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Letter to the editor

How far can regulating TRIM16 help reduce malignant transformation of OPMD's to OSCC?

Wirth quoted in his paper about chemopreventive agents for squamous cell carcinoma (SCC) in head and neck 'Getting the drug right is, of course, the holy grail of chemoprevention" [1]. Regrettably, he too accepted, a clear winner has not yet emerged irrespective of several themes over decades.

For that matter, Vitamin A and its biologically active derivatives, retinal and retinoic acid (RA), collectively with a gamut of synthetic analogues referred to as retinoids [2] are well-known to induce growth arrest, cell death, and differentiation in cancer cells [3]. A complete network of nuclear receptors have now been acknowledged to mediate the action of retinoids and can impede cell proliferation signals by interacting with transcription factors [3]. Retinoids are also known to exert an impact on the role immune cells including macrophages, T cells and dendritic cells (DCs) in tumour tissue to execute anti-tumour actions [4]. The use of retinoids in chemoprevention strategies, understanding the cellular consequences of activated retinoid receptors and retinoid-induced signalling pathways may altogether augment the future therapeutic strategies of malignant transformation of oral potentially malignant disorders (OPMD's) to oral squamous cell carcinoma (OSCC) [2].

In latest scientific realm, it has been established that cancer cells can modulate the cell stress mechanism. Under the direction of tripartite motif-containing protein 16 (TRIM16), cells adapt to survive severe stressful environment including oxidative stress [5]. TRIM16, a member of a large family of tripartite motif (TRIM) proteins (also known as the RBCC family or oestrogen-responsive B box protein (EBBP gene)) is located on chromosome 17p11.2. This protein family is characterized by three zinc-binding domains, a RING, a B-box type 1, and a B-box type 2, followed by a coiled-coil region [6]. TRIM proteins are well known to be associated with diverse cellular processes, ranging from innate immunity, oncoprotein, and tumor suppressor roles [7]. As a well-recognized retinoid signalling molecule TRIM 16, its known to regulates keratinocyte differentiation and acts as a tumour suppressor in retinoid-sensitive neuroblastoma [7,8].

Understanding its association with several types of carcinomatous changes, few of the studies revealing TRIM 16's association to retinoids are described below:

- Cheung et al., concluded in 2012 that vimentin was directly bound and down-regulated by TRIM16 and was required for TRIM16-reduced cell migration suggesting that loss of TRIM16 expression was instrumental in the development of cutaneous squamous cell carcinoma (SCC) and is a determinant of retinoid sensitivity [6].
- In a different study, Cheung et al., found overexpression of TRIM16 reduced cell viability and proliferation in multiple melanoma tumor cell lines. It also decreased cell migration and induced apoptosis in melanoma cells [7].
- Kim et al., in 2016 have identified transactive response DNA-binding protein 43 (TDP43) as a novel TRIM16 binding protein and showed that TRIM16 inhibits cancer cell viability by a novel mechanism involving interaction and stabilisation of TDP43 with consequent effects on E2F1 and pRb proteins [8].

As stated in the paper by Jena et al., TRIM16 streamlines the process of stress-induced aggregate clearance and protects cells against oxidative/proteotoxic stress-induced toxicity both in vitro and in vivo. Literature search reveals, along with quantification of allelic imbalance, including loss of heterozygosity (LOH) or allelic amplification, TP53 mutation, non-genomic activation of pro-proliferative signaling by the epidermal growth factor receptor (EGFR) and cyclooxygenase-2 (COX-2), field cancerization, etc., oxidative stress too can propagate the evolution from normal to premalignant to frankly malignant cell populations [9].

Though TRIM16 has not been relevantly studied in OPMDs and OSCC still Human Protein Atlas [10] shows a high expression in squamous epithelial cells of oral mucosa. Therefore, a well-planned strategy can be proposed to target this signalling molecule to curb the malignant transformation in form of therapeutics.

Conflict of interest

None.

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