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Molecular Perceptions on Tumour Metastasis in Oral Squamous Cell Carcinoma (OSCC): Potential for Therapeutic Interventions

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Abstract

Oral cancer is a foremost health concern and India accounts for about one third of its universal burden. About 80% of oral cancers in India are oral squamous cell carcinoma. They are associated with alarming fatality rates and the inability to prevent tumour metastasis being a prime reason. Considerate knowledge on the molecular events of tumour progression may give insight on developing rationale for the targeted prevention. This review intends to highlight the critical role of primary tumour and the tumour microenvironment in initiating metastasis and the mechanisms underlying the establishment of metastatic foci. Better understanding of these processes may help in targeting more research into the control of metastasis and thus disease control.

Keywords: Oral squamous cell carcinoma, Premetastatic niche, Metastasis, Tumour microenvironment.

INTRODUCTION

Solid tumours are now viewed to be a biologically systemic disease. Emerging researches urge to revise the concept of basic cancer biology for effectively controlling and targeting tumour. Tumour cells are no more considered to be a lump of cells that proliferate but rather tumorigenesis is a tuned process that requires the whole participation of organism. Cancer tissue communicate between themselves forming an ecosystem that interacts with a systemic pathogenic network that deals with tumour progression [1].

Tumours form a complex network of sub clonal tumour cells with heterotypic multicellular interactions that coexist in an evolving fashion [1].

Oral cancers are heterogenous tumour and still remain as a global concern. India along with other Asian countries encompass about half load of oral and pharyngeal malignancies of the world with predominantly higher incidence being ascribed with region-specific epidemiological factors and carcinogenic exposures [2]. An increasing prevalence among younger population associated without any habit is an alarming trend. About 60% increase in the number of tongue cancer in younger population over past 30 years. These are associated with severe morbidity. Despite of advances in treatment modalities, [3] inability in controlling the metastatic process is one of the common reasons for treatment failure.

Carcinogenesis is a complex multi – step process resulting after multiple mutations [3]. The tumor formation occurs due to the clonal expansion of single precursor cell. During this process of transformation cells attain the ability to proliferate, stimulates neovascularization, invasion and metastasis [4, 5]. Metastasis is a process in which genetical instability of primary tumour fuels cell heterogeneity, permitting cloning of a few metastatic cells that ultimately emerge and spread tumour. The evolving paradigms in the study of tumour progression have revealed many of the molecular events and biological principles of the metastatic cell and its pathways. This review looks into some of these molecular events that denote tumour aggressiveness towards locoregional and systemic spread of the disease.

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I. Methodology

In this review we searched the Pubmed data base with the following key words like: Oral squamous cell carcinoma, Premetastatic niche, Metastasis, Tumour microenvironment, Organ Remodelling. Mesh terms like oral cancers were also considered in literature search. Only full text articles from 2000-2021 were included.

Description	Specification
Date of search (specified to date, month and year)	12/30/2021–2/1/2022
Databases and other sources searched	PubMed database
Search terms used (including MeSH and free text search terms and filters).	Oral Cancers, Pre metastatic niche, Oral Squamous cell carcinoma, Metastasis
Timeframe	2000–2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	Full texted Articles written in English related to tumour metastasis included. Any articles which are not written in English were excluded.
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The selection process was done by primary author.

II. Molecular events in the tumour and its microenvironment facilitating tumour progression and metastasis

The tumour characteristics and the microenvironment are primarily responsible for deciding how the tumour grows or responds to treatment. Cells of different lineages affect it directly or indirectly. The microenvironment can either have a facilitatory or inhibitory effect on tumour progression.

1. Tumour cells & Tumour Microenvironment (TME)

Tumours progress in intricate environment and these cells solely depend upon on its environment for sustained growth, invasion and metastasis. Tumour microenvironment are mostly genetically stable unlike tumour cells [6]. Tumour micro environment comprises of basement membrane, extracellular matrix (ECM), tumour-infiltrating immune cells, cancer-associated fibroblasts (CAFs), endothelial cells, adipose cells, neuroendocrine cells and pericytes. The tumour microenvironment regulates tumour survival, aggressiveness, dissemination, colonization and metastasis [7]. Cancer associated stroma represent a dominant factor that impacts tumour initiation, progression and prognosis. TME also have a significant role in the defining the metastatic capacity of most tumours. However, TME has mixed capacities to induce both beneficial as well as adverse consequences in tumorigenesis[8]. Formative researches suggests that certain TME can overwhelm malignancy but mostly tumours overcome these restraints by exploiting the supporting cells to increase metastatic potential [8].

Bidirectional communications among cells and their microenvironment are critical for tumour progression. Unfamiliar immune responses and variations in homeostasis influence tumorigenesis. The synchronized intercellular-cellular interactions are disrupted in tumour and it acquires the capability to evade normalizing signals from the microenvironment [6]. The microenvironment evolves to accommodate the growing tumour and the related stroma at primary tumour site to support cancer growth. The TME cellular and structural components interacts thus permitting cell motility along with dissemination of tumour from the primary site [7]. Basement membrane remodelling is obligatory for tumour invasion and malignancy.

2 Role of Immune cells

The immune system has a key protective role against OSCC but TME impairs it by its anti-cancer response modulated by T helper cells endorsing an anti-inflammatory environment. During carcinogenesis process, $CD8^+$ T cells and natural killer (NK) cells may control metastatic outgrowth of tumour cells. Exhaustion of these cells augments metastasis without disturbing primary tumour growth [9-10] Cancer cells devise ways to avoid immune surveillance as well as induce systemic responses to enhance their metastatic competence during tumour progression [8].

Macrophages have a prominent role in maintaining tissue homeostasis and immune responses. Macrophages exhibit a great degree of plasticity. Activated M2 macrophages have immunoregulatory role and are involved in the tissue remodelling, wound healing, angiogenesis and tumour progression [11]. Primary tumours acquire macrophages to their microenvironment thus increasing tumour cell migration, invasion and intravasation [12]. The functional plasticity of macrophages enables tumour progression and are also associated with treatment resistance of many tumours [13] Tumour associated macrophages increases angiogenesis thus facilitating metastatic cell escape. Higher level of infiltration of Tumour associated Macrophages (TAMs) is related poor outcome, which may be also considering as a potential prognostic marker in head and neck SCC [14].

Immune suppression is another critical step in the malignant progression, suppression of the host immune system is by myeloid-derived suppressor cells (MDSCs) and Treg cells [15]. MDSCs facilitates tumour angiogenesis and ECM degradation by producing a significant level of MMPs, specifically MMP-9 [15]. The increased Tregs indicated poor survival rates in head & neck tumours but in OSCC its relation to prognosis remains controversial [12].

Natural killer cells (NK cells) are another set of immune cells that have a critical role in detecting and killing malignant cells and inhibiting tumour progression. Mast cells also contributes in innate and acquired immune responses. Several studies underway on the part of blood platelets in tumorigenesis.[16] In recent years numerous studies are focused on platelets and its role in tumour progression and tumour biology [17].

3 Role of Cancer associated fibroblasts

Fibroblasts are multi-functional predominant connective tissue cell mediating normal heomostasis [18]. In the TME, a group of activated fibroblasts with significant heterogenicity and plasticity are known to be cancer-associated fibroblasts (CAFs). CAFs modulates TME mainly by secreting various cytokines and growth factors like epidermal growth factor, vascular endothelial growth factor, hepatocyte growth factor, chemokine ligands etc which are critical for invasion, metastasis and drug resistance. CAFs are also generated by epithelial-to-mesenchymal transition (EMT) during tumorigenesis. CAFs possess mesenchymal-like phenotype which enhances metastasis where in normal fibroblasts suppress metastasis [19]. After arrival and deposition of CAF in the TME, these get triggered by various growth factors and cytokines. Monocyte chemotactic protein and secreted proteases also have been associated with CAF activation [20]. After activation CAFs support tumorigenesis and persuades vascular permeability [21]. CAFs also produce of MMPs and thus modulating the microenvironment, which ultimately results in tumour promotion and progression[20]TME augments metastatic cells primed to flourish in specific foreign microenvironments [15] Few studies have suggested endothelial-to-mesenchymal transition to be of importance but strong evidence in this is yet to come [22].

III. Mechanism of metastasis

Metastasis are disseminated cancer cells initiating new tumours at distant organ sites which consists of a series of sequential and interconnected steps. Growing evidences suggests that the metastatic

process consists of a cascade of events like local invasion, intravasation, existence in the circulation, extravasation and colonization [23] Like primary tumours, metastatic lesions are biologically heterogeneous cell populations with more varied characteristics in karyotype, antigenicity, immunogenicity, enzyme profile, invasiveness, and metastatic potential [24].

It is now well documented that several molecular events of implication for tumour spread occur at the tumour–host interface or advancing front, where the deepest and presumably most aggressive cells reside [25]. Tumour cells at the advancing front attain motility and are exposed to sustained autocrine stimulation or by the cancer associated peri tumoral stroma leading to the migration and metastasis [26] Gestures from the primary tumour induces a wide variation in target organs and initiate metastasis process [27].

Formation of pro-metastatic milieu

As discussed earlier there has an active interaction in tissue microenvironment which may intensely alter the pattern of gene-expression of their residing cells and cancer cells, thus tumour behaviour and growth [28]. Alterations in the premetastatic ECM are among the first steps in the formation of the premetastatic niche. The extracellular matrix in TME vigorously influence the behaviour of cells and the remodelling of extracellular matrix thus forming pro-metastatic milieu. An array of secretory remodelling enzymes is involved in post translational modification of ECM. Interaction of cell surface receptors and ECM components regulates proliferation, differentiation, migration and apoptosis [29]

Perhaps the striking perception of the pre-metastatic niche is the systemic signalling of tumour cells to initiate the host cells for ECM remodelling of the target organ. These imperative changes occur before the arrival of the metastatic cell known to be pre-metastatic niche escalating the subsequent survival and growth of metastatic cells [30] These promotes the colonization of metastatic cancer cells and establish metastasis in future.

Researches established the existence of "pre-metastatic niche (PMN)," in breast tumours and remodelling of microenvironment of metastatic site before the arrival of circulating tumour cells (CTCs) [31, 32]. Modification of target organ niches and their interaction with milieu provides tumour cells a higher sustainability in that environment results in colonization of tumour cells [33]. The colonization of these metastatic cells in target organ are called metastatic niche formation [34].

Though PMN are now extensively recognized in promoting metastasis in many solid tumours, speculations still exists whether it is a true biological processes mandatory for OSCC metastases [34]. The key vascular events in the pre-metastatic niche formation in Head and Neck tumours may be lymph angiogenesis and high endothelial venule (HEV)remodelling induced by the primary tumour leading to lymphatic remodelling even before the arrival of tumour cells [31-4]. Minderman et al. [33] in their study on melanoma suggested that metabolic reprogramming of stromal fibroblasts favours a pre-metastatic microenvironment.

ECM restructuring of target organ is presumed to be significant in cancer metastasis, as it directly affects CTCs establishing into it. [35] CTCs are potential seeds of metastasis which may form metastatic sites in either singleton or cluster way. Interactions occurs between CTC and metastatic niche and after circulation. CTCs settles and begins the colonization process in this niche which is a castigatory process for cancer cells. So, in order for their existence in this niche, either CTCs have to compete in the prevailing milieu or has to create a new niche, through cross-talks with the local cells. CTCs overcome these hurdles to spread to distant organs for its survival through multiple mechanisms.

Exosomes shown to have a critical role in the formation of premetastatic niches [35] with conflicting views on its role. Evidences of exosomes promoting PMN is evident in ovarian tumours. Exosomes shown to create an immunosuppressive premetastatic microenvironment in head and neck tumour [37].

Characteristics of the PMN

PMN thus created have six enabling characteristics like immunosuppression, inflammation, angiogenesis/vascular permeability, lymph angiogenesis, organotropism, and reprogramming characteristics which promote tumour cell colonization and metastasis [38].

Immunosuppression

It is critical for tumour cells to overcome host immunosurveillance mechanism for the formation of immunosuppressive pre-metastatic niche [12, 14, 38].

Inflammation

Inflammatory milieu formation at a secondary site, is crucial for seeding, survival, and proliferation of tumour cells in PMN [38]. Chronic inflammation has been considered as one of hallmarks of tumour. Many studies evolved relating inflammation and tumour development in head and neck tumours [39].

Angiogenesis and Vascular Permeability

The preliminary phase in tumour progression and succeeding metastasis is the increasing the vascular permeability within PMN [38]. The secretion and synthesis of numerous proangiogenic factors results in the formation of capillary network from the adjacent host tissues [40].

Lymph angiogenesis

Lymph angiogenesis in PMN is important in the metastasis. Lymphatic vessels are the early route of tumour lymphatic dissemination. Tumour-derived VEGF-A and VEGF-D may induce lymph angiogenesis and are allied with higher lymph node metastasis [38]

Sequences of activity in the PMN

PMN promotes metastasis by the following phases

Priming phase - Primary tumours may undergo uncontrolled proliferation, thus getting converted to a hypoxic and inflammatory state in this phase [40]. Primary tumour cells produce many soluble factors, which initiate immature pre-metastatic niche in the distal organ or in the same organ away from the primary tumour [40].

Licensing phase- Immuno suppressive cells are recruited into the secondary sites during this phase. The sustained host- stroma interactions and favourable microenvironment leads to a mature PMN formation. Potential seeding and CTCs colonization occurs after the mature PMN formation [40].

Initiation phase- CTCs arrive and colonize at PMN, where they survive or enter dormancy phase awaiting a favourable environment. A favourable PMN can support the seeding, colonization, tumour cell growth, finally in micro metastases [40, 41].

Progression phase- PMN can now directly promote metastatic tumour cells growth, expansion and progression at the niche resulting in macro metastases [40, 41].

Organotropism: Organ specificity in metastasis

Definitely a key step in tumour metastasis is the capability of cancer cells to efficaciously colonise in the distinct organ [22]. Tumour metastasis to different organs show organ-specific preference and is not a random process which was proposed as a seed and soil hypothesis by Stephen Paget [31]. Specificity of organ influence metastatic niche formation regulating the tumour survival and metastatic progression. Still there is

much more to unlock about the metastasise of tumours to particularly a specific organ while others show lower specificity [29]. Cancer cells grown experimentally in dissimilar sites, showed different proteins expression. Cancer cells in diverse environments responds differently to chemotherapy which may have a greater impact in therapeutic intervention. Oral cancerous cells like many other tumours can survive and colonize in the adverse microenvironment [32].

Reprogramming

Metabolic, stromal and epigenetic reprogramming are revealed to be involved in PMN-promoted tumour metastasis [33-4]. Metabolic reprogramming regulates and determine the future target organ of tumour cells [41-2]. Tumour cells may recruit non-malignant stromal cells into the PMN, thus reprograming tumour cells to promote tumour dissemination [36]

Concept of the 'sleepy niche' or Tumour cell dormancy

Recent literatures emphasis on active and silent PMNs in the processes of metastasis. Instead of developing PMN, certain tumour cells could endure in a dormant state which can extensively delay the metastasis process, known as sleepy niche [43]. Niche-based signals function only in specific tissue and organ specificity have a greater impact on tumour dormancy. Even after standard curative intent therapies, patients may characteristically show metastatic relapse after being clinically asymptomatic for decades may be due to sleepy niche [44].

Does PMN act as a target of early detection or intervention for metastasis?

Many tumours including OSCC at its clinically detectable stage might have likely seeded cancer cells to secondary sites. Few clinical evidences also support that curative intent tumour surgeries paradoxically augment tumour seeding [45]. Chemo or radiotherapy initiating PMN formation is debatable but treatment failure of metastatic tumour remains as a common event [46]. Even many chemotherapeutic agents may also fail to reach the PMN. Hence, targeting earliest stages of metastasis may not be achievable, so it may be ideal to target the most ineffective phase of metastasis, overtly the organ remodelling and colonisation. Consolidative targeting of numerous common molecular and cellular events that primes in PMN formation may be more competent. Targeting of the metastatic cell and its supportive microenvironment, there by inhibiting colonization, the phases of circulating tumour cells when they have not yet found places to settle, or the PMN of future metastatic organs to prevent tumour cell colonisation may be the way forward.

Evaluating the molecular and cellular events leading to PMN formation may help in diagnosis of cancer metastasis. Several primary tumour derived factors and secretory vesicles, molecular events in TME remodelling and organotropism can also be considered as potent biomarkers.

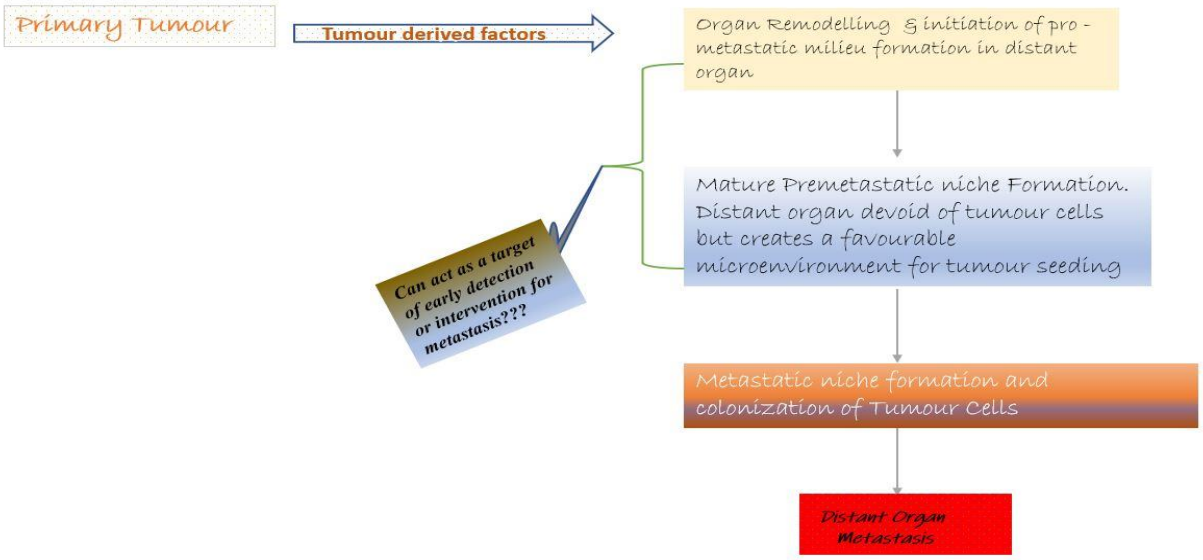

Figure 1: Primary Tumour induced organ remodelling, premetastatic niche and metastatic niche formation

CONCLUSION

Despite immense advances in understanding events of tumour biology and effective treatment strategies, metastasis still remains as the major cause of cancer fatality. Challenges still persist in detecting metastatic dissemination before overt metastasis. Tumour microenvironment is facilitatory or inhibitory to tumour growth depending on the cellular events. The emerging evidences of formation of premetastatic niche and organ specificity in metastasis make them areas for continued research. Better understanding the process of these premetastatic events may help in developing earlier diagnostic as well as therapeutic interventions.

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Conflicts of interest

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REFERENCE

1. Hornberg JJ, Bruggeman FJ, Westerhoff HV, Lankelma J. Cancer: Asystems Biology disease. Biosystems. 2006;83(2-3):81-90. doi: 10.1016
2. Krishna Rao SV, Mejia G, Roberts-Thomson K, Logan R. Epidemiology of oral cancer in Asia in the past decade--an update Asian Pac J Cancer Prev. 2013;14(10):5567-77. doi: 10.7314/apjcp.2013.14.10.5567. PMID: 24289546

3. Jayant K, Deo MG. Oral cancer and cultural practices in relation to betel quid and tobacco chewing and smoking. Cancer Detect Prev. 1986;9(3-4):207-13. PMID: 374250
4. Martín de Civetta MT, Civetta JD. Carcinogénesis [Carcinogenesis]. Salud Publica Mex. 2011;53(5):405-14. Spanish. doi: 10.1590/s0036-36342011000500008. PMID: 22218794.
5. Pitot HC, Dragan Y, Xu YH, Peterson J, Hully J, Campbell H. Nakahara Memorial Lecture. Pathways of carcinogenesis--genetic and epigenetic. Princess Takamatsu Symp. 1991;22:21-33. PMID: 1844243
6. Anderson NM, Simon MC. The tumour microenvironment. Curr Biol. 2020;30(16):R921-R925. doi: 10.1016/j.cub.2020.06.081. PMID: 32810447; PMCID: PMC819405
7. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nature reviews. Cancer. 2009;9:239-252.
8. Albini A, Magnani E, Noonan DM. The tumor microenvironment: biology of a complex cellular and tissue society. Q J Nucl Med Mol Imaging. 2010;54(3):244-8. PMID: 20639811
9. Areeg Elmusrati Justin Wang and Cun-Yu Wang Tumour microenvironment and immune evasion in head and neck squamous cell carcinoma, International Journal of Oral Science (2021) 13:24 ; https://doi.org/10.1038/s41368-021-00131-7
10. Forster M, & Devlin M. Immune checkpoint inhibition in head and neck cancer. Front Oncol. 2018;29:310
11. Hu Y, et al. Tumor-associated macrophages correlate with the clinicopathological features and poor outcomes via inducing epithelial to mesenchymal transition in oral squamous cell carcinoma. J Exp Clin Cancer Res. 2016:1756–9966 (Electronic)). [PMC free article] [PubMed]
12. Petruzzi M, Cherubini K, Salum F, De Figueiredo M. Role of tumour associated macrophages in oral squamous cells carcinoma progression: an update on current knowledge. Diagn. Pathol. 2017;12:1-7
13. Seminerio I, et al. High infiltration of CD68+ macrophages is associated with poor prognoses of head and neck squamous cell carcinoma patients and is influenced by human papillomavirus. Oncotarget. 2018;9(13):11046-11059. doi: 10.18632/oncotarget.24306
14. Umansky V, Blattner C, Gebhardt C, Utikal J. The role of myeloid-derived suppressor cells (MDSC) in cancer progression. Vaccines 2016;4:36
15. Barbora Peltanova, Martina Raudenska, , Michal Masarik Effect of tumor microenvironment on pathogenesis of the head and neck squamous cell carcinoma: a systematic review Mol Cancer. 2019;18:63. doi: 10.1186/s12943-019-0983-5
16. Parker K, Beury D, Ostrand-Rosenberg S. Myeloid-derived suppressor cells: critical cells driving immune suppression in the tumor microenvironment. Adv. Cancer Res. 2015;128:95-139
17. Liu T, Zhou L, Li D, Andl T, Zhang Y. Cancer-associated fibroblasts build and secure the tumor microenvironment. Front Cell Dev. Biol. 2019;24:60
18. Qin X. et al. Cancer-associated fibroblast-derived IL-6 promotes head and neck cancer progression via the osteopontin-NF-kappa B signaling pathway. Theranostics 2018;8:92-940.
19. Jianan Zhuyan, Mingyu Chen, Tianhao Zhu Xunxia Bao Timing Zhen, Kaichen Xing, Qiubo Wang et al Critical steps to tumor metastasis: alterations of tumor microenvironment and extracellular matrix in the formation of pre-metastatic and metastatic nichehuyan et al. Cell Biosci 2020;10:89 https://doi.org/10.1186/s13578-020-00453-9
20. Isaiah J Fidler, Sun-Jin Kim, and Robert R. The Role of the Organ Microenvironment in the Biology and Therapy of Cancer Metastasis Langley Journal of Cellular Biochemistry 2007;101:927-936.
21. Clere, Sarah Renault and Isabelle Endothelial-to-Mesenchymal Transition in Cancer Ni Front. Cell Dev. Biol., 14 August 2020 | https://doi.org/10.3389/fcell.2020.
22. Fidler IJ. The pathogenesis of cancer metastasis: The 'seed and soil' hypothesis revisited (Timeline). Nat Rev Cancer 2003;3:453-458.
23. Fidler IJ. Biology of cancer metastasis. In: Abeloff MD, Armitage JO, Niederhuber JE, Kastan MB, McKenna WG, editors. Clinical oncology, 3rd edition. Philadelphia, PA: Elsevier Science. 2004, 59-79.
24. Isaiah J. Fidler The organ microenvironment and cancer metastasis Differentiation. 2002;70:498-505 C Blackwell 2012
25. Bankfalvi A, Piffko J. Prognostic and predictive factors in oral cancer: The role of invasive tumor front. J Oral Pathol Med. 2000;29:291-8.
26. Carr I. Lymphatic metastasis. Cancer Metastasis Rev. 1983;2:307-317
27. Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. Nat Rev Cancer 2002;2:563-572
28. Peinado H, Lavotshkin S, Lyden D. The secreted factors responsible for pre-metastatic niche formation: old sayings and new thoughts. Seminars in cancer biology. 2011;21:139. 46. [PubMed: 21251983]
29. The pre-metastatic niche: is metastasis random ? Thomas R Cox 1, Alison Gartland 2 and Janine T Erler 1 BoneKEy Reports 1 80 (2012) | doi:10.1038/bonekey.2012.80 © 2012
30. Psaila B, Lyden D. The metastatic niche: adapting the foreign soil. Nat Rev Cancer. 2009;9(4):285-93.
31. Psaila B, Kaplan RN, Port ER, Lyden D. Priming the 'soil' for breast cancer metastasis: the pre-metastatic niche. Breast Dis. 2006-2007;26:65-74. doi: 10.3233/bd-2007-26106. PMID: 17473366
32. Lionel Gillot, Louis Baudin, Loïc Rouaud, Frédéric Kridelka, Agnès Noël. "The premetastatic niche in lymph nodes: formation and characteristics", Cellular and Molecular Life Sciences. 2021.
33. Minderman H, Sen A, Ciesielski MJ, Collins KA, Bush PJ, Singh P, Wang X, Morgan M, Qu J, Bankert RB, Whiteside TL, Wu Y, Ernstoff MS. Metabolic reprogramming of stromal fibroblasts by melanoma exosome microRNA favours a pre-metastatic microenvironment. Sci Rep. 2018 . doi: 10.1038/s41598-018-31323-7.
34. Xuyang Yang, Yang Zhang, Yaguang Zhang, Su Zhang, Lei Qiu, Zixuan Zhuang, Mingtian Wei, Xiangbing Deng, Ziqiang Wang, and Junhong Han The Key Role of Exosomes on the Pre-metastatic Niche Formation in Tumors Front Mol Biosci. 2021;8:703640
35. Winkler J, Abisoye-Ogunniyan A, Metcalf KJ *et al.* Concepts of extracellular matrix remodelling in tumour progression and metastasis. *Nat Commun* 2020;11:5120 https://doi.org/10.1038/s41467-020-18794-x
36. Di Martino JS, Akhter T, Bravo-Cordero JJ. Remodeling the ECM: Implications for Metastasis and Tumor Dormancy. Cancers (Basel). 2021;13(19):4916. doi: 10.3390/cancers13194916. PMID: 34638400; PMCID: PMC8507703
37. Guo Y, Ji X, Liu J *et al.* Effects of exosomes on pre-metastatic niche formation in tumors. *Mol Cancer* 2019;18:39 https://doi.org/10.1186/s12943-019-0995-1
38. Hao Wang, Junjie Pan, Livnat Barsky, Jule Caroline Jacob, Yan Zheng Characteristics of pre-metastatic niche: the landscape of molecular and cellular pathways landscape of molecular and cellular pathway, Molecular Biomedicine 2021.
39. Bonomi M, Patsias A, Posner M, Sikora A. The role of inflammation in head and neck cancer. Adv Exp Med Biol.

2014;816:107-27. doi: 10.1007/978-3-0348-0837-8_5. PMID: 24818721
40. Yang Liu Xuetao Cao Characteristics and Significance of the Pre-metastatic Niche Cancer Cell 2016;30(5):P668-681, Open ArchiveDOI:https://doi.org/10.1016/j.ccell.2016.09.011
41. Shibue T, Weinberg RA. Metastatic colonization: settlement, adaptation and propagation of tumor cells in a foreign tissue environment.
42. Dvorak HF, Nagy JA, Feng D, Brown LF, Dvorak AM. Vascular Permeability Factor/Vascular Endothelial Growth Factor and the Significance of Microvascular Hyperpermeability in Angiogenesis. In: Claesson-Welsh L. (eds) Vascular Growth Factors and Angiogenesis. Current Topics in Microbiology and Immunology, vol 237. Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-59953-8_6
43. Hernández-Barranco A, Nogués L, Peinado H. Could Extracellular Vesicles Contribute to Generation or Awakening of "Sleepy" Metastatic Niches? Front Cell Dev Biol. 2021;9:625221. doi: 10.3389/fcell.2021.625221. PMID: 33738282; PMCID: PMC7960773
44. Ghajar CM, Peinado H, Mori H, Matei IR, Evason KJ, Brazier H, Almeida D, Koller A, Hajjar KA, Stainier DY, Chen EI, Lyden D, Bissell MJ. The perivascular niche regulates breast tumour dormancy. Nat Cell Biol. 2013;15(7):807-17. doi: 10.1038/ncb2767. Epub 2013 Jun 2. PMID: 23728425; PMCID
45. Samer Tohme, Richard L Simmons Allan Tsung et al Surgery for Cancer : A trigger for metastasis Cancer Res 2017;77(7):1548-552.
46. Condeelis and Maja H. George S. Karagiannis, John S.Oktay Chemotherapy-Induced Metastasis: Molecular Mechanisms, Clinical Manifestations, Therapeutic Interventions DOI: 10.1158/0008-5472.CAN-19-1147 September 2019.