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Review Article

Role of Cyclooxygenase-2 – Peroxisome Proliferator-Activated Receptor Gamma Pathway in the Pathogenesis of Sebaceous Gland Carcinoma

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Abstract

Sebaceous gland carcinoma (SGC) is an uncommon malignancy of the skin, known to be very aggressive, recurrent and with a tendency to metastasize. Owing to a low global prevalence, there are significant lacunae in understanding the pathogenesis of SGC. In this review, the role of Cyclooxygenase-2-Peroxisome proliferator-activated receptor gamma signaling pathway in SGC including that of the eyelids has been discussed. Findings of a moderate to high expression of Cyclooxygenase-2 (COX-2) activity in a few studies suggest its probable role as a marker for pathogenesis of SGC. Peroxisome proliferator-activated receptor (PPAR) subtype, PPAR γ is also reported to show association with the level of differentiation in sebaceous gland tissues, especially in case of SGC. Also, PPAR γ agonists are evidenced to show anti-tumorigenesis properties. In eyelid SGC, studies are suggestive of an overexpression of COX-2. Further, successively decreasing levels of PPAR γ expression is shown to be associated with significant loss of differentiation. Though the evidence available is discussed, however, to better understand the role of COX-2 – PPAR γ pathway in pathogenesis of SGC further research is warranted.

Keywords: Cyclooxygenase-2 (COX-2); Sebaceous Gland Carcinoma (SGC); Peroxisome Proliferator-Activated Receptor Gamma (PPAR γ); Eyelid

Introduction

Non-melanoma skin cancers are the predominant variety of cancers of the periocular region, primarily including basal cell carcinoma (BCC), squamous cell carcinoma (SCC) and sebaceous gland carcinoma (SGC) [1]. Being the more preponderant varieties, both BCC and SCC are extensively studied, whereas, the etiology of SGC is least explored except for evidence of its high prevalence in the eyelids [2]. At the molecular level, apart from the involvement of p53 tumor suppressor gene, Wnt, c-myc and hedgehog signaling pathways [3,4], not much is known regarding pathogenesis of SGC.

Extensive research for identification of molecular markers indicates over expression of proteins related to angiogenesis, inflammation and cell proliferation in SGCs. Cyclooxygenase-2 (COX-2) is one such protein whose over expression may be associated with SGC [5,6]. It is a subtype of cyclooxygenases, which are enzymes involved in the metabolism of fatty acids and primarily conversion of arachidonic acid to prostaglandin. With the extensive study of the role of COX-2 in tumor development and progression, elevated expressions of this enzyme are reported in several types of cancer [7-9].

Cell proliferation of sebaceous gland cells leads to an increase in lipogenesis and thus sebum formation, one of the proteins responsible for which is Peroxisome Proliferator Activated Receptor Gamma (PPAR γ) [10]. It belongs to the nuclear hormone receptor family that is known to modulate the function of adipose tissues, inflammation and regulation of cell cycle. PPARs are also known to regulate the growth of cancer cells [11,12].

The COX-2 – PPAR γ signaling pathway is therefore suggested to be playing a significant role in the pathogenesis of SGC.

Sebaceous Glands and its Carcinoma

Sebaceous glands: Development, function and regulation

Excluding the palms and soles, sebaceous glands are ubiquitous in areas of the skin having hair follicles. With preponderance on the face and scalp, these secrete a waxy, lipid-rich fluid called sebum that nourishes the hair follicle [13]. Sebaceous glands are composed of three distinct zones: the peripheral, the maturation and the necrotic zones. Cells of the peripheral zone constantly undergo mitosis and move towards the center of the gland while differentiating. Cells of the maturation zone are called sebocytes, store lipids in their cytoplasm and thereby gradually increase in size. Once fully grown, they move towards the necrosis zone where they are fragmented and the lipid content is released as sebum [4,13,14].

The major role of sebum is to act as a barrier on the surface of the skin, defending it against pathogens and protecting it from dehydration. Cholesterol, cholesteryl esters, triacylglycerides, diacylglycerides and other fatty acids are the main components of human sebum [4]. The type of sebum produced in the eyelids is called meibum as it is secreted by the meibomian glands. Meibum averts the sticking of lower and upper eyelids with each other by providing lubrication and delays the evaporation of tears [15].

A variety of hormones, cytokines, signaling molecules and other factors involved in lipid metabolism maintain the homeostasis of the sebaceous glands. Signals sent to its progenitor cells bring about the renewal of these glands thereby controlling the balance between their proliferation and differentiation [13]. An imbalance leads to various pathologies of the sebaceous gland.

The sebaceous glands play a reasonably important role in our body. Origin of several skin disorders including SGC has been directly linked to the down-regulation of skin homeostasis and imbalance in the reparative process of sebaceous glands [14]. Three pathways are known to play a role in the development and functional regulation

of sebaceous glands, namely, the Wnt, c-myc and the Hedgehog signaling pathways [4]. An imbalance in any of these pathways may be responsible for tumorigenesis in the sebaceous glands (Table 1). Also, a significant nuclear over expression of p53 is observed in periocular SGC tissue [16]. Studies also suggest that mutational inactivation of p53 may be involved in the development of SGC [17].

Sebaceous gland carcinoma: Distribution, diagnosis and therapy

SGC accounts for upto 4.6% of all malignant skin tumors and can be broadly classified into peri-ocular/ocular and extra-ocular, with the former having an incidence of nearly 75% [18-20]. Its similarity in appearance with benign lesion/nodules and difficulty in identifying poorly differentiated cells during histopathological analyses are the main reasons for its frequent misdiagnosis. This leads to its diagnosis at an advanced stage of the disease and therefore delayed treatment.

As per the current guidelines, the mainstay of treatment of ocular SGC that is diagnosed early is wide surgical resection under frozen section or Moh's micrographic surgery control followed by eyelid reconstruction. An emerging technique of posterior lamellar resection of the eyelids with reconstruction, holds the promise of decrease in of its recurrence [21,22]. Recently through a retrospective analysis, Takagawa et al., suggested radiotherapy as an alternative to surgery for provided the tumor is localized and is less than 10mm in size [23].

In late cases - orbital exenteration, cryotherapy, radiation therapy, chemotherapy, or combination therapy are used [21]. Chemotherapy with carboplatin and pembrolizumab after orbital exenteration has been reported to be an effective treatment in a recent case of recurrent and metastatic SGC [24]. Neoadjuvant chemotherapy combining 5-Fluorouracil with carboplatin was also found to be useful in management of SGC [25]. Further, in late cases, multimodal therapy has been shown to improve both visual prognosis and survival [21,26].

Role of COX-2 – PPAR γ PATHWAY in the Development of SGC

The probable role of COX-2 and PPAR γ in the pathogenesis of SGC is reviewed in the following sections.

Role of COX-2 in cancer and SGC

Cyclooxygenases are known to be present as two isoforms: COX-1 and COX-2. COX-1 is expressed in most tissues and controls physiological functions like maintenance of gastric mucosal lining and renal blood flow regulation by mediating prostaglandin synthesis [27]. COX-2, uncommon in normal tissues, is induced in response

Table 1: Signalling Pathways associated with SGC

Pathway	Abnormal Expression	Association with SGC	References
Wnt/ β -catenin	Overexpression of β -catenin	Initiation of sebaceous tumors, metastasis	[85–87]
C-myc	Overexpression of c-myc	Hyperplasia of sebaceous glands	[88,89]
Hedgehog	Ectopic hedgehog expression (due to gain-of-function mutation in its receptor)	Hyperplasia of sebaceous glands, metastasis, Overexpression of c-myc	[87,90,91]
p53	Expression of mutant form of p53	Neoplasia of sebaceous glands	[16,17]

to growth factors; pro-inflammatory cytokines, mechanical tissue damage, and UV light [28]. Many recent studies report higher expressions of COX-2 mRNA in colorectal, lung, breast and prostate cancers, thereby suggesting a possible role of COX-2 in promoting tumor development [29].

Overexpression of COX-2 is evidenced to be associated with inhibition of apoptosis, angiogenesis and metastasis. This enzyme also shows peroxidase activity that can result in the conversion of pro-carcinogens to carcinogens. COX-2 has the potential to co-oxidize xenobiotics like benzopyrene to mutagens by its peroxidase activity in tissues like colon [30]. Also, reactive metabolites formed due to catalysis of arachidonic acid by COX-2, reportedly have carcinogenic properties [11,31]. Additionally, chronic inflammation that is a risk factor for carcinomas is associated with increased synthesis of prostaglandins induced by overexpression of COX-2 [10].

In a study on SGC tissue samples of human head and neck regions, Erovic et al., showed all tissues to be positive for COX-2 with 82% showing COX-2 overexpression [5]. Meyer et al. investigating COX-2 expression in skin tumors using tissue microarray technique, showed 86.9% of sebaceous adenomas to be COX-2 positive [12]. This indicates that COX-2 might have a significant role in the pathogenesis of sebaceous gland neoplasms.

At the molecular level, transgenic and/or knockout technologies are believed to have established the link between COX-2 and tumorigenesis [32]. Tachibana et al., report overexpression of COX-2 gene in mammary glands in a study using transgenic mice which, in multiparous females led to the formation of tumors with local and distant metastasis [11].

When treated with 7,12-dimethyl-benz[α]anthracene (DMBA, a carcinogen), transgenic mice are seen to develop several sebaceous gland adenomas of the skin. When studied further, prominent COX-2 overexpression and high prostaglandin production in basal sebocytes are observed in them [8], suggesting a probable association between the genesis of sebaceous adenoma and increased sebum production.

Another reason behind COX-2 being involved in tumor development could be attributed to its role in angiogenesis. Tsuji et al. report the pro-angiogenic effects of COX-2 overexpression in colon cancer cells, when inhibited by a selective COX-2 inhibitor - NS-398 [33]. It is a well-established fact that angiogenesis is one of the main features of cancer cells as new blood vessels provide nutrients to the growing tumor. An experimental model designed to include COX-2 overexpressing Caco-2 cells (transfected) and HCA-7 (Human colon adenocarcinoma cell line) cells expressing COX-2 constitutively, show high levels of angiogenic factors [34]. In colon cancer, overexpression of COX-2 promotes the formation of capillary-like networks by increasing the production of vascular endothelial growth factors [33].

From the aforementioned studies, it can be assumed that the level of COX-2 expression has a role in various cancers. Nevertheless, more studies are required to ascertain the exact association of COX-2 with SGC.

Role of PPAR γ in cancer and SGC

PPARs belonging to the super family of nuclear hormone receptors are transcription factors that regulate the expression of genes in a ligand dependent manner. They function by forming heterodimers with specific ligands and retinoid X receptors (RXR), binding to specific DNA elements called PPAR response elements (PPRE). PPARs are frequently linked to regulation of cell differentiation, development, metabolism and tumorigenesis in higher organisms. A significant correlation of PPARs with various types of cancers such as lung, liver, colon, breast and skin cancers is well established [35,36].

The three subtypes of PPARs - PPAR α , PPAR δ and PPAR γ show varied tissue distribution and different functions [36]. It is the involvement of PPARs in adipogenesis and lipid metabolism that links them to sebum production in the sebaceous glands. Rosenfield et al., in their study on rat preputial cells (that serve as a model for human sebocytes), report the presence of PPAR δ and PPAR γ mRNAs using RNase protection assay. Further, they report the accumulation of lipid droplets because of induction by ligands of PPAR α and PPAR γ [37]. This suggests a possible role of PPARs in regulating sebum production in human sebocytes.

Gene expression analyses show PPAR α to be one of the main regulators of genes involved in lipid metabolism [38]. Devchand et al., in a study done on transgenic mice, show the deficiency of PPAR α results in prolonged inflammatory response to lipid mediators, indicating that PPAR α has a physiological role in suppressing inflammation [39]. PPAR α is expressed in cultured sebocytes and in human sebaceous glands where it increases the synthesis of anti-inflammatory cytokines [40]. PPAR α is also implicated for hepatocarcinogenesis in mice; however, there is no evidence of a similar effect in humans [41].

The role of PPAR δ (also known as PPAR β) in cancer is, however, unclear. Few studies report its tumor promoting effect in many cancers while, others state that administration of its agonists suppresses cancer development [42]. Though PPAR δ is known to play a significant role in lipid accumulation and terminal differentiation in keratinocytes, there is no evidence of its association with SGC [43].

The role of PPAR γ as an anticancer agent is suggested in various studies as PPAR γ agonists play a substantial role in promoting apoptosis, inducing terminal differentiation and impeding cell proliferation [42]. Arachidonic acid metabolites, 15d-PGJ2 and PGD2 act as the natural ligands for PPAR γ [36]. Several experiments using pancreatic cancer cells reported PPAR γ expression and these when treated with its ligands/agonists such as thiazolidinediones/3,3-diindolylmethane, resulted in apoptosis via endoplasmic stress cell response [44].

PPAR γ expression facilitates sebocyte differentiation and lipid synthesis in sebaceous glands. Studies in mice lacking PPAR γ in the skin cells demonstrate that development of sebaceous glands and adipose tissues require a functional PPAR γ [37]. Keratinocytes of mice lacking PPAR γ are shown to have increased epithelial tumor progression [45].

A recent study reports the definitive role of PPAR γ in regulation of lipogenesis and cell proliferation in SZ95 sebocytes [46]. Dozsa et al., suggest that PPAR γ is differentially expressed in human sebocytes that were normal as compared to those that were diseased. They emphasize that the level of expression of PPAR γ is significantly lower in case of sebaceous adenomas and SGC as compared to in normal sebaceous gland tissue [47].

Role of COX-2 – PPAR γ pathway

Prostaglandins that are produced by the action of cyclooxygenases on arachidonic acid also act as endogenous ligands of PPARs [48]. Further, arachidonic acid itself is a PPAR γ ligand [49]. Interestingly, non-steroidal anti-inflammatory drugs (NSAIDs) such as thiazolidine derivatives are not only inhibitors of COX-2 but are also observed to act as ligands of PPAR γ [50].

The archetypical inhibitor of COX-2, NSAIDs are known to reduce the risk of many cancers thus making COX-2 a major clinical target for anticancer therapy [51]. Selective COX-2 inhibitors like celecoxib and rofecoxib are proven to suppress and prevent tumorigenesis [52]. The growth of tumors is typically associated with immune suppression. It is believed that selective inhibition of COX-2 can restore the balance between interleukins 10 and 12 thereby promoting anti-tumor activity [53]. Further, treatment by NSAID sulindacsulfide reversed the apoptotic resistance shown initially by rat intestinal epithelial cells engineered to overexpress COX-2 [54]. Moreover, inhibition of cyclooxygenases by NSAIDs is said to result in an altered pathway for the metabolism of arachidonic acid. This is shown to decrease the number and size of intestinal polyps in case of colon cancers and suppression of skin related tumor developments [31]. Selective COX-2 inhibitors are observed to be effective in treating colorectal cancers that evolve from adenomas [55]. In SZ95 (immortalized human sebaceous gland cell line) sebocytes, differentiation and lipid synthesis is regulated by a PPAR γ /COX-2-mediated signaling pathway [56].

All of these are suggestive of the presence of a COX-2 – PPAR γ signaling pathway (Figure 1). The conversion of the fatty acid - arachidonic acid to prostaglandin PGH2 is catalyzed by COX-2. Many enzymes catalyze PGH2 to produce prostaglandins such as PGE2 and PGD2 among others. Overexpression of both PGE2 and COX-2 are reported to promote carcinogenesis. Prostaglandin PGE2 is also pro-inflammatory in nature. Conversely, PGD2 is converted to 15d-PGJ2 that has been shown to have anti-inflammatory properties. Interestingly, 15d-PGJ2 has been observed to inhibit COX-2. The 15d-PGJ2 acts as an endogenous ligand of PPAR γ that is a transcription factor involved in the activation of genes that suppress cancer development [9,57,58]. Moreover, it has been proposed in a study that COX-2 expression might be significantly controlled by a negative feedback loop which is regulated by PPAR γ [59].

The reported involvement of this pathway in various types of cancers including, but not limited to, that of the breast, prostate gland, pancreas and lung is indicative of its association with cancer development [9,60,61]. Few studies suggest that COX-2 and its signaling pathway are strongly linked with non-melanoma skin carcinogenesis [62].

SGC of the Eyelids

Distribution

Among non-melanoma cancers of the eyelid, BCC is the most common type accounting for 80-95% of eyelid cancers and originates mostly from the lower eyelid or the medial canthus [1,63]. This is followed by SCC that accounts for about 9.2% and usually manifests as a nodular or ulcerative lesion. Periocular SCC commonly arises from the lower eyelid, upper eyelid or canthi [1,64]. It may in even originate from the bulbar or palpebral conjunctiva [65]. SGC accounts for only 1-5% of eyelid malignancies, but is the most aggressive amongst them [1]. Clinico-pathological studies based on the Indian subpopulation, however, suggest that BCC and SGC are more prevalent (upto 48% and 31% respectively), while SCC is the rarer variety (13-22%) of eyelid cancer [66,67].

The most common location of BCC is the face. SCC can occur in other areas and are often caused by constant and prolonged local irritation [68,69]. BCC and SCC affect particularly areas of the skin that are exposed to sunlight, especially ultraviolet (UV) radiation [69]. In contrast, there is little effect of UV exposure on the etiology of SGC [70]. However, a recent study has reported mutations caused by UV damage in 32 SGC cases by whole-exome sequencing and has found similarities with SCC [71].

Pathogenesis and diagnosis

Periocular SGC tumors can arise from the tarsal meibomian gland, the Zeis gland of the hair follicles or in rare cases from the sebaceous glands of the lacrimal caruncle [18,72,73]. These are highly aggressive tumors found predominantly in older women and tend

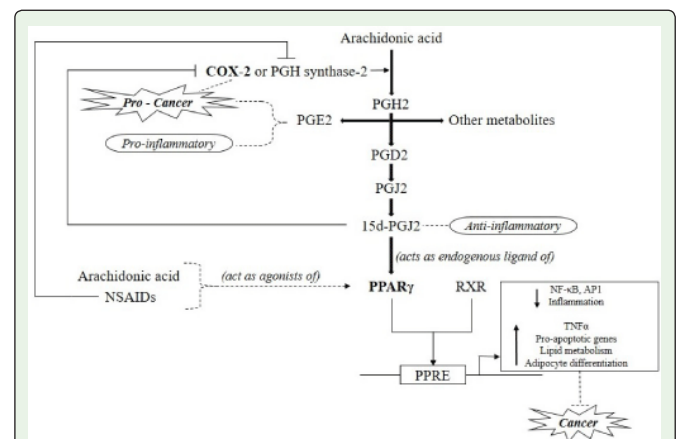


Figure 1: COX-2 – PPAR γ Signalling Pathway- The conversion of the fatty acid - arachidonic acid to prostaglandin PGH2 is catalysed by COX-2. Enzymes catalyze PGH2 to produce other prostaglandins (PGE2 and PGD2). PGD2 is converted to 15d-PGJ2 which acts as a ligand of PPAR γ (9,57,59)

Abbreviations: PGH2 – Prostaglandin H2, PGE2 – Prostaglandin E2, PGD2 – Prostaglandin D2, PGJ2 – Prostaglandin J2, 15d-PGJ2 – 15-deoxy- Δ 12,14-PGJ2, NSAIDs – Non steroidal anti-inflammatory drugs, RXR – Retinoid X Receptor, PPRE - Peroxisome proliferator response element, NF- κ B – Nuclear factor kappa-light-chain-enhancer of activated B cells, AP1

to invade the regional lymph nodes as well as metastasize to various body parts including the brain [74]. In 50-60% cases, however, the cell of origin remains unknown [2].

Histopathological analysis reveals that well-differentiated tumor tissue appears as lobular masses with foamy, vacuolated cytoplasm that sometimes show central necrosis [26]. Poorly differentiated SGC tissue appears to have cells with pleomorphic nuclei and 'appliqué pattern' or peripheral cell necrosis [75]. Further, it reportedly shows pagetoid spread, a distinctive superficial pattern of 'upward' invasive spread of cancerous cells which is more prominent in the upper eyelids due to the abundance of meibomian glands [22,76].

Poorly differentiated eyelid SGC are frequently incorrectly diagnosed as SCC or BCC [21,22,77]. In its early stages, the SGC tumors mimic benign conditions like blepharconjunctivitis or chalazion [78]. This often leads to misdiagnosis and a delay in treatment resulting in widespread local and distant metastases [2]. Recently, a study has reported 'polymorphous vessels with yellow backgrounds' as a characteristic feature of periocular SGC using dermoscopy [19].

Initially, SGC may develop as a painless chalazion-like nodule, an ulcerative lesion or as a thickening/inflammation of the eyelid akin to blepharitis [79,80]. It can subsequently spread to the conjunctiva and masquerade as conjunctivitis. Progressive loss of eyelashes has also been reported in a SGC case that was earlier misdiagnosed to be blepharconjunctivitis [78]. As both COX-2 and PPAR γ play a prominent role in inflammation, a feature commonly seen in earlier stages of SGC, it is possible that they may be involved in the development of SGC of the eyelids. Further, it has been reported that SGC nodules when visualized closely, appear yellowish because of their high lipid content [19,76]. This may be another reason to explore the role of PPAR γ in SGC due to its direct involvement in lipogenesis.

COX-2 and PPAR γ in eyelid SGC

Patel et al., from Canada, reported COX-2 overexpression in non-neoplastic sebaceous glands surrounding the tumor tissue in about half of the eyelid SGC tissue samples. The authors suggest that the expression of COX-2 may be an early indicator of neoplastic transformation and the aggressiveness of SGC [34]. Jayaraj et al., in a study based on the Indian subpopulation, report strong cytoplasmic overexpression of COX-2 in 80.6% eyelid SGC tissues (including both well and poorly differentiated SGC tissues). Further, they report a substantial association of COX-2 overexpression with reduced disease-free survival and suggest that COX-2 overexpression could be a prognostic predictor of aggressiveness in SGC [81]. These studies indicate that irrespective of the geographical distribution, COX-2 is overexpressed in SGC.

Overexpression of COX-2 may also be partially responsible for the loss of eyelashes and alopecia. Müller-Decker et al., in a study on transgenic mice, show COX-2 overexpression leads to sebaceous gland hyperplasia and consequent excessive sebum production in addition to delayed emergence of hair shaft and reduced density of hair follicle [82].

A few studies have reported that PPAR γ is required by sebaceous glands for their proper differentiation [13,83,84]. In their study on eyelid SGC cases, Jayaraj et al. report negligible PPAR γ expression in poorly differentiated SGC in contrast to PPAR γ overexpression in 90.4% of well-differentiated SGC cases. Its high expression is also observed in cases of eyelid sebaceous adenoma and hyperplasia; which are suggestive of PPAR γ being a possible diagnostic marker of well-differentiated SGC as the level of expression of PPAR γ reduces with the loss of differentiation in the SGC tissue [81].

Though presently evidence of the possible association between COX-2 – PPAR γ signaling pathway and pathogenesis of SGC especially that of the eyelids is not very strong, this possibility is worth exploring. Further, significant overexpression of COX-2 and progressive decline in PPAR γ expression has been reported suggesting the presence of an inverse correlation between COX-2 and PPAR γ in eyelid SGC.

Conclusion

There is substantial evidence of a functioning prostaglandin pathway in sebaceous glands. Prostaglandins are important for lipogenesis and adipogenesis in these glands and they are known to play a role in tumorigenesis. As COX-2 is involved in generation of prostaglandins, it is indicative that COX-2 plays a significant role in generation of benign tumors as well as in carcinogenesis. Several studies indicate an overexpression of COX-2 in SGC; nevertheless, more conclusive evidence is necessary to ascertain its role in pathogenesis of SGC. The role of PPAR γ in lipogenesis and sebocyte differentiation is well established. However, only a few studies emphasize its association with SGC.

In eyelid SGC, over expression of COX-2 and reduction in PPAR γ with loss of tumor differentiation is indicated. Therefore, COX-2 PPAR γ pathway is possibly another molecular pathway in the pathogenesis of eyelid SGC. However, further studies are necessary to validate this theory.

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