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Review

Tumor microenvironment – Unknown niche with powerful therapeutic potential

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ABSTRACT

Head and neck squamous cell carcinomas (HNSCC) are in a group of cancers that are the most resistant to treatment. The survival rate of HNSCC patients has been still very low since last 20 years. The existence of relationship between oncogenic and surrounding cells is probably the reason for a poor response to treatment. Fibroblasts are an important element of tumor stroma which increases tumor cells ability to proliferate. Another highly resistance, tumorigenic and metastatic cell population in tumor microenvironment are cancer initiating cells (CICs). The population of cancer initiating cells can be found regardless of differentiation status of cancer and they seem to be crucial for HNSCC development.

In this review, we describe the current state of knowledge about HNSCC biological and physiological tumor microenvironment.

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1. Head and neck cancers

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy worldwide and represents 5% and up to 50% of all cancers in developed and developing countries, respectively.[1,2] According to the Polish National Cancer Registry (www.onkologia.org.pl), cancers of the oral cavity and lip account for approximately 4% in men and 1% in women of all cancers cases in Poland. The development of HNSCC is mainly caused by the carcinogens present in tobacco and alcohol as well as oncogenic viruses (HPV and EBV) and a wrong diet.[3–5]

The treatment method depends on the patient's status, clinical stage of the tumor, its localization and histological differentiation. Basic methods of HNSCC treatment are surgery, radiation and chemotherapy, used alone or in combination and recently also with targeted therapy agents . In the case of treatment involving conventional methods, the prognosis of HNSCC patients in advanced stages is largely unsatisfactory due to loco-regional recurrence.[6–9] The use of specific biomarkers, such as mRNA, lncRNA, miRNA or circulating RNA, is proposed as a good prognostic or predictive tool with clinical significance.[10–17] However, molecular characterization of patients' tumor is only used to a limited extent in standard diagnostic procedures.

2. Tumor microenvironment

Tumor microenvironment (TME) differs essentially from the environment of normal tissues. The TME is a complex of cellular components such as cancer-associated fibroblasts (CAFs), myofibroblasts, adipocytes, endothelial cells, epithelial cells, immune inflammatory cells as well as extracellular components which surround tumor cells.[18,19] TME does not only surround the tumor cells, it also actively contributes to tumor development and progression, drug resistance and metastasis.[20,21] As far as tumor progress is concerned, the microenvironment of cancer cells is activated through constantly existing paracrine communication and promotes further changes in the microenvironment and expansion of tumor.[19–23] Recent studies suggest that tumor microenvironment plays a crucial role not only in the progression but also in malignant transformation.[20] The exact role of selected TME components and their interactions with cancer cells are described below.

Cancer-associated fibroblasts (CAFs) are heterogeneous population of irreversibly activated fibroblasts. They play various roles and are an important element of tumor stroma which increases tumor ability to proliferate, phenotype changes, resistance to therapy as well as metastasis.[23–25] CAF secrets many factors (such as cytokines, chemokines, growth factors and other proteins) influencing both cancer cells and TME elements.[24] Many cancers have altered cellular receptors such as members of fibroblast growth factor receptors (FGFR) family: FGFR1/2/3/4. They are transmembrane kinase receptors (RTKs) involved in basic cell cycle processes, such as differentiation, proliferation, cell survival, adult-tissue homeostasis and tumorigenesis[26] as well as the formation of new blood vessels, wound repair and embryonic development.[27] FGFR alterations can be divided into three main classes: gene amplification, gain-of-function coding mutation and gene fusion, with high impact in three most common malignancies worldwide.[26] Aberrations in FGFR pathways play a critical role in cancer resistance to therapy. Chae et al. reported that FGFR1 amplification occurs in 10–17% of HNSCC patients.[28] Additionally, Vairaktaris et al. demonstrated that a higher expression of FGFR1/2/3 contributes to early-stage cancer progression in HNSCC.[29] FGFR2/3 high expression was found in the majority of HNSCC cell lines.[28] Another interesting finding is that the reduction of FGFR3 level in HNSCC cell lines caused a 35% decrease of cell proliferation; furthermore – it caused their higher radiation sensitivity.[30]

Fibroblasts activation by tumor microenvironment, creating CAF phenotypes, depends on exogenous signals specific for a cancer type.[31] However, mechanisms for their activation in HNSCC microenvironment remain ambiguous.[32] Kellermann et al. revealed that oral fibroblasts transform to CAFs after co-culturing with oral squamous cell carcinoma (OSCC) cell lines. They demonstrated that cancer cell-derived TGF-β induced trans-differentiation of human gingival fibroblasts into CAF-line cells.[33] Another group reported that TGF-β and IL-1 β might play a crucial role in CAF induction.[34]

In HNSCC, CAFs activation launches mechanisms involved in downregulation of tumor suppressor genes, such as p21 and CAV-1.[32] They may also represent a resistant stromal cell type engaged in tumor relapse. CAFs are involved in remodeling and reprogramming the extracellular matrix (ECM) and tumor microenvironment. In primary tumor it may enhance cancer cell invasion leading to metastasis. Metabolic reprogramming of CAFs can contribute to enhancing cancer cells adaptation influencing tumor progression. They also play a crucial role in the secondary tumor growth because CAFs may enhance metastasis by releasing growth factors and cytokines into the circulation. That stimulates the growth and invasiveness of cancer cells at a distant site. Moreover, CAFs have also direct or indirect pleiotropic immunomodulatory functions. However, the most crucial role of CAFs is their impact on cancer therapy response caused mostly by modulations in CAF-ECM pathways interactions.[31]

Myofibroblasts are one of the carcinoma-associated fibroblasts which help to preserve stemness of cancer initiating cells (CICs). Myofibroblasts secrete cytokines, growth factors, chemokines, hormones, inflammatory mediators, adhesion and ECM proteins. This kind of fibroblasts is found in the stroma of carcinomas, particularly in the invasive front of a tumor. Their activity causes a rise of cancer cells proliferation, migration and invasion. The presence of myofibroblasts in cancer is correlated with lymph node involvement, disease recurrence, advance clinical staging and lower survival rates of HNSCC patients.[35,36] The analysis of all CAFs functions may give new insight into TME biology and offer a novel approach in cancer therapy.[37]

Mesenchymal stem cells (MSCs), another element of TME, are plastic, multipotential adherent cells similar to fibroblasts, but with a unique phenotype.[38] They are characterized by strong tumor tropism.[39] Liotta et al. showed that the number of MSCs (CD90+ cells) is correlated positively with tumor size but negatively with tumor-infiltrating leukocytes (CD45+ cells). Tumor-MSCs are able to inhibit proliferation