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'Omics' in oral cancer: A comprehensive overview

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Abstract

Health and disease states are dictated or accompanied by corresponding alterations in genes, mRNAs, proteins and metabolites. Over the past few decades, various 'omic' technologies have been developed to study the genome, transcriptome, proteome and metabolome respectively. Since oral cancers are one of the leading causes of death globally, much of research work has attempted to study the analytes in cancerous conditions by utilizing the various 'omic' modalities. These studies have aimed to understand the pathogenesis of head and neck cancers, aid in their diagnosis, devise new treatment strategies, and improve prognosis. It is imperative for surgeons and pathologists to be in line with the updates pertaining to various 'omic' methodologies available for studying the analytes. The present review comprehensively describes the development of various 'omic' technologies, including- genomics, transcriptomics, proteomics and metabolomics, while emphasizing their applicability in oral cancers.

KEYWORDS

Genomics; Transcriptomics; Proteomics; Metabolomics; Salivaomics

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1 | INTRODUCTION

The functioning of a biological system is dictated by regulation and interaction between numerous molecules. Genes code for proteins which are read and translated by mRNAs. The proteins produced, in turn, perform specific functions necessary for homeostasis and ultimately produce metabolites.[1] A dysregulation at genetic or molecular level may result in corresponding functional impairment. Focusing on a single gene, mRNA, molecule or metabolite would only provide limited knowledge, considering the vastness of the entire set of genes or proteins present in an organism. Therefore, there exists a need to study the totality of these biological substances or systems. The suffix '-ome' is used in biology to denote the totality of a class of substances for a species or an individual. Thus, the complete set of genes or genetic material present in a cell or organism is termed as genome. Similarly, set of mRNAs, proteins, metabolites, lipids have been termed as transcriptome, proteome, metabolome and lipidome respectively. Body tissues or fluids such as hair, blood, serum, plasma, sputum, semen, tears, nipple aspirate, urine, cerebrospinal fluid, fecal matter, etc. may

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be effectively utilized for study of various analytes.[2] Advances in technology and innovations in biotechnology has enabled researchers to study these systems or substances with a holistic approach. The relevant measurements or data from the respective interrelated fields are suffixed with '-omics'. The various fields of study applicable in biology are depicted/enlisted in Figure 1. The head and neck regions are of particular interest for almost all the different fields of 'omics'. Development and homeostasis of craniofacial structures involves various genes and complex interactions amongst numerous molecules. Disruption in these processes may lead to development of various diseases or even cancer. Cancer, particularly occurring in head and neck region, is one of the leading causes of death globally, of which Head and Neck Squamous Cell Carcinoma (HNSCC) accounts for 90% of the cases.

Early detection followed by timely intervention can drastically improve the survival rate in patients with oral cancer. Abundant research is, therefore, focused on identifying alterations in biomarkers involved in the process of carcinogenesis so that early mucosal changes can be identified.[3] Ultimately, these serve to curb the mortality as well as recurrence rates of oral cancers. Herein, we aim to review various '-omics' pertaining to oral cancer and describe them in a comprehensive manner. The present review has an objective to augment the knowledge of clinicians, particularly, pathologists with respect to various 'omic' modalities available to study the changes involved in the carcinogenic process.

2 | METHOD

Original research and review articles pertaining to various '-omics' used in oral cancer were included. An independent search was done for each '-omic' entity with keywords (("Genomics" OR "Transcriptomics" OR "Proteomics" OR "Metabolomics" OR "Salivaomics") AND ("Oral Cancer") across the databases: MEDLINE (Ovid), Pubmed, Pubmed Central, Web of Science Citation Index Expanded (SCIEXPANDED), Google Scholar with the keywords. The obtained results were checked for cross references to further identify relevant publications. The articles obtained were reviewed and analyzed by a team of four/six experts in the field of Oral Pathology, which is responsible for the final data synthesis.

3 | DISCUSSION

Role of each '-omic' modality has been described individually for ease of understanding by the readers.

3.1 | Genomics

The concept of gene as a physical entity determinant of corresponding inheritable traits in an organism was introduced in 1909. The introduction of terminologies 'genotype' and 'phenotype' closely followed. The designation of complete genetic constitution of an organism as 'genome' was suggested by Hans Winkler in 1920.[4] It was only after a few decades that DNA was demonstrated to be the hereditary material and its three-dimensional structure was illustrated by Watson and Crick model.

Sequencing DNA by breaking small fragments into larger contigs and subsequently, chromosomes by means of Whole genome shotgun technique was successfully carried out in 1980. The technique is applicable for relatively small genomes comprising of 4000 to 7000 base pairs and the earliest genome sequenced was that of cauliflower mosaic virus. Successful sequencing of genome opened up numerous possibilities for larger projects in the field of genomics. The human genome project (HGP) is the largest collaborative biological project till date.[5] It aims Identifying and mapping all of the genes of the human genomes from physical as well as function aspects. In March 1986, feasibility of the project was discussed at the "Genome Sequencing Workshop", New Mexico and HGP was formally launched in the year 1990.

Around at the same time, by the end of 1990s, several bacterial genome sequences were identified. HGP along with identification of complete Prokaryote genomes marked the beginning of the era of genomics. Genomic sequence of yeasts was also identified in quick succession.[6] Projects to identify the genomic sequence of modelling organisms, Caenorhabditis elegans (nematode) and Arabidopsis thaliana (a flowering plant) were already underway around the year 2000. Around 65,000 pairs of genes were studied systematically in C. elegans and 350 interactions were identified between genes in signaling pathways that are mutated in human diseases.[7] A certain set of genes encoding for chromatin regulators showed a

high degree of connectivity with other genes. It was hypothesized that these could act as modifier genes in various genetic disorders and were termed as 'hub genes'.[8] HGP was declared as completed in 2003, however, the level 'complete genome' was achieved only recently in May, 2021.[5] Analysis of 573 different genomes resulted in certain conclusions. First, a set of 250 highly conserved gene families encoding for essential functions was found to be common amongst 99% of species. Secondly, about 8000 gene families were expressed at variable frequencies accounting for metabolic changes. Certain genes were found to be rapidly evolving suggestive of a high turn-over rate. Over time, the genomic sequencing underwent numerous improvements leading to development of various methodologies [9] as depicted in Figure 2.

Besides the sequencing methodologies, various hybridization techniques such as Southern blot, Western blot, Eastern blot, fluorescent in-situ hybridization (FISH), flow cytometry and comparative genomic hybridization have also been developed for analysis of DNA expression. Furthermore, gene editing techniques such as Cre-LoxP system, zinc finger nucleases (ZFNs), Transcription activator-like effector nucleases (TALENs) and CRISPR-Cas9 system enable removing, editing or adding parts of a genome.[10]

Identification of gene is only an initial step towards understanding human diseases at fundamental level. Once sequencing of a genomes is completed, structures of various genes can be identified (Structural genomics), which could offer insights into their functions (Functional genomics) and which could be compared to that of other genes (Comparative genomics). Analyzing gene expression in tumors could provide insights into its origin, pathogenesis as well as functional status (for example, hypoxic areas). It could also be employed to understanding the tumor microenvironment inclusive of associated immune cells through functional genomics.[11] Genome-wide association studies identified a common nucleotide polymorphism across the genomes using an unbiased statistical method. It has been effectively employed to identify susceptible loci that constitute the mutational burden in oral cancers or its microenvironment.[20] It is now possible to sequence complete human genome within a day using massively paralleled sequencing or next generation sequencing (NGS) methods.[12] Mutations involving the SMO gene commonly noted in ameloblastoma (AM) of the maxillary jaw and BRAF V600E mutations in the mandibular AM were identified using these methods.[22]These series of findings, since their inception in the year 2014, have possibly generated newer horizons in the management of ameloblastoma.[13] Association of genetic alterations as well as loss of heterozygosity with sequential progression of OSCCs across different grades of dysplasia have also been elucidated by means of NGS methods.[14] Array comparative genomic hybridization technique in association with NGS has enabled identifying alterations in genome sequence as well as quantifying the copy numbers of genes altered. The copy number alterations increase across mild to severe grades of dysplasia and were found to be in largest numbers in OSCC.[15] Thus, it could be extrapolated that a number of genetic alterations actually occur at a stage much before development of carcinoma. Mutations in TNF-α, p16, p53, and NOTCH1 have been found to be commonly associated with oropharyngeal cancers.[16] Receptors of tyrosine kinase family are involved in growth factor signaling. Alterations in genes encoding for these receptors inclusive of EGFR, FGFR3, PDGFR and KIT were found to be preferentially associated with Human Papilloma Virus (HPV)-associated HNSCC.[14] Patients with family history of hereditary disorders or cancers can be identified and counselled from an early age. Besides the genetic mutations, modifications in the epigenome are also known to play a role in carcinogenetic process. Epigenetics involves study of these heritable alterations that are not strictly caused by changes in the DNA sequence. Epigenome is involved in regulation of DNA repair through modulation of chromatin activity.[27] Thus, cell senescence, chronic inflammation and autoimmune conditions may induce epigenetic alterations.[17] It has been postulated that epigenetic alterations may be induced by environmental factors by three possible mechanisms – (i) by activation or inhibition of chromatin, (ii) activation of nuclear receptors by means of ligands and (iii) influencing signaling cascades by means of membranous receptors. Accumulation of these epigenetic changes over time may lead to devel-

opment of cancer and other pathogenetic processes.[18] Alterations in epigenome have implications in diabetes, obesity as well as cancer. Epigenetic dysregulations have also been implicated in the pathogenesis of HNSCCs.[19] Histone modification and DNA methylation are the most common epigenetic alternations. Genome-wide hypo- as well as hypermethylation have implications in the process of carcinogenesis. These epimutations lead to silencing of tumor suppressor genes and may also cause mutations or deletions in the genome. The overall process was proposed as the 'two-hit' model of carcinogenesis by Knudson. A newer model for carcinogenesis comprising of bi-allelic inactivation by aberrant methylation of gene promoters has also been suggested.[20] Hypermethylation of various genes involved in cell cycle regulation (p16,Survivin), apoptosis (Bcl-2 Bcl-6, Bax), cell adhesion (E-Cadherin, N-Catenin), tumor suppression (PTCH, BRCA1) have been identified to play a role in carcinogenesis. Overexpression of enzyme Enhancer of zeste homolog 2 (EZH2), a histone methyltransferase, has been correlated with clinical aggressiveness and poorer survival rates in OSCC.[21] In HPV-associated OSCCs, activation of EZH2 by E7 protein of the virus leads to increased apoptotic resistance The primary aim of identifying the genetic and epigenetic markers for oral cancers is to target them by means of several gene therapy strategies. These include genetic prodrug activation therapy, gene replacement therapy, suicidal gene therapy and immunological gene therapy. Sequencing the protein-coding regions of a genome, termed as 'exome sequencing', has enabled the production of small molecule drugs.[22] Pharmacogenomics employs these drugs and can have a significant practical impact in the management of oral cancers. Identifying diverse genetic profiles in HNSCCs of different origins could aid in patient selection for the most effective targeted therapies. Not only targeted therapy, but genomics has also enabled tissue engineering of soft as well as hard tissues. Identifying and utilizing genetic factors for wound healing and bone repair can lead to accelerated healing and remodelling processes.[23] Computational analysis of genomic data is termed as 'Bioinformatics', which involves the integration of biology, biostatistics and data science. The term was first defined by Dutch theoretical biologists, Paulien Hogeweg and Ben Hesper as "the study of informatic processes in biotic systems".

3.2 | Transcriptomics

Over the past two decades, much of research work was emphasized on all types of RNA transcripts (mRNA, tRNA and rRNA). More recently, even the longer non-coding RNA (miRNA, lncRNA and piRNA) have been recognized as targets for transcriptomic studies. The total RNA content in a human cell-free whole saliva sample ranges from 0.108 ± 0.023 μg/mL to 6.6 ± 3.6 μg/mL.[24] About 200 distinct mRNAs constitute the normal salivary transcriptome core" In humans which are of particular interest for detecting abnormalities or disorders.[44] More than 500 identical transcripts have been identified across the 6400 distinct human RNA specii detected in the supernatant saliva of healthy human subjects through profiling by high-density oligonucleotide microarrays.[24] 29% of these are applicable to human array sequences, 28% for coding of proteins and the function of remainder 27.5% is yet unknown. Similar to genomics, an array of techniques is applicable for study of RNA or transcriptomics including- Northern blot, flow cytometry, FISH, comparative genome hybridization, microarrays, Real-Time Quantitative Reverse Transcription (qRT-PCR).[25] Transcriptome-wide editing of RNA can also be carried out by means of chemical modification of nucleobases, CRISPR-Cas9, RNA interference (RNAi) and other systems used for gene editing.[29] Transcriptomic studies have identified increased expression of DUSP1, Interleukins, SAT1, OAZ1 and S100P in the saliva of patients having OSCC as compared to healthy controls Important transcription factors associated with various malignant and benign neoplasms have been identified in the field of Oral Pathology, which include SOX9, SOX10, SOX11, NKX 2, NKX3, Snail, Slug, TWIST, HOX to name a few.[28-29] Similarly, miRNA-31 was upregulated, whereas eleven distinct types of miRNAs were also found to be deregulated in saliva of patients having oral premalignant and malignant lesions.[30] Transcriptomics has shown promising results in prognostication of disease and predicting treatment outcome in oncology. Furthermore, the ease of collecting samples and cost-efficiency of the technology allows automated quantification of mRNA in

a feasible manner. Caution needs to be exercised when carrying out studies involving collection of mRNAs from extracellular samples. mRNA tends to get degenerated within a few minutes as compared to rRNAs and tRNAs which are relatively more stable outside the cell.[31] As a result, mRNAs are present in lower proportion as compared to rRNAs or tRNAs in serum samples. On the contrary, genuine human mRNA is present in the supernatant whole saliva having high sensitivity (91%) and specificity (71%).[32] Salivary transcriptome is, therefore, more feasible and accurate for detection of oral cancer as compared to serum. Furthermore, 30% of salivary DNA, mRNA, proteins or metabolites are of microbial origin.[31] A significant portion of microbial content is from the bacteria present in the oral cavity, while fungi and viruses may also contribute. Sterile sample collection techniques and subsequent refrigeration at 4 degree Celsius will minimize bacterial contamination. Performing the necessary procedures within three to six hours of collection is highly recommended to further reduce the chances of infection.[29] To eliminate the bacteria by selectively impeding their growth, sodium azide may be added to the salivary sample collected. When proteomic analysis is to be carried out, it becomes necessary to control denaturation of proteins. For this purpose, protease inhibitors such as EDTA or leupeptin may be effectively employed.[33] An added advantage of utilizing saliva for transcriptome analysis is the possibility to discriminate and identify diseases by means of a panel of biomarkers. Machine learning by self-organizing maps has enabled RNA sequencing of a hundred samples at a time through microarrays.[57] An example of its utility was demonstrated in identifying p16 positive tumors in oropharynx having different prognosis.[34] It can be expected that artificial intelligence-based approaches will be developed in near future that would enable integrating data from multi-omic techniques. Well-detailed large-scale investigations pertaining to use of mRNAs as biomarkers with long-term follow-up are warranted for establishing their utility as diagnostic and prognostic biomarkers.

3.3 | Proteomics

Proteins are an important component of human saliva constituting about 14.5% of whole saliva contents in contrast to 7% of the plasma proteins.[35] The human salivary proteome is reflective of health and diseased state as well as circulatory substances. Polyacramide gel electrophoresis (PAGE) enables analysis of different proteins of similar molecular weights as well as identification of their isoforms.[60] More than 1,165 salivary proteins have been identified in total from the parotid, submandibular and sublingual gland fluids.[32] A number of techniques for proteomic analysis have been developed over the past two decades. These are illustrated in Figure 3. The techniques are based on analysis of either natural proteome (top-down approach) or the peptides created from digested salivary proteins (bottom-up approach). Two or more techniques have also been used in combination to allow identification of proteome in different stages of expression and post-translational modification.[36] Furthermore, recent development of isotope-based amino acid identification techniques has enabled quantification of various salivary proteins in changeable states. Certain proteins such as serum albumin, immunoglobulins, vitamin-D binding proteins, amylase, zinc-2 glycoprotein were found to be increased in whole saliva of patients having generalized aggressive periodontitis by means of two-dimensional gel electrophoresis method. [37] At the same time, proteins such as lactotransferrin, elongation factors, lung and nasal epithelium carcinoma-associated protein 2 were found to be decreased in these patients. Mass spectrometry following electrophoresis has also revealed differences in salivary and gingival crevicular fluid levels of S100A8 and S100A9 proteins.[38] Similary, immunoassay validation (ELISA or Immunoblotting) following shotgun proteome analysis and two-dimensional gel electrophoresis of salivary proteins revealed elevation of MRP14, CD59, M2BP, Profilin, Moesin, Involucrin, Histones, S100 proteins and Ras-related proteins by up to two-fold levels.[39] Significant upregulation of Ras-related proteins, fibrinogen proteins, heat shockcognate, Serpin, ATPase regulatory proteins, and hemoglobin subunits was also demonstrated in gingival OSCC by Papa et al.[40] They also found that certain regulatory proteins such as cornulin, cytokeratin 13, and APOA1 were reduced in cases of gingival OSCC.

Levels of enzymes such as carbonic anhydrase were

also found to be decreased. The study of enzymes in various health and disease states is termed as "Catalomics". Catalomics can be considered as a subset of proteomics, since enzymes are primarily proteins in nature. Enzymes such as Catalase, aldo-ketoreductase, tryptophan ligases and synthases were also found to be significantly increased in oral cancer.[39,40] Similar to their corresponding protein substrates, the regulatory enzymes such as α-amylase, lactate dehydrogenase and ubiquitin carboxyl-terminalhydrolase, were found to be decreased.[41]

3.4 | Metabolomics

Numerous reactions are involved at cellular and molecular level in functioning and homeostasis of tissues. These subsequently result in production of various metabolites that are derived from proteins, carbohydrates, fats and vitamins consumed in the process. A diseased state, for instance, a tumor would naturally have an altered metabolome produced owing to increased/decreased metabolic activity. The global assessment of these endogenous small-molecule metabolites is studied by various metabolomic techniques. Lipidomics and glycomics also constitute a subset of metabolomics. Analysis of metabolome in tissue, saliva, serum or other body fluids can provide an insight into the diseased state or nature of the metabolic activity taking place within a diseased tissue.[42] It can be expected that the levels of salivary metabolites would be affected after meals, consequently affecting the metabolomic screening if the collection is performed at that time. Collection of salivary samples after a 12-hour fasting period is deemed as optimal for metabolomic analysis.[43] A study by Wei et al. has demonstrated a positive predictive value of metabolomics to be 81.6% and 87.5% in oral cancer and leukoplakia respectively through Ultraperformance liquid chromatography coupled with quadrupole/time-of-flight mass spectrometry (UPLCQTOFMS). The high sensitivity (90%) and specificity (83%) yielded a satisfactory accuracy of about 0.89 to 0.97 for the procedure when valine, lactic acid and phenylalanine were considered for metabolomic analysis.[44] A metabolic profile of 109 metabolites was detected in tissues of patients with HNSCC by Yonezawa et al.[45] They found that 41 metabolites were significantly increased in tumor tissues as compared to normal controls, while 15 metabolites were found to be significantly decreased. The levels of metabolites related to glycolytic pathway were found to be lower, while the levels of several amino acids were raised in tumor tissue. The need for increased energy production by neoplastic cells is fulfilled by active aerobic glycolysis rather than oxidative phosphorylation. This depletes the glucose content in the tumor microenvironment and at the same time, raises the amino acid level through degradation of the extracellular matrix. The autophagic and cannibalistic degeneration occurring in cancer cells further adds to the protein content.[46] A difference was also observed in the metabolic profile of the patients that presented with relapse as compared to those with no evidence of disease on follow-up. It has been suggested that increased metabolites from the glycolytic pathway detected in saliva or serum of patients after surgical treatment of HNSCC may aid in early identification of cases susceptible to recurrence.[45] Similarly, establishing chemical fingerprints through metabolomic analysis of cells can aid in the assessment of tumor response to chemotherapy as well as the identification of new therapeutic biomarkers. Lactate, glutamate and aspartate are deemed suitable biomarkers for determining the efficacy of induction chemotherapy. In this manner, a personalized chemotherapy regimen may be tailored for each patient according to the response observed through metabolomic analysis.

3.5 | Salivaomics

Although one may study analytes in various samples obtained from body fluids or tissues it is evident from our review that most of the transcriptomic, metabolomic and proteomic analysis in cases of oral pathologies were carried out on salivary samples. Saliva is a rich source of various clinically important molecules such as bacterial products, DNA and mRNA of tumor origin, metabolic products, hormones that are produced locally in the oral environment.Additionally, these biomolecules may also reach saliva through active transport and passive diffusion from the serum. Therefore, the biomarkers detected in saliva may reflect the underlying disease condition. Saliva being a virtually inexhaustible biofluid, provides a generous supply of these biomarkers required in various diagnostic and

prognostic studies. The comprehensive study of biomarkers in saliva was termed as 'Salivaomics' in the year 2008.[47] Therefore, all the 'omic' modalities utilized to study the biomarkers in saliva can be collectively included under Salivaomics. Nanotechnology-based point-of-care technologies have also been introduced recently that allow identification of multiple analytes through highly sensitive biomarkers.[79] These portable systems can be utilized for highly sensitive and specific chair-side screening of oral cancers. Web-based resources and databases such as Salivaomics Knowledge Base (SKB), saliva ontology (SALO) and SDxMart are available that allow storage and comparison of data from various saliva-based omic studies across the globe.[48] These databases allow researchers to access available data and extrapolate new hypothesis pertaining to salivaomics.

3.6 | Microbiomics

The totality of microbes inhabiting the human body, their genomes and ecosystems encompasses the microbiome.[81] The microbiome influences host physiology, pathobiology, and immunity.[49] Study of impact of dysbiosis on these processes comprises the essence of 'Microbiomics'. Recent evidence correlating the human microbiome with states of health and disease has led to unfolding in this novel expansive frontier. Dysbiosis in the microbial ecology of the large intestine has been implicated in a spectrum of diseases including colon cancer. Microbiomic studies have identified both, cancer-suppressive and well as cancer-promoting species microbial species. Microbiota associated with tumor microenvironment has been demonstrated to initiate and advance various signalling pathways in oral cancer.[49] Several mechanisms by which microbes lead to the development of cancers have been identified by microbiomic studies. These include: (i) Direct or indirect damage to the DNA by microbes leading to genomic instability and mutations, (ii) Stimulation of proliferation by binding to growth receptors, and (iii) Cytokine-mediated damage due to activation of inflammatory cells (cancer-promoting inflammation). Most of the patients, particularly in developing countries such as India, have poor oral hygiene status. Studies have linked poor oral hygiene and periodontal condition with increased risk of cancers of the oral, gastric and pancreatic regions. The oral mucosa also gets sensitized to the carcinogenetic effects of alcohol owing to the presence of certain pathogenic oral microbial species.[86] Tumor-promoting inflammation plays a key role in microbiome-dependent carcinogenesis. Therefore, polymorphic microbiomes were rightly included among the newly described hallmarks of cancer.[50] Various techniques employed for microbiomic studies in oral cancer include conventional – Culture analysis, microscopy, enzyme assays and immunoassays and metagenomics – RNA sequencing, Pyrosequencing and Shotgun sequencing.[49] Despite numerous advantages, modern 'omic' technologies are still not entirely integrated with diagnostic and theranostic protocols. In developing countries such as India, lack of financial resources poses a major hurdle when utilizing modern 'omic' techniques for large-scale research projects. This makes it difficult to obtain samples from large population sizes in order to avoid bias in results. Considering the high sensitivity of the 'omic' techniques, samples needed are of much less quantity but should also be free of contamination. Obtaining such a sample is difficult from the oral cavity which is laden with millions of commensal microbes. While identification of target oncogenes and tumor suppressor genes has shown promising results by 'omic' technologies, significant challenges still exist in the transformation of these biomarkers into targets of therapies.

4 | CONCLUSION

The field of cancer diagnostics has improved by leaps and bounds in the past two decades owing to rapid improvements in 'omic' technologies. Analysis of multiple biomarkers within a short frame of time is now possible, which can provide huge amounts of information pertaining to nature and prognosis of cancers. Identification of established chemical fingerprints can aid in early identification of diseased states including oral precancer and cancer which would consequently improve the survival rate of patients. Furthermore, personalized targeted therapy can be tailored for each patient with accurate gauging of response to treatment. Integration of point-of-care 'omic' technologies with bioinformatics can enable monitoring of cancer on a global scale

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Conflict of interest

The authors have no conflicts of interest to declare.

Supporting Information

Additional supporting information may be found at the journal's website.

References

1. Mauger DM, Siegfried NA, Weeks KM. The genetic code as expressed through relationships between mRNA structure and protein function. FEBS letters 2013;587(8):1180-8. https://doi.org/10.1016/j.febslet.2013.03.002
2. Segal A, Wong DT. Salivary diagnostics: enhancing disease detection and making medicine better. Eur J Dent Education 2008;12(1):22-29. https://doi.org/10.1111/j.1600-0579.2007.00477.x
3. Santosh AB, Jones T, Harvey J. A review on oral cancer biomarkers: Understanding the past and learning from the present.J Cancer Res Ther 2016;12(2):486-92 https://doi.org/10.4103/0973-1482.176414
4. Noguera-Solano R, Ruiz-Gutierrez R, Rodriguez-Caso JM. Genome: twisting stories with DNA. Endeavour 2013;37(4):213-9. https://doi.org/10.1016/j.endeavour.2013.05.003
5. Human Genome Project. Available at https://en.wikipedia.org/wiki/Human_Genome_Project [Last Accessed: 20 Sept, 2021].
6. Goffeau A, Barrell BG, Bussey H, Davis RW, Dujon B, Feldmann H, et al. Life with 6000 genes.Science 1996;274(5287):546-67. https://doi.org/10.1126/science.274.5287.546
7. Lehner B, Crombie C, Tischler J, Fortunato A, Fraser AG. Systematic mapping of genetic interactions in Caenorhabditis elegans identifies common modifiers of diverse signaling pathways. Nature genetics 2006;38(8):896-903. https://doi.org/10.1038/ng184
8. Tanke HJ. Genomics and proteomics: the potential role of oral diagnostics. Ann N Y Acad Sci. 2007;1098(1):330-4. https://doi.org/10.1196/annals.1384.042
9. França LT, Carrilho E, Kist TB. A review of DNA sequencing techniques. Q Rev Biophys.2002;35(2):169-200. https://doi.org/10.1017/s0033583502003797
10. Agapito-Tenfen SZ, Okoli AS, Bernstein MJ, Wikmark OG, Myhr AI. Revisiting risk governance of GM plants: the need to consider new and emerging gene-editing techniques. Front Plant Sci. 2018;9:1874. https://doi.org/10.3389/fpls.2018.01874
11. Saidak Z, Lailler C, Testelin S, Chauffert B, Clatot F, Galmiche A. Contribution of genomics to the surgical management and study of oral cancer. Ann Surg Oncol. 2021;28(11):5842-5854. https://doi.org/10.1245/s10434-021-09904-0
12. Buermans HP, den Dunnen JT. Next generation sequencing technology: advances and applications. Biochim Biophys Acta. 2014;1842(10):1932–41. doi: https://doi.org/10.1016/j.bbadis.2014.06.015
13. Gomes CC, Diniz MG, Gomez RS. Progress towards personalized medicine for ameloblastoma. J Pathol. 2014;232(5):488–91. https://doi.org/10.1002/path.4331
14. Zhang P, Mirani N, Baisre A. Molecular heterogeneity of head and neck squamous cell carcinoma defined by next-generation sequencing. Am J Pathol. 2014;184(5):1323-30. https://doi.org/10.1016/j.ajpath.2014.01.028
15. Salahshourifar I, Vincent-Chong VK, Kallarakkal TG, Zain RB. Genomic DNA copy number alterations from precursor oral lesions to oral squamous cell carcinoma. Oral Oncol. 2014;50(5):404-12. https://doi.org/10.1016/j.oraloncology.2014.02.005
16. Al-Swiahb JN, Huang CC, Fang FM, Chuang HC, Huang HY, Luo SD, et al. Prognostic Impact of p16, p53, Epidermal Growth Factor Receptor, and Human Papillomavirus in Oropharyngeal Cancer in a Betel Nut–Chewing Area. Arch Otolaryngol Head Neck Surg. 2010;136(5):502-8. https://doi.org/10.1001/archoto.2010.47
17. Ray D, Yung R. Immune senescence, epigenetics and autoimmunity. Clin Immunol. 2018;196:59-63. https://doi.org/10.1016/j.clim.2018.04.002

18. Takeshima H, Ushijima T. Accumulation of genetic and epigenetic alterations in normal cells and cancer risk. NPJ Precision Oncol. 2019;3(1):1-8. https://doi.org/10.1038/s41698-019-0079-0

19. Sandoval J, Esteller M. Cancer epigenomics: beyond genomics. Curr Opin Genet Dev. 2012;22(1):50–5. https://doi.org/10.1016/j.gde.2012.02.008

20. Mutter RW, Riaz N, Ng CK, Delsite R, Piscuoglio S, Edelweiss M, et al. Bi-allelic alterations in DNA repair genes underpin homologous recombination DNA repair defects in breast cancer. J Pathol. 2017;242(2):165-77. https://doi.org/10.1002/path.4890

21. Shih CH, Chang YJ, Huang WC, Jang TH, Kung HJ, Wang WC, et al. EZH2-mediated upregulation of ROS1 oncogene promotes oral cancer metastasis. Oncogene. 2017;36(47):6542-54. https://doi.org/10.1038/onc.2017.262

22. Hoelder S, Clarke PA, Workman P. Discovery of small molecule cancer drugs: successes, challenges and opportunities. Molecular Oncol. 2012;6(2):155-76. https://doi.org/10.1016/j.molonc.2012.02.004

23. Dawson DR, El-Ghannam A, Van Sickels JE, Naung NY. Tissue engineering: what is new?. Dental Clinics. 2019;63(3):433-45. https://doi.org/10.1016/j.cden.2019.02.009

24. Hu S, Wang J, Meijer J, Ieong S, Xie Y, Yu T, Zhou H, et al. Salivary proteomic and genomic biomarkers for primary Sjögren's syndrome. Arthritis Rheum. 2007;56(11):3588-600.https://doi.org/10.1002/art.22954

25. Ishida Y, Sugiura Y, Magome T, Kamakura T, Takimoto Y, Hanada Y, et al. Expression Analysis of Serotonin Receptors, Serotonin Transporter and l-Amino Acid Decarboxylase in the Mouse Sphenopalatine Ganglion by RT-PCR, Northern Blot Analysis and In Situ Hybridization. Neuroscience. 2019;411:23-36. https://doi.org/10.1016/j.neuroscience.2019.05.028

26. Grünewald J, Zhou R, Garcia SP. Transcriptome-wide off-target RNA editing induced by CRISPR-guided DNA base editors. Nature. 2019;569(7756):433-7.https://doi.org/10.1038/s41586-019-1161

27. Wang X, Kaczor-Urbanowicz KE, Wong DT. Salivary biomarkers in cancer detection. Medical Oncology. 2017;34(1):1-8. https://doi.org/10.1007/s12032-016-0863-4

28. Padam KS, Chakrabarty S, Kabekkodu SP. In silico analysis of HOX-associated transcription factors as potential regulators of oral cancer. Oral Surg, Oral Med, Oral Pathol and Oral Radiol. 2021;132(1):72-79. https://doi.org/10.1016/j.oooo.2021.01.002

29. Serafini MS, Lopez-Perez L, Fico G. Transcriptomics and Epigenomics in head and neck cancer: available repositories and molecular signatures. Cancers Head Neck. 2020;5(1):1-10. https://doi.org/10.1186/s41199-020-0047-y

30. Huat Siar C, Ng KH. Differential expression of transcription factors Snail, Slug, SIP 1, and Twist in ameloblastoma. J Oral Pathol Med. 2014;43(1):45-52. https://doi.org/10.1111/jop.12065

31. Fabian TK, Fejerdy P, Csermely P. Salivary genomics, transcriptomics and proteomics: the emerging concept of the oral ecosystem and their use in the early diagnosis of cancer and other diseases. Curr genomics. 2008;9(1):11-21. https://doi.org/10.2174/138920208783884900

32. Wong DT. Salivary diagnostics powered by nanotechnologies, proteomics and genomics. J Am Dent Assoc. 2006;137(3):313-21. https://doi.org/10.14219/jada.archive.2006.0180

33. Wei GX, Bobek LA. Human salivary mucin MUC7 12-mer-L and 12-mer-D peptides: antifungal activity in saliva, enhancement of activity with protease inhibitor cocktail or EDTA, and cytotoxicity to human cells. Antimicrob Agents Chemother. 2005;49(6):2336-42. https://doi.org/10.1128/AAC.49.6.2336-2342.2005

34. Locati LD, Serafini MS, Iannò MF, et al. Mining of self-organizing map gene expression portraits reveals prognostic stratification of HPV-positive head and neck squamous cell carcinoma. Cancers (Basel).2019;11(8):1057. https://doi.org/10.3390/cancers11081057

35. Loo JA, Yan W, Ramachandran P. Comparative human salivary and plasma proteomes. J Dent Res. 2010;89(10):1016-23.

https://doi.org/10.1177/0022034510380414

36. Chhabra D, Gaurav K, Hake N. Proteomics and Oral Cancer: The Road Less Travelled. Eur J Mol Clin Med. 2020;7(7):1816-25. https://doi.org/10.1177/0022034510380414
37. Wu Y, Shu R, Luo LJ. Initial comparison of proteomic profiles of whole unstimulated saliva obtained from generalized aggressive periodontitis patients and healthy control subjects. J Periodontol Res. 2009;44(5):636-44. https://doi.org/10.1111/j.1600-0765.2008.01172.x
38. Ngo LH, Veith PD, Chen YY. Mass spectrometric analyses of peptides and proteins in human gingival crevicular fluid. J Proteome Res. 2010;9:1683–93. https://10.1021/pr900775s
39. Hu S, Arellano M, Boontheung P, et al. Salivary proteomics for oral cancer biomarker discovery. Clin Can Res. 2008;14(19):6246-52. https://doi.org/10.1158/1078-0432.CCR-07-5037
40. Papa F, Siciliano RA, Inchingolo F, Mazzeo MF, Scacco S, Lippolis R. Proteomics pattern associated with gingival oral squamous cell carcinoma and epulis: A case analysis. Oral Sci Int. 2018 Jul 1;15(2):41-7. https://doi.org/10.1016/S1348-8643(17)30044-7
41. Singh HP. Estimation of salivary biomarkers in patients with squamous cell carcinoma. Int J Clin Diagn Pathol. 2018;1(1):29-31. https://10.5125/jkaoms.2020.46.5.301
42. Washio J, Takahashi N. Metabolomic studies of oral biofilm, oral cancer, and beyond. Int J Mol Sci. 2016;17(6):870. https://10.3390/ijms17060870
43. Ishikawa S, Sugimoto M, Kitabatake K, Tu M, Sugano A, Yamamori Iet al. Effect of timing of collection of salivary metabolomic biomarkers on oral cancer detection. Amino acids. 2017;49(4):761-70. https://doi.org/10.1007/s00726-017-2378-5
44. Wei J, Xie G, Zhou Z, et al. Salivary metabolite signatures of oral cancer and leukoplakia. Int J Can. 2011;129(9):2207-17. https://doi.org/10.1002/ijc.25881
45. Yonezawa K, Nishiumii S, Kitamoto-Matsuda J. Serum and tissue metabolomics of head and neck cancer. Can Genom Proteom. 2013;10(5):233-8.
46. Fais S, Overholtzer M. Cell-in-cell phenomena, cannibalism, and autophagy: is there a relationship?. Cell Death Dis. 2018;9(2):95.https://doi.org/10.1038/s41419-017-0111-7
47. Wong DT. Salivaomics. J Am Dent Assoc. 2012;143(10):19–24. https://doi.org/10.14219/jada.archive.2012.0339
48. ThamaraiSelvi VT, Brundha MP. Salivaomics-A Review. Eur J Mol Clin Med. 2020;7(1):2914-31.
49. Zarco MF, Vess TJ, Ginsburg GS. The oral microbiome in health and disease and the potential impact on personalized dental medicine. Oral Dis. 2012;18(2):109-20. https://doi.org/10.1111/j.1601-0825.2011.01851.x
50. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Discov. 2022; 12(1):31-46. https://doi.org/10.1158/2159-8290.CD-21-1059

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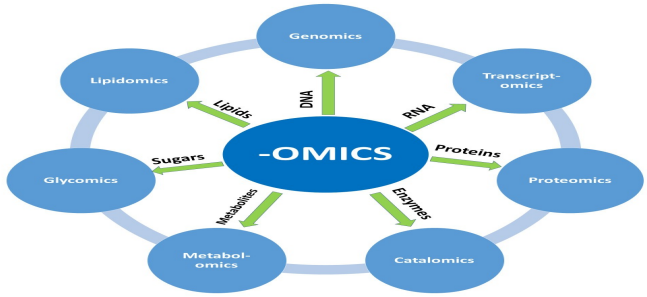

FIGURE 1 Various -omic modalities and their respective analytes

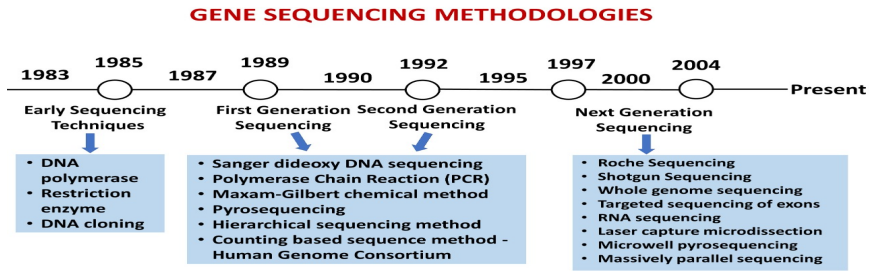

FIGURE 2 Timeline of development of gene sequencing methodologies

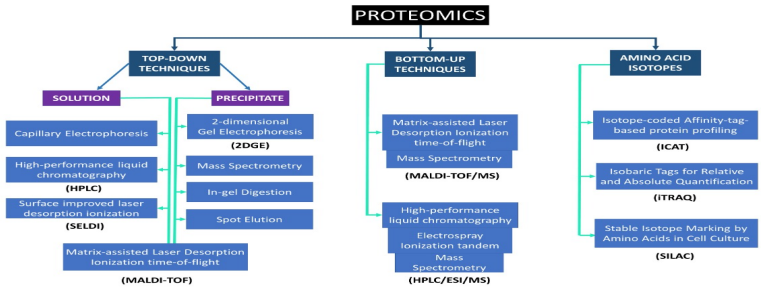

FIGURE 3 Techniques for analysis of proteome