr>
<td>Hepatocellular carcinogenesis</td>
<td>–</td>
<td>Alcohol-related liver disease [68]</td>
</tr>
<tr>
<td>Cholangiocarcinogenesis</td>
<td>CD163</td>
<td>Tumor cells and macrophages occasionally expressed PD-L1 in BilIN and IPNB in occupational cholangiocarcinoma [69]</td>
</tr>
<tr>
<td>Uterine cervical carcinogenesis</td>
<td>CD68</td>
<td>Progression of human uterine cervical neoplasia [70]</td>
</tr>
<tr>
<td></td>
<td>CD68 and CD163</td>
<td>The association between both CD68+ and CD163+ macrophages and high-risk HPV infection [71]</td>
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<tr>
<td></td>
<td>CD163</td>
<td>HPV infected cervical lesion severity [72]</td>
</tr>
<tr>
<td>Endometrial carcinogenesis</td>
<td>CD68</td>
<td>PR loss and progression of precancerous endometrial lesions [73]</td>
</tr>
<tr>
<td>Ovarian epithelial carcinogenesis</td>
<td>CD68, CD163, and CD204</td>
<td>Higher number of macrophages in borderline and malignant tumors than in benign tumors [74]</td>
</tr>
<tr>
<td>Prostate carcinogenesis</td>
<td>CD68 and CD204</td>
<td>The high CD204+ versus CD68+ ratio increased in PIN and adenocarcinoma [75]</td>
</tr>
<tr>
<td>Breast carcinogenesis</td>
<td>CD68</td>
<td>Higher levels of CD68+ macrophages in high-grade DCIS [76]</td>
</tr>
<tr>
<td></td>
<td>CD163</td>
<td>Stromal M2 macrophages in DCIS predict recurrence [77]</td>
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</tbody>
</table>

CD, cluster of differentiation; IL, interleukin; PD-L1, programmed death-ligand 1; BilIN, biliary intraepithelial neoplasia; IPNB, intraductal papillary neoplasm of the bile duct; HPV, human papillomavirus; PR, progesterone receptor; PIN, prostatic intraepithelial neoplasia; DCIS, ductal carcinoma in situ.
dometrium, ovary, prostate, and breast (Table 1). The immunohistochemical investigations leading to these observations used CD68 [63, 67, 70, 71, 73–76], CD163 [64, 67, 69, 71, 72, 74, 77] or CD204 [65, 66, 74, 75] as macrophage markers in human clinical samples. Interestingly, several studies of human squamous cell carcinogenesis identified CD163 as a suitable marker. However, the investigations of other types of carcinogenesis also used CD163. It has been speculated that the association between macrophage markers and carcinogenic stage might differ depending on the histological type involved.

Interestingly, only one study showed the significance of intraepithelial macrophages in laryngeal epithelial dysplasia using human clinical samples [64]. Although the significance of the interaction between epithelial cells and macrophages has been well established by in vitro or in vivo experiments, further studies of epithelial cell-macrophage interaction focusing on macrophage distribution are required.

Recently, the contribution of macrophages to alcohol-related liver carcinogenesis was studied [68]. Several investigators demonstrated a relationship between macrophages and human papillomavirus infection [71, 72]. Because human papillomavirus infection is widely known to be major risk factors of OSCC [5], it is speculated that the carcinogenic mechanism proposed in these studies of cervical cancer could be applied to the progression of oral precancerous lesions. The macrophage skewing depends on each risk factor, and it is the combination of these that constitutes the carcinogenic microenvironment.

Suitable Macrophage Markers in Oral Carcinogenesis

Most studies of macrophages in oral carcinogenesis have been performed focusing on CD163 expression [62, 78, 81–84, 91]. We previously confirmed that the number of infiltrating CD163+ macrophages but not the numbers of CD206+ and CD204+ macrophages significantly correlated with various clinicopathological factors in patients with tongue leukoplakia (TL) [78]. Another study relying on immunohistochemical analyses demonstrated CD68+ and CD163+ macrophage infiltration in carcinoma in situ (CIS), while the number of CD204+ cells was substantially lower [79]. Meanwhile, CD204+ macrophages significantly correlated with the recurrence and cancerization of patients with oral epithelial precancerous lesions [80]. The reason for this discrepancy is unknown. Since oral precancerous lesions include multiple diseases in addition to OL [5], the expression of these markers may differ depending on the pathogenesis of each disease.

Macrophage Polarization in Oral Carcinogenesis

Regarding macrophage polarization in oral carcinogenesis, M1/M2 dichotomy should be carefully considered. The first reason is that no ideal immunohistochemical markers exist to detect M1 macrophages [29]. Additionally, in a monoculture assay, it was reported that monocytes weakly express CD163 [79]. Mori et al. [62] demonstrated that CD163+ macrophages in OL express STAT1, which is known as an M1-related marker. In OL with malignant transformation tissue, the number of macrophages expressing CD11c, one of the M1 markers, was significantly higher than in OL with nontransformation [81]. Another study of OL focused on signal regulatory protein α (SIRPα), which primes phagocytosis of cancer cells. This study showed that the percentages of CD163+ or CD68+ macrophages coexpressed with SIRPα were higher in OL as compared with OSCC, and a coculture system of macrophage-like cells and oral cancer cells revealed transitory upregulation of SIRPα expression [82]. It was speculated that macrophages are educated by M1-inducible stimulation and are switched to the M2 phenotype due to acquired resistance by any mechanism(s) in oral carcinogenesis. It would be reasonable to hypothesize that macrophages show overlapping phenotypes of M1 and M2 during oral carcinogenesis.

Interestingly, a study using human OSCC samples revealed that in contrast to macrophages expressing CD163, inducible nitric oxide synthase-positive macrophages were distributed in the tumor periphery, the peritumoral noncancerous area, and in the subepithelial stroma of OL. This study suggested that macrophages are educated by tumor cells to polarize from M1 to M2 along with carcinogenic progression [83]. It could be expected that the biological features of macrophages located in the stroma are not identical to those of the intratumoral macrophages.

Moreover, we previously evaluated the role of macrophages in benign lesions that are difficult to distinguish from oral cancer. In oral candidiasis, oral lichen planus, and aphthous stomatitis, CD163+ macrophages were present in the subepithelial area but not in the epithelial area [84]. In oral verruciform xanthoma, which is a rare reactive lesion characterized by accumulation of foamy macrophages in the stroma, it was suggested that foamy
cells express the M2 marker CD163+ and may be involved in morphogenesis by vascular endothelial growth factor expression-mediated angiogenesis [85]. These findings stress that it is difficult to establish a discrimination system of M1 and M2 macrophage phenotypes in oral mucosal lesions based only on macrophage markers.

**The Distribution of Macrophages in Oral Carcinogenesis**

Forty-five years ago, researchers observed macrophages in oral dysplastic epithelium. The macrophages phagocytosed dysplastic epithelial cells [86, 87]. In 1995, it was showed that macrophages were rarely present in healthy oral epithelium [88]. It was also reported that the number of macrophages increased in the subepithelial tissue of OL with dysplasia [88]. In 2015, an immunohistochemical study was performed based on macrophage polarization and revealed that CD163-expressing macrophages are deployed to the stromal area in OL [62]. The important point to note is that many researchers have proposed that most macrophages in OL infiltrate into the subepithelial stroma [62, 78, 82, 83, 88–91]. Reportedly, in early stages of squamous cell carcinoma of the lower lip, neoplastic epithelial cells recruited macrophages into their microenvironment to escape antitumor immune responses [92]. We previously demonstrated the correlation of subepithelial CD163+ macrophage infiltration with immunosuppressive cytokine IL-10 expression in TL [78]. A "distant" crosstalk separated by the basement membrane between epithelial cells and stromal macrophages may be formed in the early stage of oral carcinogenesis.

Meanwhile, some studies observed intraepithelial macrophages in CIS [79, 93]. Our retrospective immunohistochemical analysis using TL biopsy specimens and consecutive resected specimens revealed that the TL with invasive cancer had significantly higher numbers of intraepithelial CD163+ macrophages than the TL with non-invasive cancer [84]. We recently observed intraepithelial CD163+ macrophages in a case of oral lichenoid disease with malignant potency [94]. Interestingly, Weber et al. [81] demonstrated that malignant transformation of OL is significantly associated with macrophage infiltration toward the epithelium using not only CD163 but also CD11c, which is an M1-related marker. Their findings support the theory that the M1 macrophage phenotype overlaps with the M2 phenotype in oral carcinogenesis. They also suggest that macrophages exhibit different biological features depending on the compartment that they infiltrate and that direct contact of macrophages with epithelial cells is important in the malignant transformation of OL. In fact, macrophages/oral cancer cell adhesion via ICAM-1 was reported based on both in vitro assays and immunohistochemical examination [95]. Additionally, macrophages cocultured directly with oral cancer cells induced CD204 expression [79].

These findings indicate that the dramatic change in macrophage localization could help identifying OL patients with malignant potential, and it has been speculated that the adhesion of these cells contributes to oral carcinogenesis. Meanwhile, microscopic observations revealed that the number of epithelial cells is substantially higher than macrophages. Therefore, it is reasonable to consider that not only these adhesive mechanisms but also interaction through humoral factor(s) should be taken into consideration. This “close” crosstalk between epithelial cells and macrophages may be an important promoter of oral carcinogenesis.

**The Association of Macrophages with Risk Factors of Oral Cancer**

Considering oral cancer as a wound that does not heal, it would appear relevant to hypothesize that the “close” crosstalk between epithelial cells and macrophages, which is induced by smoldering inflammation, contributes to oral carcinogenesis. There are some reports on the relationship between macrophages and specific smoldering inflammation in the oral cavity. Incisional biopsy-induced tissue trauma skewed macrophage polarization toward the M2 phenotype and promoted tumor progression [96]. This mechanism may also be triggered by inadequately fitting dentures, rough teeth surfaces, or inadequate tooth brushing. In addition, it was reported that intraepithelial entrapped blood vessels in CIS are broken down by mechanical stress from growing neoplastic cells [97]. This study hypothesized that macrophage expression of CD163 may be induced to scavenge the collapsed vessels.

With respect to links between macrophages and other risk factors, matrix metalloproteinase 12 expressed in most macrophages plays a significant role in remodeling events occurring in connective tissue during exposure to sunlight in actinic cheilitis [98]. In addition, it was shown that the expression of CD204-positive macrophages in female OSCC patients was higher than that in male patients [80]. Therefore, sex-related hormonal abnormalities or autoimmune diseases may be involved in macrophage infiltration in oral carcinogenesis.
Although periodontal bacterial infection is widely accepted as an independent risk factor in several cancers, including OSCC [99], to the best of our knowledge, the relationship between macrophages in periodontitis and oral carcinogenesis has not been fully clarified. The main reason may be that it is difficult to tease out the M1/M2 dichotomy in periodontitis. In a mouse model, both M1 and M2 macrophage phenotypes were observed in normal gingival tissue, and it was speculated that this mixture of phenotypes might be necessary for tissue homeostasis and immune defense against the commensal oral flora [100]. Furthermore, it was also reported that the prickle cell layer of the masticatory mucosa, including the dorsum of the tongue, gingiva, and palate, expresses PD-L1 under physiological conditions [101]. These reports suggest the peculiarity of the oral mucosa with potentially complex mechanisms in place to prevent excessive inflammation. Further investigation of the role of macrophages in periodontitis-related oral carcinogenesis using human samples is required.

### Table 2. The role of macrophages in oral carcinogenesis

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<th>Topic</th>
<th>Remarks (references)</th>
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<tr>
<td>Macrophage marker</td>
<td>The significance of macrophages in oral carcinogenesis focusing on CD163 [62, 78, 81–84, 91]</td>
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<tr>
<td></td>
<td>CD206* macrophages were overtly less in number when compared with CD163* macrophages in OL [78]</td>
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<td></td>
<td>The lower level of infiltration of CD204* macrophages compared with CD68* and CD163* macrophages in CIS [79]</td>
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<tr>
<td></td>
<td>The correlation of CD204* macrophages with the recurrence and cancerization of oral epithelial precancerous lesions [80]</td>
</tr>
<tr>
<td>Macrophage polarization</td>
<td>CD163* macrophages in OL express STAT1, which is known as an M1-related marker [62]</td>
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<td></td>
<td>The association of malignant transformation of OL not only with CD163 but also with CD11c [81]</td>
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<tr>
<td></td>
<td>The proportions of CD163* or CD68* macrophages coexpressed with SIRPα were increased in OL compared with OSCC [82]</td>
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<td>Compared with CD163* macrophages, iNOS* macrophages were more commonly distributed in the subepithelial stroma of OL [83]</td>
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<tr>
<td>Distribution of macrophages</td>
<td>Macrophages in phagocyte dysplastic epithelial cells [86, 87]</td>
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<td></td>
<td>Macrophages in oral normal epithelium were rare [88]</td>
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<td></td>
<td>Infiltration of macrophages into the subepithelial stroma of OL [62, 78, 82, 83, 88–91]</td>
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<td>The immunosuppressive activity of the M2 macrophages is particularly important in the early stages of lip carcinogenesis [92]</td>
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<td></td>
<td>Observations of intraepithelial macrophages in CIS [79, 93]</td>
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<td></td>
<td>High numbers of intraepithelial CD163* macrophages were observed in TL with invasive cancer compared with TL with noninvasive cancer [84]</td>
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<td>Malignant transformation of OL correlated with macrophage infiltration toward the epithelium [81]</td>
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<td>Intraepithelial CD163* macrophages were observed in OLD with malignant potency [94]</td>
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<td>Incisional biopsy-induced tissue trauma skewed macrophage polarization toward the M2 phenotype [96]</td>
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<td></td>
<td>Macrophage-derived MMP12 in remodeling events in the connective tissue of AC [98]</td>
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<tr>
<td></td>
<td>The relationship between macrophages involved in periodontitis and oral carcinogenesis remains to be clarified [no previous report]</td>
</tr>
</tbody>
</table>

CD, cluster of differentiation; TL, tongue leukoplakia; OL, oral leukoplakia; SIRPα, signal regulatory protein α; OSCC, oral squamous cell carcinoma; CIS, carcinoma in situ; iNOS, inducible nitric oxide synthase; SCC, squamous cell carcinoma; OLD, oral lichenoid disease; MMP, matrix metalloprotease; AC, actinic cheilitis.
Discussion and Future Perspective

Many studies have shown the contribution of macrophages to oral carcinogenesis (Table 2). Most of these findings focused on CD163 as a macrophage marker. A strict distinction between M1- and M2-type macrophages may be of limited relevance in studies of oral carcinogenesis. It is speculated that this situation may be specific to the oral epithelium, which is continuously exposed to various inflammatory risk factors. Therefore, alternative views on the role of macrophage feature and methods to differentiate these in oral carcinogenesis are warranted.

Figure 1 provides morphological and CD163 immunohistochemical images of the multistage oral carcinogenesis involved in a surgically resected specimen. In Figure 2, we propose our working hypothesis on the interaction between macrophages and epithelial cells in oral carcinogenesis. When “smoldering inflammation” occurs in the oral mucosa, CD163+ macrophages are deployed to the subepithelial stroma, especially to beneath the basement membrane, to prepare for cancer immunoediting. Following this, the “distant” interaction between macrophages and epithelial cells induces the migration of macrophages to the epithelial area through switching of immunoediting from tumor dormancy to uncontrolled tumor outgrowth. More importantly, once the lesion develops into invasive cancer after the appearance of a few intraepithelial macrophages, more CD163+ macrophages infiltrate into the cancer nest and in the tissue surrounding the invasive cancer, and the “close” crosstalk between epithelial cells and macrophages is initiated. Macrophages are further polarized to the M2 phenotype (so-called...
TAMs) and stimulate the invasive and metastatic potential of the epithelial cells. Here, we would like to propose that the clarification of oral carcinogenesis focusing on the alteration of crosstalk between epithelial cells and macrophages from “distant” to “close” may provide noteworthy targets for prevention and early detection of OSCC.

**Conclusion**

In conclusion, the biological features of macrophages in oral carcinogenesis differ drastically depending on the anatomical compartment that they infiltrate. Targeting the alteration of macrophage compartment may be pivotal in early detection and effective therapeutics of OSCC.
Acknowledgements

The authors are grateful for the assistance provided by all present members of the Division of Pathology, Department of Pathology, Kobe University. We are also grateful to Emeritus Prof. Takahide Komori (Kobe University) and all collaborators who kindly supported the research.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Funding Sources

This work was supported by Grant-in-Aids for Scientific Research (19K19157) from the Japan Society for the Promotion of Science.

Author Contributions

M.S. contributed to conceiving the idea, searching the literature, and drafting the manuscript. Y-I.K. and M.N. revised the manuscript. M.A. contributed to reviewing the data. H.Y. supervised the study. All authors reviewed and approved the final version of the manuscript.


Novel View on Oral Carcinogenesis
Focusing on Macrophages


