What do the microRNA signatures have to say about oral squamous cell carcinoma?

Oral squamous cell carcinoma (OSCC), the most common type of head and neck squamous cell carcinoma (HNSCC) ranks eighth worldwide.\(^1\) The poor prognosis related to OSCC in majority of the instances is either due to delayed diagnosis or the disease presenting at an advanced stage.\(^2\) The earlier and more precise diagnosis of OSCC may be facilitated by the use of reliable molecular markers which in addition help in determining the prognosis.

For about 30-40 years, changes in tumor promoter and suppressor genes have been thought to be the chief drivers in carcinogenesis.\(^3\) The field of cancer biology has become increasingly more complex than it was thought before, by the advent of thousands of genes that transcribe noncoding RNA molecules. The molecular regulators at various levels participate in both the development as well as in maintenance of the phenotypes of cancer. Among these molecules, recent reports have shown that microRNAs (miRNA) have drawn significant attention, attributed to their effects as regulators and as potential biomarkers for human cancer development.

Originally found in Caenorhabditis elegans, miRNA is present in many eukaryotes, inclusive of humans. miRNAs are small single-stranded, noncoding RNA molecules which are evolutionarily conserved. These miRNA generated from diverse loci of human genome play an important role in the regulation of gene expression, thus controlling various cellular and metabolic pathways. miRNA molecules bind target mRNA and thus prevent protein synthesis.\(^4,6\)

Even though the biological functions of the miRNA are not completely understood, their expression profiles furnish details on their regulation and function.

There is a lot to unfold about the expression profiles of these tiny molecules, but the basic expression profiling is found to be clinically relevant to diagnosis and prognosis of cancer.

A single miRNA is capable of regulating the expression of hundreds of target mRNAs and further, the protein synthesis involved in several biological processes (such as proliferation of cells, differentiation, apoptosis, signal transduction, migration and so on), have significant impact on cancer development.\(^7\) Many miRNAs may function either as tumor promoters or as suppressors. A good number of miRNAs functioning as oncogenes have been reported to be upregulated in OSCC; miR-21 is one such molecule. The oncogenic role of the miR-21 is by enhancing the cell proliferation, anti-apoptosis, invasion, and chemoresistance.\(^8-11\) One more oncogenic miRNA, miR-31 is found to be upregulated in oral leukoplakia and OSCC. miR-31-factor-inhibiting hypoxia-inducible factor (HIF)-HIF-vascular endothelial growth factor regulatory cascade has been found to affect cell proliferation, migration and epithelial-mesenchymal transition in OSCC cells.\(^12\)

The mir-134 expression has been shown to be upregulated in HNSCC tissues and cells. miR-134 targets the WW domain-containing oxidoreductase.\(^13\)

Various miRNAs have been shown to be downregulated in OSCC. miR-320 is one such molecule and its expression is inversely correlated with the vascularity.\(^14\) miR-7 is found to function as tumor suppressor in OSCC by regulating insulin-like growth factor 1 receptor (IGF1R)/IRS/Pi3K/Akt signaling pathway by posttranscriptional regulation of IGF1R.\(^15\)

Evidence has shown that miRNA has a role to play in the regulation of components of extracellular matrix such as matrix metalloproteinases and integrins.\(^16\)

The expression of miRNA molecules in the serum and saliva has made them to be very useful for non-invasive clinical application.\(^17,18\)

There are reports suggesting that the signatures of miR-16, let-7b, miR-338-3p, miR-223, and miR-29a might be used as potential biomarkers for detection of oral cancer.\(^19\) miR-21, miR-31, miR-17/20a, and miR-155 signatures have been found to be associated with prognostic predictors.\(^10,19,20\)

Accumulating evidence has shown that altered expression of several miRNAs is important for oral carcinogenesis and its further progression. Much more light is to be shed by tracking the identified miRNA signatures, to pave the way for their future clinical use in the diagnosis, management, and prognosis of OSCC.

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