Original Article

"Neuroectodermal influence of CD 99 immunoexpression correlates with the clinical behavior of odontogenic cysts and tumors"

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Abstract

Background: Odontogenic tumors show a variety of characteristic features that are dependent on the tumor cell origin and the stage of tumor cell differentiation. Odontogenic cysts arise from the enamel organ or remnants of dental epithelium which influences their pathogenetic model and further clinical behavior of these lesions.

Aim: The study aims at assessment of CD 99 immunoexpression in odontogenic keratocyst (OKC) and ameloblastoma (in tooth bearing [anterior to third molar] and nontooth bearing areas [molar ramus area]) to postulate neural influence in their pathogenesis and the clinical behavior.

Materials and Methods: Immunohistochemical analysis for CD 99 was performed on paraffin-embedded tissue sections on 50 histopathologically confirmed cases of OKC and ameloblastoma (25 each) arising within the oral cavity and were scored qualitatively, topographically, and according to cellular localization.

Statistical Analysis: The resulting data were analyzed using the SPSS software version 20.0. The significance of the parameters was tested by the Pearson's Chi-square test ($P \leq 0.05$ as statistically significant).

Results: CD99 immunoreactivity was distributed in both tooth bearing and nontooth bearing groups of OKC and ameloblastoma with an increased immunoexpression in basal and suprabasal layers of OKC in nontooth bearing area and in peripheral cells of ameloblastoma in nontooth bearing area confined to the cell membrane.

Conclusions: The results point toward the role of CD99 in the pathogenesis and aggressive behavior of such odontogenic lesions and it can be used as a promising therapeutic target.

Keywords: Ameloblastoma, CD 99, neuroectodermal influence, odontogenic keratocyst

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INTRODUCTION

Odontogenesis is the culmination of copious sequential genetic and epigenetic events. Peculiar proliferations in the consequence of disturbances in control mechanisms of these ordered events can result in an array of odontogenic cysts and tumors, which may arise from the odontogenic

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apparatus and its remnants at any stage of life in an individual.[1] Teeth develop from interaction of epithelial cells and cranial neural crest-derived ectomesenchymal cells in the developing oral cavity.[2]

The World Health Organization (WHO) defines odontogenic tumors as the lesions derived from epithelial, ectomesenchymal, or mesenchymal elements that still are or have been part of the tooth forming apparatus.[3] Similarly, odontogenic cysts arise from the enamel organ or remnants of dental epithelium. Odontogenic keratocyst (OKC) has been shown to be a locally aggressive lesion with high local recurrence rate comparable to ameloblastomas.[4] Jiang *et al*. reported that under exceptional conditions, a subset of basal cells in the adult gingival epithelium could revert to the fetal form that was capable of ameloblastic differentiation, subsequent proliferation, and eventually, uncontrolled growth.[3] During early embryogenesis, neural crest cells (NCCs), a multipotent cell population, migrate from the crests of the neural folds into the ventral embryo and give rise to various cell, tissue, and organ structures throughout the whole body, especially the major part of mesenchymal cell population in the craniofacial region.[5]

CD 99 is a 32-kD type I cell surface transmembrane glycoprotein expressed in various tissues such as in the epidermal basal cell layer, hair bulge, outer root sheath, and dermal papilla. CD 99 is strongly expressed in immature basal keratinocytes and there is an evidence for strong positivity of CD 99 for populations of stem cells located at the basal layer of the epidermis and the hair follicle bulge.[6] It is involved in many essential cellular functions such as cell adhesion and migration, cell death and differentiation, intracellular protein trafficking, endocytosis and exocytosis, and metastasis of tumor cells through multiple and still controversial mechanisms of action, thereby emerging as a novel therapeutic target.[7]

A point open to speculation is that an abnormal triggering of odontogenic signalling pattern in the tissues at any point of time after cessation of odontogenesis could initiate a similar process leading to the proliferation of oral epithelium. Recent insights into the channel of molecular mechanisms accountable, the earliest of formative stages of cells can be studied in a coherent manner enabling us to assimilate knowledge on the development of tissues and further, disturbances in physiological mechanisms which are recapitulated in the pathogenesis of odontogenic lesions. Thus, the present study was designed to analyze and interprets the immunoexpression of CD99 in OKC and ameloblastomas (in tooth bearing [anterior to third molar] and nontooth bearing areas [molar ramus area]). Further, to postulate their neural influence in the formation of odontogenic lesions (OKC and Ameloblastoma) and to interpret the biological behavior of odontogenic lesions (OKC and Ameloblastoma) through CD 99 immunoexpression.

MATERIALS AND METHODS

Patients and tissue samples

The study was conducted in the Department Of Oral and Maxillofacial Pathology and Microbiology, I. T. S Dental College, Muradnagar, Ghaziabad, on archival tissue samples which were submitted for the histopathological evaluation. Study samples consisted of total 50 histopathologically confirmed cases of OKC and ameloblastoma (25 each) arising within the oral cavity. The samples were fixed in 10% neutral-buffered formalin and embedded in paraffin wax to obtain 3μ sections for immunohistochemistry procedure. Ethical approval from the institutional review board was obtained for this study.

Grouping of tissue specimen

Tissue specimens were grouped based on histopathological criteria mentioned in the WHO book as Group 1 – OKC-25 cases and Group 2 – Ameloblastoma-25 cases. Complete clinicopathologic data of the cases were retrieved, cases with biopsy of adequate size-minimum 4 mm × 4 mm in diameter was taken and any biopsy having processing/fixation artefact was omitted. Recurrent/secondary cases of odontogenic lesions with any therapeutic interventions were excluded.

Immunohistochemistry with CD99

Three-micrometer-thick sections from archival formalin-fixed paraffin-embedded tissues were placed on poly-L-lysine-coated slides for immunohistochemistry. CD99 immunoexpression was analyzed by the immunohistochemical examination with the antibody. For each case, the deparaffinized tissue sections were placed in 10 mmol/L citrate buffer, pH 6.0 and heated to cycles of 95°C and 98°C for 13 min. Immunohistochemical staining for the protein was performed by the avidin-biotin complex procedure with a streptavidin biotin complex peroxidase kit. Primary antibody-monoclonal anti monoclonal anti-CD99 antibody (Biogenex Ind Pvt. Ltd., Clone number-EP8, Catalogue number-AN850-5M) along with secondary antibody-poly-HRP secondary detection system (Biogenex Ind Pvt Ltd) were used. For CD99, Ewing sarcoma served as the positive control. Positive staining for CD99 was seen as localization in both membrane and cytoplasm within the cell in the form of crisp brown color.

Assessment of immunoscoring

CD99 immunostaining in study cases was evaluated using a modification of the criteria described by Renshaw[8] In each case, the intensity of immunostaining in the epithelial cells in five randomly selected high-power fields (×40 magnification) were scored on a scale of 0 to + 3 after comparing the intensity with positive control. The CD99 immunoexpression was also evaluated on the basis of cellular localization (according to Pelosi *et al*.)[9] as 0 – absence of staining, 1 – membranous only, and 2 – membranous and cytoplasmic. Topographical analysis of the immunoexpression for OKC immunoexpression was evaluated only in basal layer, basal and suprabasal layer and in basal, suprabasal and superficial layer, whereas in ameloblastoma, immunoexpression was evaluated as only in peripheral cells, only in central cells and in both central and peripheral cells.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS, IBM Inc. California, USA). The data collected were first visualized to confirm their normal distribution. The descriptive statistics like frequency distribution of data was calculated. The significance of the parameters was tested by Pearson's Chi square test. The 95% confidence interval and 5% level of significance was used for analysis of data. A $P \leq 0.05$ was considered statistically significant.

RESULTS

Demographic data

Among the study groups of OKC, 52% cases were above 30 years of age with 56% male preponderance. Seventy-six percent cases were present in mandible and 24% in the maxilla. Eighty-four percent cases were present in tooth bearing area and 16% cases in nontooth bearing area (molar ramus area). Similarly, the distribution of ameloblastoma study groups showed 72% cases of age above 30 years with 72% male preponderance. Eighty-eight percent cases were present in mandible and 12% cases in the maxilla. Twenty-four percent cases were present in the tooth bearing area and 76% cases in nontooth bearing area (molar ramus area) [Figures 1 and 2].

Qualitative, topographical and cellular localization assessment of CD99 immunoexpression in tooth bearing and nontooth bearing area of study cases

Among the 25 cases in each group, 17/25 (68%) cases were positive and 8/25 (32%) were negative in OKC group, whereas 22/25 (88%) cases were positive and 3/25 (12%) cases were negative in ameloblastoma group. Among the study cases in OKC, 84% cases were distributed in tooth bearing area and 16% cases in nontooth bearing area. CD99 immunoexpression was positive in 14 cases of tooth bearing area and 3 cases of nontooth bearing area, whereas among the study cases in ameloblastoma, 24% cases were distributed in tooth bearing area and 76% cases in nontooth bearing area. CD 99 immunoexpression was positive in all cases of tooth bearing area and 13 cases of nontooth bearing area [Figure 3].

Among the 84% cases of OKC in tooth-bearing area, majority of cases showing weak immunostaining, whereas among the 16% cases in nontooth bearing area, majority showed intense staining. Similarly, among the 24% cases of ameloblastoma in tooth bearing area, majority of cases showed weak immunoexpression of CD99, whereas 33.3% cases showed moderately intense staining. In the nontooth bearing group of ameloblastoma, 15.7% cases were negative for immunoexpression of CD99, followed by 31.5% cases showed weak immunostaining, 26.3% showed moderate intensity and 26.3% cases showed strong intensity [Table 1].

For the topographical analysis, among the 84% cases of OKC in tooth bearing area, 33.3% cases showed negative immunoexpression of CD99 followed by majority of cases with immunoexpression in the basal layer. Similarly, among the 16% cases in nontooth bearing area, 25% cases each showed the presence of immunoexpression in basal, basal and suprabasal and all layers, respectively. Among the 24% cases of ameloblastoma in tooth bearing area, majority of cases (50%) showed positive immunoexpression of CD99 in only the central cells. In the nontooth bearing group of ameloblastoma, majority of cases showed positive immunoexpression in only the peripheral cells. For the cellular localization of CD99 immunoexpression, all the cases of OKC present in nontooth bearing area showed immunoexpression confined to membrane of the cell, whereas in tooth bearing area, 61.9% cases showed immunoexpression in the membrane and 9.5% showed immunoexpression in both membrane and cytoplasm. In ameloblastoma, all cases of tooth bearing area showed immunoexpression in the cell membrane only, whereas 47.3% cases showed membranous expression in nontooth bearing area.

DISCUSSION

Basal cell layer of the oral epithelium has been rightfully regarded as a potential source of odontogenic tumors and cysts but without substantial evidence.[10] Studying the expression of neuroectodermal marker in the OKC

Table 1: Correlation of CD99 immunoexpression intensity, topographical and cellular localization assessment in tooth bearing and nontooth bearing area of odontogenic keratocyst and ameloblastoma

Parameter	Study group	Intensity	Tooth bearing area (%)	Nontooth bearing area (%)	*P*
Intensity	OKC	Absent	7/21 (33.3)	1/4 (25)	≤0.05
		Weak	8/21 (38)	1/4 (25)	
		Moderate	4/21 (19)	0	
		Intense	2/21 (9.5)	2/4 (50)	
	Ameloblastoma	Absent	0	3/19 (15.7)	>0.05
		Weak	4/6 (66.6)	6/19 (31.5)	
		Moderate	2/6 (33.3)	5/19 (26.3)	
		Intense	0	5/19 (26.3)	
Topographical immunoexpression	OKC	Absent	7/21 (33.3)	1/4 (25)	≤0.05
		Basal	9/21 (42.8)	1/4 (25)	
		Basal and suprabasal	4/21 (19.0)	1/4 (25)	
		Basal, suprabasal and superficial	1/21 (4.7)	1/4 (25)	
	Ameloblastoma	Absent	0	3/19 (15.7)	>0.05
		Peripheral	1/6 (16.6)	9/19 (47.3)	
		Central	3/6 (50)	1/19 (5.2)	
		Peripheral and central	2/6 (33.3)	6/19 (31.5)	
Cellular localization	OKC	Absent	6/21 (28.5)	0	>0.05
		Membranous only	13/21 (61.9)	0	
		Membranous and cytoplasmic	2/21 (9.5)	4/4 (100)	
	Ameloblastoma	Absent	0	3/19 (15.7)	>0.05
		Membranous only	6/6 (100)	9/19 (47.3)	
		Membranous and cytoplasmic	0	7/19 (36.8)	

OKC: Odontogenic keratocyst

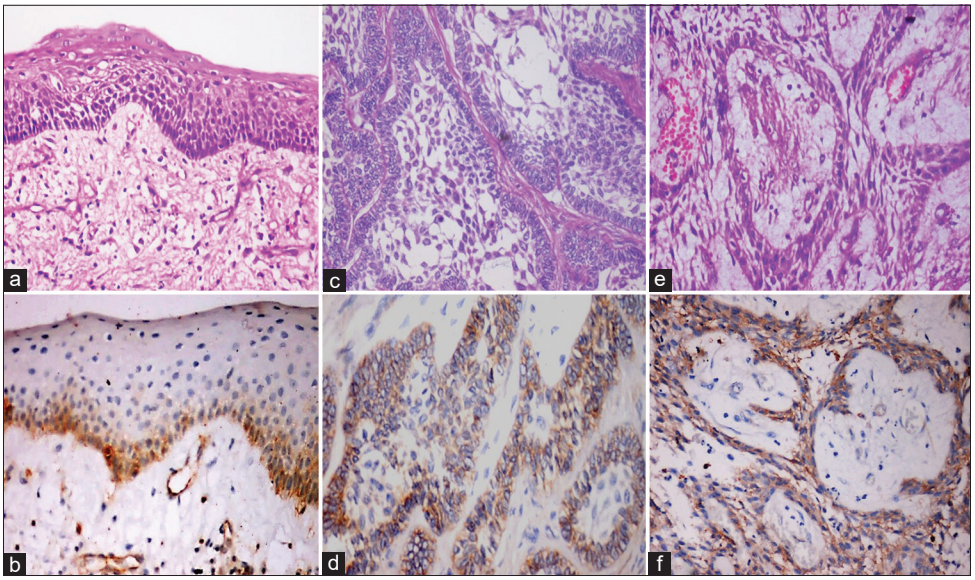

Figure 1: (a) Hematoxylin and Eosin stained section of Odontogenic Keratocyst (H and E stain, ×40 magnification), (b) CD99 immunoexpression seen as positive membranous and cytoplasmic staining in the basal and suprabasal cells of Odontogenic Keratocyst (Immunohistochemistry, ×40 magnification), (c) Hematoxylin and Eosin stained section of Follicular Ameloblastoma (H and E stain, ×40 magnification), (d) CD 99 immunoexpression seen as positive membranous and cytoplasmic staining in the peripheral cells of Follicular Ameloblastoma (Immunohistochemistry, ×40 magnification), (e) Hematoxylin and Eosin stained section of Plexiform Ameloblastoma (H and E stain, ×40 magnification), (f) Moderately intense positive membranous immunoexpression of CD99 seen in the peripheral and central cells of Plexiform Ameloblastoma (Immunohistochemistry, ×40 magnification)

and the amelobastoma might throw light on such an assumed potential thus providing an insight to their origin, tumorigenesis and prognosis. Tooth development occurs from a restricted region of anterior cranial neural crest. The neural crest, a quintessential vertebrate tissue has the potential for odontogenesis, thus having a developmental and evolutionary significance which is recapitulated during the pathogenesis of odontogenic lesions.[5]

CD99 is a transmembrane molecule that is encoded by the MIC2 pseudoautosomal gene (Pasello *et al.* 2018) and its highly O-glycosylated and together with Xga and CD99 antigen-like 2 constitutes a family of molecules that show no homology to any other known family.[11] In variable set of tumors, CD99 delivers oncosuppressor signaling and its re-expression leads to reversal of malignancy. CD99 regulates neural differentiation of Ewing sarcoma cells

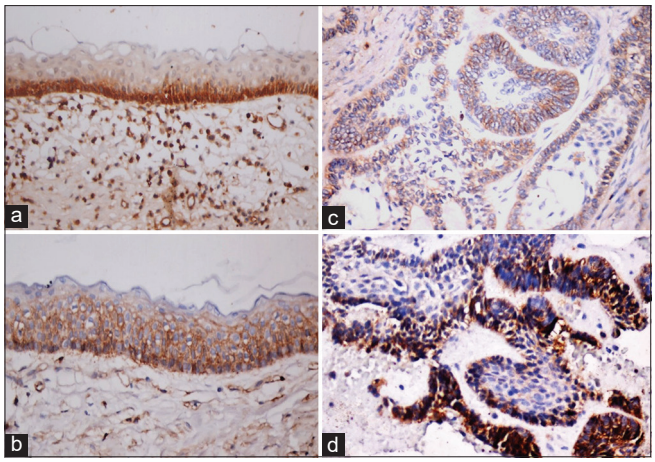

Figure 2: (a) CD99 immunoexpression seen as strong positive membranous and cytoplasmic staining in the basal cell layers of Odontogenic Keratocyst in tooth bearing area (Immunohistochemistry, ×40 magnification), (b) CD99 immunoexpression seen as strong positive membranous in the basal, suprabasal and superficial cell layers of Odontogenic keratocyst in nontooth bearing area (Immunohistochemistry, ×40 magnification), (c) CD99 immunoexpression seen as moderately intense membranous staining in the peripheral cells of Ameloblastoma in tooth bearing area (Immunohistochemistry, ×40 magnification) (d) CD99 imunoexpression seen as strong positive membranous staining in the peripheral and central cells of odontogenic islands of nontooth bearing Ameloblastoma (Immunohistochemistry, ×40 magnification)

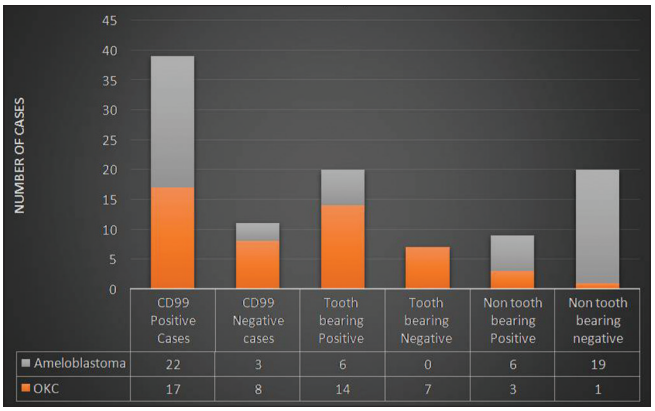

Figure 3: Comparison of CD99 immunoexpression in tooth bearing and nontooth bearing region of Odontogenic Keratocyst and Ameloblastoma

through miR-34a-Notch-mediated control of nuclear factor-kappa B signaling which is the evidence to the downstream regulation of various proliferative pathways.[12] The increased intensity of expression in few cases can be taken into account for the various other roles manifested by CD99 such as motility, anti-apoptotic property and aggressiveness as well as its neuroectodermal influence can be regarded for their pathogenesis.

Takeda *et al.* studied immunohistochemical expression of neural tissue markers such as neuron specific enolase (NSE), glial fibrillary acidic protein and S100 in other odontogenic tumors, i.e. ameloblastic fibrodentinoma. They had suggested that the functional significance of NSE expression in reactive and neoplastic cells may be related to the increased metabolic demands of neoplasia.[13] Kusafuka *et al.* assessed immunohistochemically ameloblastoma which showed positivity for CD56 and N-cadherin in outer columnar cells of odontogenic islands suggesting that the cells might be transdifferentiating to the neuroectodermal cells during tumorigenesis.[14]

It has been shown previously using proliferative markers (such as PCNA and Ki67), that basal and suprabasal layers show increased proliferative activity Li *et al.*[15] el Murtadi *et al.*,[16] and Piattelli *et al.*[17] de Oliveira *et al.*[18] believe that OKC exhibits proliferation and maturation patterns differ from other odontogenic cysts. Li *et al.*[15] hypothesized that a unique epithelial differentiation process exists, in which the basal cells assume some characteristics of preameloblasts, indicating that it might have entered, to some extent, toward ameloblast differentiation. Browne[19] supported this hypothesis by stating that for a cell to enter a differentiation pathway, it must first leave the cell cycle. The presence of differentiated cell in the basal layer probably accounts for the fact that the major proliferation compartment is suprabasal. This peculiar distribution of proliferative cells in a suprabasal location in OKC could be due perhaps to inductive influences of the underlying connective tissue as suggested by Piattelli *et al.*[17] Similarly, the increased expression of CD99 can be correlated with the level of proliferative pool in the basal and suprabasal layers of OKC confined mostly to the cell membrane. This can be accounted due to the fact that CD99 induces extracellular signal-regulated protein kinases ERK activation, increasing its membrane bound/cytoplasmic form rather than affecting its nuclear localization which is a further signal transducer of other proliferative pathways. ERK 1 and 2 are the members of the mitogen-activated protein kinase super family that can mediate cell proliferation and apoptosis.[20]

Huysseune[21] stated that there are two phases in the process of securing the formation of a replacement tooth, that are likely acting independently: the development of a successional lamina linked to the eruption of the predecessor and the start of morphogenesis and differentiation of the tooth germ proper, which can, but not necessarily does, immediately follow the formation of the successional lamina.[21] Among the OKC in tooth bearing area, 66% were positive for CD99 immunoexpression, whereas 75% cases of nontooth bearing area were positive for CD99 immunoexpression [Figure 3] pointing toward the role of basal cell hamartias in the origin of cases

lying in molar ramus region which are incorporated in the bony structure during the time of development. In our study, we had only 24% cases from tooth bearing area in ameloblastoma, whereas 76% were present in molar ramus area, of which 68.4% were positive for CD99 immunoexpression [Figure 3].

In our study, we also correlated the immunoexpression of CD99 in tooth bearing and nontooth bearing areas of OKC and ameloblastoma qualitatively, topographically and according to cellular localization [Table 1]. Our findings suggested that the qualitative immunoexpression was more intense in nontooth bearing area group of OKC (50% cases) as compared to the tooth bearing area group of OKC (38% cases). Similarly, none of the case in tooth bearing area group of ameloblastoma showed intense staining with 42.8% cases showing <25% cells positive, whereas 26.3% number of cases each showed moderate to intense staining for CD99. This point towards the more aggressive nature of nontooth bearing area OKC and ameloblastoma.

In the present study, OKC of tooth bearing area group, majority, i.e. 42.8% cases showed CD99 immunoexpression confined only to the basal layer whereas in the nontooth bearing area cases, immunoexpression was equally distributed in all the cell layers. The expression in the basal layer is accountable to be constitutive as the epithelium derives from NCCs.

Remnants of the epithelial lining, satellite cysts and microcysts left in the overlying mucosa are all factors that have been proven to contribute to increased pathogenesis, origin and recurrence of the cyst and tumors.[22-26] Satellite cysts and epithelium remnants also referred to as basal cell hamartia may be preserved in the proximal bone after surgical modalities. Although OKC and ameloblastoma is thought to arise from the odontogenic epithelial remnants, the neuroectodermal differentiation phenotype in these lesions and the relationship between tumorigenesis and NCCs remain unknown.[27] CD99 is involved in multiple pathways which involve not just its neuroectodermal influence but also other characteristics that need to be studied in an integrated and comprehensive manner, to use it as a target molecule in the therapeutic intervention beneficially [Figure 4].[28-30]

CONCLUSIONS

Basal cell layer of the oral epithelium has rightfully been regarded as a potential source of odontogenic cysts and tumor especially in nontooth bearing areas where the odontogenic apparatus is missing to be incorporated in their pathogenesis. This assumption has got credence in since the immunoexpression of CD99 is increased especially in nontooth bearing area groups of OKC and ameloblastoma. The accounts in the literature for varying aggressive behavior of odontogenic lesions need to be explained since all the lesions arise *de novo* from developing odontogenic apparatus. This differing behavior could be related as seen in the present study to the critical role of the patterns of neuroectodermal differentiation taking place. The varying mode, patterns and sustained activity of CD99 seen in our study could actually be the triggering factor for neuroectodermal influence in odontogenic lesions.

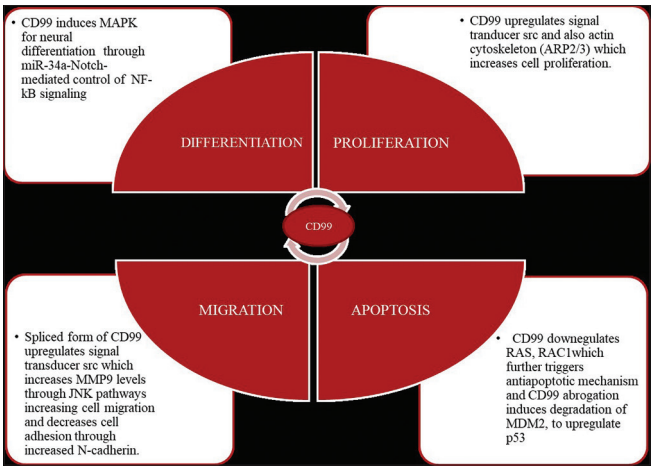

Figure 4: Multidirectional role of CD99 in disease progression: The isoforms of CD99 i.e., wild type and spliced variety that have role in various downstream pathways such as cell adhesion and migration, cell death and differentiation, intracellular protein trafficking and apoptosis which results in its designation as oncojanus molecule with both oncogenetic and oncosuppressive role. Apart from being a key molecule in neural differentiation, CD99 regulates molecules such as MMP for migration of tumor cells, src signal transducer for proliferation of cells and p53 for dysregulation of cells

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Conflicts of interest

There are no conflicts of interest.

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