

## Editorial – Epigenetic mechanisms in oral cancer: new diagnostic and therapeutic strategies

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Complexity and heterogeneity are frequently present during the development and progression of carcinogenesis and, in the last 15 years, significant progress made in clinical research underlines the role of some epigenetic mechanisms. The most important characteristics of the epigenetic concept are that these events are reversible, not related to modifications in the structure of DNA and may drive fundamental cell signaling alterations<sup>1</sup>. Among these systems of communication in normal and pathological conditions, also microbiome and staminal cells<sup>2</sup> seem to be important. These new profiles of pathological communication develop novel diagnostic, prognostic and therapeutic tools.

Like other types of cancers, also oral malignancies have been intensely studied and the most interesting results regard specific epigenome modifications like DNA methylation, acetylation and de-acetylation of Histones and non-coding RNA-related modifications, especially miRNAs, start to be proposed (Figure 1). Oral cancer is one of the most common worldwide in terms of both incidence and mortality and epigenetic modifications of specific genes (APC, cadherin, surviving, PTEN, FLT4, KDR, and TFPI2) are frequently found hyper-methylated in oral cancer samples and also in cell lines. An increasing number of studies provide evidence for the possible use of epigenetic modifications in oral cancer, including DNA methylation, numerous histone modifications, long non-coding RNAs (lncRNA, >200 nt) and small non-coding RNAs like MicroRNAs (<200 nt).

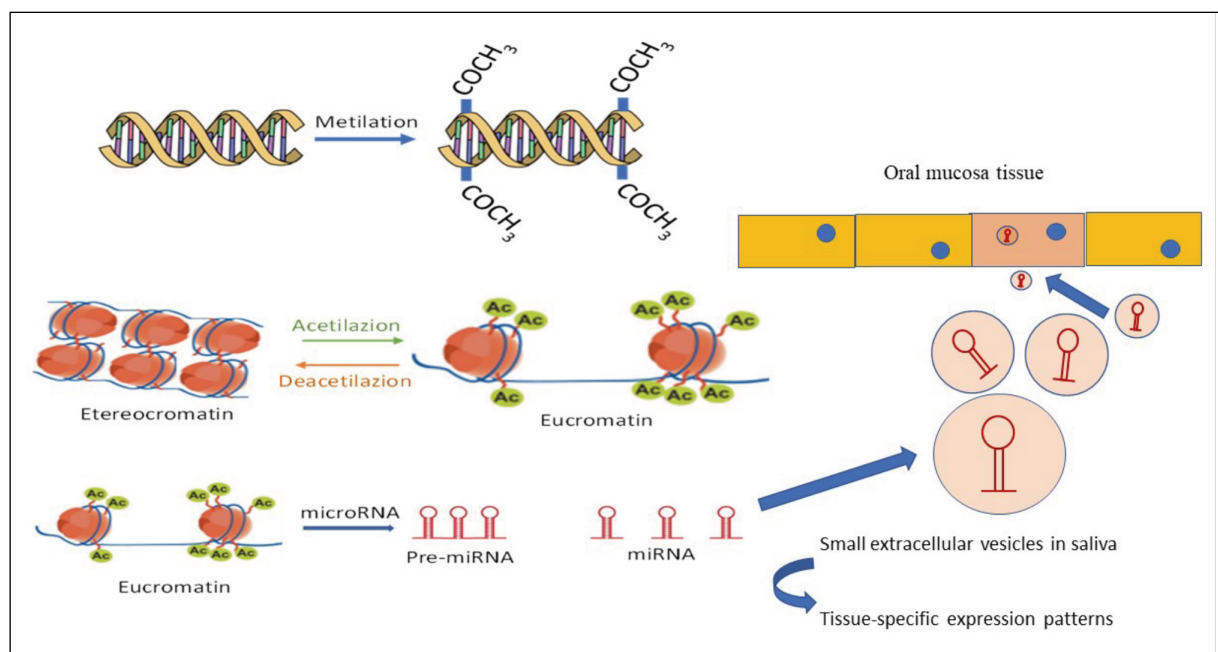
These epigenetic mechanisms are in part responsible for abnormal cellular growth, adding not only additional complexity in terms of cancer heterogeneity but also new diagnostic and therapeutic opportunities.

Non-invasive or minimally invasive procedures based on sampling collection from oral brushing, mouth rinsing, or saliva and analysis of epigenetic markers start to be proposed as a diagnostic aid to identify patients at risk of developing oral cancer<sup>3</sup>. Abnormal DNA methylation status in the initial and late stages of oral carcinogenesis, before any morphological changes, may silence tumor suppressor genes and/or activate oncogene patterns, including hypermethylation of gene promoter regions<sup>4</sup>. Thus, the identification of gene methylation may provide an appropriate marker useful for more complete classification but also for establishing alternative therapeutic strategies.

Histone proteins can be modified in different ways (ubiquitylation, sumoylation, methylation, acetylation, and also phosphorylation), influencing gene transcription and several biologic signaling pathways. In particular, histone deacetylase was found to be increased in oral cancer-derived cell lines and in clinical specimens<sup>5</sup>. A large volume of evidence has demonstrated that these small non-coding RNAs, containing 20-22 nucleotides, play key roles in oral cancer growth, cell migration and invasion. These small molecules are able to bind the regulatory regions (UTR) of the mRNA and block the translation of the target gene or, can induce complete degradation of the transcript<sup>6</sup>.

Therefore, miRNAs may be used as possible molecules able to modulate the expression of target genes in order to maintain the normal state of the organism and more and may be considered as novel prognostic and therapeutic tools for these diseases<sup>7</sup>.

The cancer-revealing miRNA is often carried from oral neoplastic cells in extracellular lipidic vesicles, thus circulating in saliva<sup>8</sup>. Its detection by molecular tools in salivary fluid, such as real-time PCR or droplet PCR, could be a powerful prognostic tool for follow-up after treatment for oral cancer. This laboratory method appears crucial if used in combination with new promising therapeutic procedures such as photodynamic therapy (PDT).



**Figure 1.** Schematic representation of the epigenetic events involved in the regulation of gene expression.

Photodynamic therapy (PDT) involves the use of a phototoxic drug, called a photosensitizer, which is activated by light irradiation (not only laser) of a specific wavelength that corresponds to an absorbance band of the sensitizer, that destroys selectively neoplastic cells<sup>9</sup>. A recent meta-analysis on PDT and surgery treatment in early-stage suggests that there was no statistically significant difference in recurrence rates between the two interventions<sup>10</sup>. Different types of photosensitizers are proposed in the scientific literature in PDT for oral cancer: ALA excited by wavelength ( $\lambda$ ) of 635 nm; porphyrin derivative  $\lambda = 530$  nm; chlorine-mediate  $\lambda = 664$  nm; curcumin with UVA or visible light<sup>11</sup>. Despite the promising performance of PDT against oral cancer, the therapeutic strategy in terms of a number of treatments, times, and light power, remains unknown at this time. In this context, a PDT therapy based on salivary mRNAs profile could be a good and innovative clinical path.

In addition, the use of conventional therapies does not preclude the use of PDT and the use of PDT does not compromise future surgical interventions, radiation therapy, or new therapeutic strategies<sup>12</sup>. PDT has already proven efficacy and safety for other oral diseases<sup>13</sup>. In this context, new fluorescent receptors can be easily internalized in the tumoral cell and, encapsulated in injectable nanoparticles, could be used as new photosensitizers for targeted delivery<sup>14,15</sup>.

Based on these considerations, even if further research is necessary to expand clinical application, it is now clear that epigenetic mechanisms are part of heterogeneous cancer signaling<sup>16-18</sup>. These preliminary results in oral cancer are promising and are mandatory to expand the application of new types of therapeutic agents (epigenetic modifiers) in the clinical practice and in laboratory diagnosis strategies by using procedures and methods already used in other pathologies.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

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