Microenvironment in Oral Potentially Malignant Disorders

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The microenvironment of Oral potentially malignant disorders (OPMDs) refers to the ecosystem that surrounds the potentially malignant cells. It is a complex structure comprised of cellular and non-cellular components. Cellular components include potentially malignant cells, normal epithelial cells, fibroblasts, and immune cells. While the non-cellular environment is composed of molecules including cytokines and cell surface molecules, and structures such as blood vessels and lymphatic vessels. According to its multi-dimensional characteristics, the microenvironment can be categorized into the immune, metabolic, mechanical, and neural microenvironment. The microenvironment of OPMDs is closely related to carcinogenesis and cancer progression by regulating the immune response, cell metabolism, mechanical trait, and neural activity. Meanwhile, it also undergoes extensive changes during the carcinogenesis of OPMDs and gradually develops into an immunosuppressive, acidic, and stiff one. In addition, there is a wide range of interactions among immuno–metabolic–mechanical–neural microenvironments, which regulate the carcinogenesis of OPMDs synergistically.

Keywords: cancer chemoprevention ; carcinogenesis ; immune–metabolic–mechanical microenvironment

1. Introduction

Oral potentially malignant disorders (OPMDs) refer to any oral mucosal abnormality associated with an increased risk of developing oral squamous cell carcinoma (OSCC) [1]. They mainly include oral leukoplakia (OLK), oral lichen planus (OLP), oral submucous fibrosis (OSF), oral lichenoid lesions (OLL), and oral erythroleukoplakia (OEL) [1]. The overall rate of carcinogenesis across all OPMDs types is 7.9% [2]. The rate of carcinogenesis in the individual OPMDs is 1.4% for OLP, 9.5% for OLK, 3.8% for OLL, 5.2% for OSF, and 33.1% for OE [2]. The 5 year overall survival rate of OSCC patients is still less than 60%, which affects the patient's quality of life and mental health greatly [3].

The microenvironment of OPMDs means the cells, molecules, and structures (such as blood vessels) that surround and support the cells and tissue of OPMDs. It undergoes changes and promotes the carcinogenesis of OPMDs significantly [4][5][6][7]. The potentially malignant cells, which refers to the cells that have a potential for carcinogenesis, undergo metabolic reprogramming. It usually inhibits the activation and function of immune cells, and remodels the extracellular matrix (ECM) [4][6]. The immune cells also undergo metabolic reprogramming and remodel the ECM to adapt to adverse conditions [8][9]. Vice versa, the changes in the ECM impede the immune cell response and change potentially malignant cells' metabolic behaviors [10][11]. Meanwhile, the nervous system plays a regulatory role in these microenvironments [7]. Furthermore, there are extensive and profound interactions among microenvironments, which amplify the carcinogenic effects [12][13]. Therefore, it is significant to elucidate the dynamic changes in microenvironments and look for targets for cancer chemoprevention.

2. Immune Microenvironment

The immune microenvironment refers to the complex milieu associated with various cellular and non-cellular components, including immune cells, cytokines, and cell-surface molecules [14]. It mainly exerts immunosurveillance, and plays a vital role in maintaining microenvironment homeostasis [15]. However, the immune microenvironment gradually becomes suppressive as OPMDs progress and favors the immune escape.

2.1. Cellular Components

The cellular components of the immune microenvironment is mainly comprised of immune cells and fibroblasts. The former is divided into innate and adaptive immune cells, while the fibroblasts are now acknowledged as a non-classical branch of the innate immune system [16][17]. The innate immune cells exert immune effects through phagocytosis, antigen

presentation, and cytokine secretion, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α) [18]. Additionally, the adaptive immune cells are involved in immunosurveillance through humoral and cellular immune responses [19]. The cell components change significantly during OPMDs carcinogenesis, from a protective to a carcinogenic response, which determines the fate of the OPMDs progression, and is an exciting issue to figure out.

Neutrophils are the first line of innate immune defense, maintaining the chronic inflammatory state by circulating cytokines [20]. Neutrophil infiltration is observed in both OLP and OLL [21]. Furthermore, increased activated neutrophils from the peripheral blood flow into the oral tissue in the presence of chronic inflammation [22]. Neutrophils are proven to be associated with the potential transformation to OSCC. The N1 to N2 phenotype conversion of neutrophils triggered by the B-cell activating factor inhibits the immune response in OLP and, thus, may favor the carcinogenesis progression [23]. N1 and N2 neutrophil phenotypes are classified depending on their functions. N1 neutrophils mainly promote immune responses, while N2 neutrophils exhibit immunosuppressive effects [20]. In addition, neutrophils can also produce neutrophil extracellular traps (NETs) to participate in the progression of OPMDs [24]. Existing evidence indicates that the role of NETs in OLP carcinogenesis is relatively complex. Jablonska et al. [25] reveal that the neutrophils isolated from OLP exhibit a strong ability to produce NETs, with the accompanying characteristic changes of components such as citrullinated histone H3 and myeloperoxidase. The citrullinated histone H3 stimulates the immune cells to generate TNF-α. TNF-α is proven to induce changes in both stroma and epithelial cells, by enhancing the invadopodia development of keratinocytes and matrix degradation [26][27][28]. However, the myeloperoxidase in neutrophils serves a vital role in killing the potentially malignant cells [29]. Hence, NETs production shows bidirectional functions, both in carcinogenic and anti-carcinogenic effects, by immune regulation and cell behavior modulation. It is not currently clear which effect is dominant.

Dendritic cells (DCs) are considered the most professional antigen-presenting cells bridging innate immunity to adaptive immunity. They play essential roles in immunosurveillance, mainly through T cell activation [30]. Compared with OSCC, more CD1a+ and CD207+ DCs infiltrate in OSF and OLK [31]. DCs are proven to inhibit the carcinogenesis of OPMDs. Anna et al. [32] found that the vaccine, which is a mix of DCs collected from femur bone marrow and premalignant tissue lysate, significantly decreases the lesion burden in 4NQO-treated mice. It can increase the total infiltration of lymphocytes and their immunosurveillance function, thus, preventing the carcinogenesis of OPMDs effectively [32].

Macrophages perform a potent immunosurveillance function, based on their ability in phagocytosis, cytokine secretion, and antigen presentation [33]. Macrophages can be typically divided into M1- and M2-polarized subtypes, according to their functions. M1 macrophages are pro-inflammatory, while M2 macrophages are anti-inflammatory [34]. Due to their indispensable roles in modulating the immune response, macrophages are essential in OPMDs carcinogenesis. The infiltration of macrophages, especially CD163+ M2 macrophages, is positively associated with the carcinogenesis of OPMDs [35]. Shigeoka et al. [36] found that OLK with high CD163+ M2 macrophage infiltration is associated with higher degrees of epithelial dysplasia. The M2 macrophages exert strong immunosuppressive and pro-carcinogenic effects, by producing anti-inflammatory cytokines, especially IL-10, and promoting the activation and function of Tregs [36]. However, Bouaoud et al. [37] observed an unexpected anti-carcinogenic effect of M2 macrophages. The high expression of the M2 macrophage gene is significantly positively correlated with oral cancer-free survival in 4NQO-treated OPMDs mice. This may be relevant, as the biological features of macrophages in oral carcinogenesis differ drastically depending on the anatomical compartment that they infiltrate [38]. Meanwhile, macrophages are extremely plastic during macrophage polarization, so they may not be completely either the M1 or M2 type, which affects the OPMDs carcinogenesis in different ways [37]. All in all, the more complex roles of macrophages require more attention and further investigation.

Mast cells are major innate and adaptive immune effector cells by potent degranulation [39]. Previous studies show that the mast cells may be involved in OPMDs carcinogenesis [40][41]. The mast cell density is statistically higher in OSCC than in OPMDs [40][41]. In addition, the mast cells promote angiogenesis through improving the expression of angiogenic factors, such as vascular endothelial growth factor (VEGF) and basic fibroblast growth factor in vascular endothelial cells [40][41]. The increased angiogenesis is a sign of carcinogenesis. That is, one of the mechanisms of mast cells promoting carcinogenesis is to promote angiogenesis, but more mechanisms remain to be studied.

Myeloid-derived suppressor cells (MDSCs) can induce strong immunosuppressive activity by expressing various cytokines and inhibiting the activity of T and NK cells [42]. MDSCs are also intimately associated with OPMDs carcinogenesis. The infiltration of CD33+ MDSCs in OSCC is significantly higher than in OPMDs. Further, MDSCs induce immunosuppression via inhibiting the activation and function of NK cells and cytotoxic T lymphocytes (CTLs), and secreting various cytokines, such as IL-10 and TGF-β [43]. The increased infiltration of MDSCs is consistent with the formation of a suppressive immune microenvironment during OPMDs carcinogenesis. These results suggest that MDSCs participate in the formation of an immunosuppressive microenvironment and the carcinogenesis of OPMDs, to a certain extent.

T cells are one kind of critical adaptive immune cell, which can be further subdivided into helper T cells (Th cells), CTLs, and regulatory T cells (Tregs) according to their immune functions. Th cells mainly secrete various cytokines, such as interferon-γ (IFN-γ), TNF-α, IL-2, and IL-4, to mediate immunity. CTLs can directly kill targeted cells via cytotoxic effect. Tregs mainly secrete cytokines such as IL-2, IL-10, and TGF-β, to exert an immunosuppressive effect [44]. Different studies have controversial conclusions about various T cell subtypes infiltrations in OPMDs and OSCC. Some studies found that CD4+ and CD8+ T cells infiltration in OSCC is lower than OLK [45], while others reach the opposite conclusions [46]. Such a large discrepancy may relate to the differences in samples and experimental conditions between different studies. Although T cells infiltration is different in different studies, the immune changes mediated by T cells is consistent. The immune response mediated by T cells is gradually suppressed as the OPMDs progress. On the one hand, the Foxp3+ Treg expression is positively correlated with the grade of OLK dysplasia [47]. On the other hand, the function of CTLs is gradually inhibited with the carcinogenesis process, and the expression of inhibitory immune checkpoints, such as programmed cell death protein-1 (PD-1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), and lymphocyte-activation gene-3 (LAG-3), are up-regulated [48]. In addition, the cytokines such as IL-10 and TGF-β, secreted by T cells, also increase gradually with the progression from OLK without dysplasia, low-grade OLK, and high-grade OLK to OSCC [4]. In this case, CD4+ Th cells and CD8+ CTLs become exhausted, and the anti-carcinogenesis effect is gradually diminished. Meanwhile, the activation and function of Tregs are enhanced, leading to enforced immunosuppression.

Fibroblasts are the predominant cellular components of stroma, emerging as critical immune sentinel cells in regulating the immune response [49]. They are involved in immune regulation by activating inflammatory pathways [49]. In view of the critical role of fibroblasts in immune regulation, they may also be involved in regulating OPMDs immune microenvironment. Khalid et al. [50] found that αSMA+ myofibroblasts increase with the progression of OPMDs from mild, moderate, and severe dysplasia to eventual OSCC. Functionally, the activated fibroblasts are primarily involved in immunosuppression. They recruit MDSCs and Tregs, inhibit the function of T cells, and secrete TGF-β [17]. In addition, the fibroblasts increase the risk of OPMDs carcinogenesis, by enhancing the chance of infection by exogenous pathogenic microorganisms [51]. Previous research of a group proved that oral leukoplakia-associated fibroblasts reduce CX3CL1 secretion by inhibiting the ERK signaling pathway, thus, resulting in reduced resistance of OLK to candida albicans [51]. Further, the infection of candida albicans is recognized as a promotion factor for OLK carcinogenesis [52]. There are more relationships between fibroblasts and OPMDs to be recognized, and further carcinogenic mechanisms to be discovered.

2.2. Cytokines and Immune Checkpoints

The non-cellular components of the immune microenvironment mainly include cytokines and immune checkpoints, which are primarily involved in mediating cell communication and the functional state of cells. They are the main regulatory factors of immune responses, and control the proliferation, differentiation, and survival of immune cells [53]. The cytokines and immune checkpoints also exert an indispensable role in the carcinogenesis of OPMDs.

With the progression of carcinogenesis in OPMDs, the production of pro-inflammatory cytokine IL-17 decreases, and the production of anti-inflammatory cytokine TGF-β increases. It is possible that the immunosuppression induced by TGF-β plays a dominant role in carcinogenesis, rather than IL-17 [54]. In addition, cytokines also exert immunomodulatory effects by influencing the activation and function of immune cells. There is a close positive correlation between various cytokines and CD4+ and CD8+ T cells in 4NQO-treated OPMDs mice [55]. The immune checkpoints, including PD-1, CTLA-4, Ig and ITIM domains (TIGIT), LAG-3, and T cell immunoglobulin and mucin domain-containing pro-tein-3 (TIM-3), are the predominant cell-surface molecules. These cell-surface molecules significantly influence the immune response and regulate the functional status of immune cells [56]. Several results show the expression of PD-1/PD-L1 in the majority of OPMDs and OSCC samples, and their expression correlates with increased progression [57][58][59]. Blocking PD-1 or PD-L1 significantly reduces the number of oral lesions, and prevents the process of carcinogenesis in 4NQO-treated mice. It significantly increases the recruitment of CD4+, CD8+, and CTLA-4+ T cells and the expression levels of IFN-γ, STAT1, and granzyme B [60][61]. CTLA-4 is another important immune checkpoint, expressed in T cells in 4NQO-treated mice [62]. Blocking CTLA-4 also results in a significant reduction in Tregs and, thus, prevents OPMDs carcinogenesis [61][63].

3. Metabolic Microenvironment

The process of OPMDs carcinogenesis is due to the fact that cells constantly struggle with the surrounding environments. At the metabolic level, the potentially malignant cells constantly change their metabolic behaviors. These changes affect a wide range of cellular activities, and ultimately promote OPMDs development. The characteristics and the role of the OPMDs metabolic microenvironment is illustrated as follows.

3.1. Potentially Malignant Cells

A major feature of OPMDs carcinogenesis is the increased proliferation of potentially malignant cells. It requires an increase in metabolism to provide critical energy and substrates. However, the potentially malignant cells always proliferate away from the blood supply [64][65]. Subsequently, the high demand of metabolic activities and inadequate irrigation leads to increased anaerobic glycolysis, which leads to lactate accumulation in potentially malignant cells. At the same time, ion-exchange proteins on the cell membrane also continuously transport H+ inside the cell to the outside. These changes result in an acidic and hypoxic microenvironment. The acidic stress in a premalignant setting may increase genetic instability, including increased DNA double-strand break and the inhibition of DNA damage repair [65][66]. Moreover, the acidic microenvironment inhibits normal cell cycle progression, inhibits cell proliferation [65][67], and induces normal cell death through p53-dependent apoptotic pathways [68]. The changes in the metabolic microenvironment have a tremendous impact on cell biological behaviors: the death of normal cells increases and cells are more prone to mutation for survival. All these provide conditions for shaping a carcinogenic microenvironment.

The changes in a metabolic microenvironment, while always “carcinogenic” in general, also place selective pressure on potentially malignant cells. Only the potentially malignant cells that adapt to these conditions have a better chance of survival. The metabolic activity of potentially malignant cells increases significantly to obtain more energy and substrates. It is shown that the glycolysis is significantly enhanced in potentially malignant cells. The level of several key enzymes in glycolysis, including glucose transporter protein-1 [69][70], lactic dehydrogenase [71], and α -enolase, is found to be higher in OSCC than OPMDs. The up-regulated glycolysis promotes OPMDs carcinogenesis in multiple ways. On the one hand, the increased lactate level attenuates NK and T cell activation [72], and stimulates the polarization of macrophages to the M2 state, which leads to immunosuppression and immune evasion [73]. On the other hand, lactate also enhances the stabilization of hypoxia-inducible factor-1α, nuclear factor-κB, and phosphatidylinositol-3 kinase signaling, and induces the secretion of VEGF from endothelial cells. Thus, it participates in the proliferation and activation of potentially malignant cells and angiogenesis [74]. In conclusion, the up-regulated glycolysis allows the potentially malignant cells to acquire greater energy and substance, to better adapt to their high-cell-proliferation characteristics, and further facilitate OPMDs carcinogenesis by influencing the biological behaviors of other cells.

Other metabolic forms in OPMDs can also provide metabolic precursors for biosynthesis and energy production. The metabolic pattern of the tricarboxylic acid (TCA) cycle also exists in OPMDs, and is proven to be involved in OLP carcinogenesis. Yang et al. [75] found the accumulation of succinic acid, a key metabolite of the TCA cycle, in primary OLP keratinocytes. The accumulation of succinic acid in OLP is proven to induce apoptosis of potentially malignant cells and suppress oxidative phosphorylation, thereby reducing the risk of carcinogenesis [75]. Glycogen is another storage form of glucose. Its metabolism also affects OPMDs carcinogenesis. Compared with OPMDs, the expression of glycogenolysis enzymes, such as glycogen phosphorylase isoenzyme BB, is up-regulated in OSCC. In contrast, glycogenesis enzymes, including glycogen synthase and phosphor-glycogen synthase, are not significantly different. It suggests that the carcinogenesis of OPMDs is associated with increased glycogen synthesis. This is also consistent with increased energy metabolism in potentially malignant cells [76]. In addition, the plasma levels of total cholesterol, lipoprotein, and triglyceride in OSCC patients are significantly lower than those in OPMDs [77]. This is due to increased lipid metabolism in potentially malignant cells, leading to the constant lipid depletion in the body. The increased lipid metabolism can provide large amounts of energy and substrates for the rapid division and proliferation of potentially malignant cells [78]. Due to the increased biosynthesis of potentially malignant cells during carcinogenesis in OPMDs, the demand for nitrogen is increased. Therefore, the amino acid metabolism also plays a vital role in carcinogenesis [79]. Previous studies show that amino acid metabolism disorders may be involved in the carcinogenesis of OPMDs, by affecting the biosynthesis and metabolism of potentially malignant cells [79]. Chen et al. [80] identified several key differential metabolites, including pyruvate, glutamine, methionine, and lysine, from oral potentially malignant cells and normal human oral epithelial cells. They may contribute to the carcinogenesis of OPMDs by reprogramming the metabolism of potentially malignant cells [80]. In addition, the serum glutamine levels are also observed to increase approximately 2–26 folds in different stages of epithelial dysplasia and OSCC in DMBA-induced hamster models of oral carcinogenesis [81]. More mechanisms of amino acid in carcinogenesis of OPMDs require further investigation.

3.2. Stroma Cells

The metabolic activities of epithelial cells and their reprogramming of the metabolic environment play an essential role in carcinogenesis. However, the shaping of the metabolic microenvironment by stroma cells cannot be ignored. The stromal cells are influenced by the surrounding microenvironment and undergo metabolic reprogramming. It makes them better adapted to the changes in the microenvironment and attempts to reverse the unfavorable conditions.

As the most abundant component in the stroma, the metabolic activities of fibroblasts in shaping OPMDs microenvironment cannot be ignored. Previous results suggest that the lncRNAH19/miR-675-5p/PFKFB3 signaling pathway is involved in glycolytic reprogramming of cancer-associated fibroblasts (CAFs) and promotes OSCC progression [82]. However, the metabolism of fibroblasts in OPMDs seems to play an unexpected anti-carcinogenic role [65]. Both the stromal and potentially malignant cells can process lactic acid collaboratively, to eliminate the extracellular lactic acid load and avoid large-scale microenvironment acidification. The extracellular lactic acid produced by potentially malignant cells can be taken up by fibroblasts and enters the TCA cycle [83]. Subsequently, the excess lactic acid is consumed. In other words, on the one hand, the fibroblasts can utilize the generated energy to supply their own survival and activities. On the other hand, fibroblasts can avoid the formation of an acidic microenvironment and favor their own survival. Similarly, the immune cells also attempt to survive and exert immune function by metabolic reprogramming. The aerobic glycolysis rate of T cells is up-regulated, which is consistent with the nutrient transporters and glycolysis enzymes. The increased glycolysis improves ATP availability to meet energy requirements and provide the metabolic precursors necessary for effector function and proliferation [84]. In summary, the representative metabolic microenvironment in carcinogenesis of OPMDs is the essential selective factor for both potentially malignant cells and stroma cells. The potentially malignant cells remodel the microenvironment into a hypoxic and acidic one, which is beneficial to themselves, and inhibits the growth and function of other cells. Though the other cells also undergo metabolic reprogramming and try to change the unfavorable conditions, it, ultimately, still fails to arrest OPMDs progression.

4. Mechanical Microenvironment

The epithelial cells with carcinogenic mutations are not always sufficient to cause cancer. Although immune and metabolic microenvironments play promotive roles, the living environment of potentially malignant cells largely determines their fate. Therefore, the mechanical microenvironment, which represents the physical properties of the environment around potentially malignant cells, cannot be ignored. The process of carcinogenesis is always accompanied by increased matrix stiffness and higher interstitial fluid pressure [85]. These mechanical properties are closely related to the carcinogenesis of OPMDs.

The increased tissue stiffness due to ECM deposition is a classic characteristic of carcinogenesis. Compared with OSF without epithelial dysplasia, the number of αSMA+ myofibroblasts in OSF with epithelial dysplasia increases. The fibroblasts increase matrix stiffness by collagen secretion [86]. Meanwhile, Young's moduli, which represent the rigidity of the object, are also significantly higher in OLK than OSCC [87]. The increased matrix stiffness is closely associated with carcinogenesis. When the premalignant epithelial cells adhere to the rigid collagen matrix, the oncogenic pathways and expression of oncogenes are activated [88]. In addition, the increased matrix stiffness is shown to inhibit cell senescence through the YAP/TAZ signaling pathway [89]. Also, the increased matrix stiffness is proven to enhance cell survival, proliferation, stemness, EMT, and anchorage-independent growth. These actions act synergistically with the inhibition of cell senescence to promote OSF cell carcinogenesis [90]. Overall, the increased matrix stiffness acts as a "mechanical force" to mediate a series of carcinogenic processes, including oncogene activation, cell proliferation, migration, and senescence.

The proliferation of potentially malignant cells makes them move further away from lymphatic and blood vessels, depriving them of nutrients and oxygen. To counteract this, the potentially malignant cells release large amounts of pro-angiogenic factors, such as VEGF and basic fibroblast growth factor, into the surrounding microenvironment, promoting the rapid formation of new blood vessels. This sudden hypervascularization compresses the growing premalignant tissues. When the fluid of blood vessels leaves the vascular system and enters ECM, the overall interstitial hydrodynamic pressure increases [85]. The increased interstitial hydrodynamic pressure is proven to participate in the carcinogenesis process [91]. On the one hand, the high pressure and mechanical stretching of the cell itself can directly promote cell proliferation [91]. On the other hand, the increased fluid flow in tissue leads to more consistent changes in fibroblasts and collagen fibers, resulting in increased matrix stiffness [92]. Further, the fluid exercise stimulates fibroblasts to produce TGF-β, thereby altering the activation status of fibroblasts and inducing sustained immunosuppressive activities [93]. In conclusion, the increased matrix stiffness and interstitial fluid pressure provide another perspective to understanding OPMDs carcinogenesis through mechanical properties, and offers unprecedented possibilities for cancer prevention in the future.

5. Neural Microenvironment

There is growing evidence that the potentially malignant cells also utilize the neural system to promote their growth and progression. Communication between nerves and potentially malignant cells mediated by neurotransmitters or neuropeptides establishes a specialized, localized microenvironment called "neural microenvironment" [94].

The neural system regulation is equally important in OPMDs carcinogenesis. It is shown that the nerve density nearly doubles as carcinogenesis progresses from premalignant lesions to overt cancers [95]. Further, the disorders of neuroendocrine function are closely related to OPMDs carcinogenesis [7]. There is a higher cortisol level in OSCC patients compared with OSF patients [7]. It is reported that the disorder of cortisol secretion resulting from chronic anxiety and depression could affect the process of OPMDs carcinogenesis, to varying degrees [7]. The excessive cortisol promotes the apoptosis resistance, proliferation, and invasion of potentially malignant cells, and is closely related to inhibition of CD8+ T cell proliferation [96]. Another neuroendocrine peptide hormone, the growth hormone-releasing hormone, and its regulator, the splicing variant 1, are also demonstrated promoting the carcinogenesis of OPMDs by stimulating keratinocyte proliferation [97]. In addition, some exogenous factors can influence OPMDs progression by regulating innervation. The HPV proteins E6 and E7 integrate into host DNA and cleave the post-synaptic density protein strands after infection. Subsequently, it drives the metaplasia of host cells [98]. Also, the trace element can regulate the secretion of hormones and, thus, participate in OPMDs carcinogenesis as one kind of exogenous factor. The expression level of copper is high in OSF, and is confirmed to promote carcinogenesis. It absorbs and reduces catecholamine levels. Further, it regulates the synthesis and secretion of melatonin and other hormones [99]. In conclusion, not only the tissue innervation disorders and neuroendocrine dysfunction but also the external factors, such as virus infection and trace elements, disrupt the balance of neural microenvironment. The disturbed neural microenvironment then participates in the carcinogenesis of OPMDs by affecting the proliferation, apoptosis, and abnormal hyperplasia of potentially malignant cells.

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