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Abstract

Basal cell carcinoma is the most common malignant neoplasm in humans, with low mortality, high morbidity, and exposure to solar radiation (UVB and UVA) is the most critical risk factor. Ultraviolet B rays generate mutagenic photoproducts in DNA and mutations in important genes regulating cellular functions, such as the tumor suppressor gene TP53. Ultraviolet A rays generate cytotoxic and mutagenic free radicals, potentiating the effects of UVB rays.. There is current evidence to support the role of inflammatory biomarkers related to tumorigenesis of basal cell carcinoma.

Keywords: basal cell carcinoma; epidemiology; pathology; biomarkers; inflammation.

1. Epidemiology

When included under the terminology of nonmelanoma skin cancer (NMSC), it includes basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), corresponding to $\frac{1}{4}$ of all registered malignant tumors. Its incidence is highest in Australia, where 1:2 residents develop BCC before age 70. In the USA, the incidence is 576 cases/100,000 people/year^[1]. In Brazil, the estimate was 85,170 new cases of non-melanoma skin cancer (NMSC) in men and 80,410 in women in 2018. This corresponds to an estimated risk of 82.53 new cases/100,000 men and 75.84/100,000 women^[2].

The male/female ratio is approximately 1.5:1.0. People with clear phototypes (Fitzpatrick I and II), positive family history of BCC (30-60%), with freckles in childhood, light eyes, and hair, are more likely to develop the neoplasm. In patients under 40 years of age, the incidence of the tumor has been increasing more in women. In high-latitude regions, the proportion of cases of BCC for each case of BCC is 4: 1. BCC globally corresponds to 70-80% of all skin cancers. In highly pigmented skin populations, it is a rare tumor, especially in parts of Africa^[1].

The epidemiological profile of the disease in recent decades has shown an increase in the incidence rate of BCC, a more considerable increase in the age groups between the 4th and 5th decade of life (younger patients), a higher incidence of the superficial subtype and tumors with histological subtype of higher risk of recurrence, more significant number of BCCs in covered areas of the body and more considerable increase in cases in people of higher social class^[1].

Other external risk factors for the development of BCC are tanning beds, chronic exposure to arsenic, ionizing radiation, chronic immunosuppression, especially in transplanted solid organs, and HIV infection^[3,4].

Despite its high incidence, metastasis rates are from 0.0028% to 0.5%, and the estimated mortality is 0.12 cases per 100,000 inhabitants. Unpublished data from Brigham and Women's Hospital, however, suggest that the risk of metastasis and death is 6.5% in tumors greater than or equal to 2.0 cm^[1].

2. Molecular pathogenesis

BCC has the highest prevalence rates of mutations of all cancers, determined by exposure to ultraviolet radiation (UV). The intracellular signaling pathway patched / hedgehog (PTCH1) plays a fundamental role in both sporadic BCC and nevoid BCC syndrome (Gorlin syndrome). Mutations in the PTCH1 gene located on chromosome 9q22.3 (58-69%) of sporadic BCCs are observed, as well as in all patients with nevoid BCC syndrome. The SHH (Sonic Hedgehog) pathway comprising the IHH, SHH, and SHH genes is crucial for development during the early stages of the embryo^[5,4,6,7,8,9,10].

In the skin, the SHH pathway supports the population of stem cells and helps in the development of hair follicles and sebaceous glands. This pathway is implicated in the cell cycle, particularly in the G1-S and G2-M transitions, and in adults, this pathway is inoperative, and its activation correlates with the appearance of BCC and other tumors. Patched protein 1 (PTCH1) inhibits smoothened protein (SMO). The SHH ligand, in contact with PTCH1, forms the PTCH1-SHH complex, which then releases SMO, a signal transducer that internalizes and releases inhibition of the suppressor of fused homolog protein (SUFU) on the glioma-associated oncogene-1 (GLI1) proteins. There are also mutations of the TP53 gene on

chromosome 17p13.1 (44-65%) of BCCs. Other genetic abnormalities that predispose to the appearance of BCCs include albinism, xeroderma pigmentosum, Rombo syndrome, Bazex-Dupré-Christol syndrome, simplex bullous epidermolysis of the Dowling-Meara type, multiple hereditary infundibulocystic and sebaceous nevus^[5,4,6,7,8,9,10].

There are no precursor lesions described for BCC, and the cells of origin are controversial. There is evidence of derivation from immature pluripotent cells of the interfollicular epidermis and cells of the external sheath of the hair follicle, based on experiments of activation of the Hedgehog signaling pathway in different compartments of the epidermis and in the expression of follicular pattern cytokeratins, which led to some authors call it a malignant neoplasm of follicular germ cells (trichoblasts). Additionally, there are reports of association of BCC with abnormalities of the embryonic gene of follicular development, SHH (Sonic Hedgehog), which supports the fact of the rarity of planar spanning BCCs^[4,11,12].

3. Clinical Picture

BCCs are more common in the head and neck region (in up to 80% of cases), but they can affect the trunk, shoulders, upper and lower limbs, lips, breasts, armpits, inguinal region, genital and perineal region. The clinical classification of BCC is based mainly on histological subtypes. The patterns most recognized by all are nodular, superficial, and sclerodermiform^[4,13].

In a recent World Health Organization classification for skin tumors (2018), according to the National Comprehensive Cancer Network (NCCN®) Guidelines, it is recommended to stratify basal cell carcinoma for purposes of staging and prognosis in low and high-risk subtypes recurrence, based on clinical and histological parameters^[3,13,14]. Figure 2 shows in an organized way the different histological subtypes of BCC, classifying them as low and high risk of recurrence.

LOW-RISK	HIGH RISK
Nodular BCC	Basal squamous carcinoma
Superficial BCC	Sclerodermiform BCC (morpheaform)
Pigmented BCC	Infiltrative BCC
Infundibulocystic BCC (A variant of BCC with adnexal differentiation)	BCC with sarcomatoid differentiation
Fibroepithelial BCC	Micronodular BCC

Figure 2. Histological subtypes of basal cell carcinoma (BCC) stratified according to the risk of recurrence.

4. Low-Risk subtypes

4.1 Nodular Basal Cell Carcinoma

It is the most common clinical form of this tumor, corresponding to 44.7%^[15,16] of all BCCs. Clinically, it presents as an asymptomatic papule or nodule, with a translucent and pearly surface. It also shows superficial vascularization with an arboriform aspect, with a pink or reddish appearance. The size of the nodular BCC can vary from 1.0 mm to several centimeters. The average is between 0.5 to 2.0 cm. In

general, it is ulcerated, and in these cases, the name is nodular ulcerated BCC, which can bleed with the formation of hematic crusts. In some cases, the ulcer has more infiltrative characteristics, with the tumor adhering to deeper planes - nodular ulcer-infiltrative BCC^[3,4,6,11,12, 17,18,19,20]. (Fig. 3).



Figure 3. Photo of nodular CBC. Source: Takita (2019).

Microscopically it is characterized by blocks of tumor cells in the dermis, at least not focally connected to the epidermis and involving the reticular dermis. The nodules vary in size and shape, and in general, in the nodules, there is a retraction artifact, peripheral palisade, and stroma in the surrounding dermis with mucinous alteration (fibromyxoid stroma), (Fig. 4). It may present focal melanin pigmentation in some nodules, besides Mitosis figures, areas of mature keratinization, nodule-cystic or cystic areas involving tumor islands, and adenoid areas with cribriform nests (adenoid CBC). We can also find areas of differentiation for clear cells, signet ring, granular, and pleomorphic giant cells^[3,6,11,12,14,17,20].

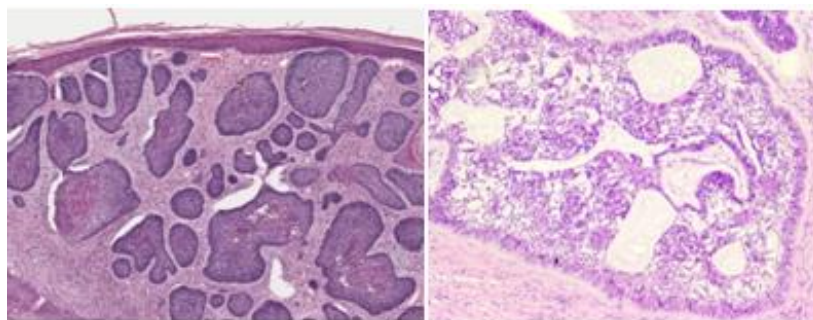


Figure 4. Histology of nodular BCC. Source: Takita (2019).

Differential diagnosis: nodular BCC can be challenging to distinguish between benign and malignant trichoblastic tumors, especially those that occur in skin damaged by sunlight (trichoblastic carcinoma/carcinosarcoma and trichoblastoma). Lesions with cystic degeneration can be challenging to distinguish from adnexal tumors, in particular, adenoid cystic carcinoma, and immunohistochemical evaluation should assist in the diagnosis. Another differential diagnosis is Merkel cell carcinoma. In this case, immunohistochemistry may show positivity for neuroendocrine markers in CBC but negativity for CK20 cytokeratin, which can be decisive in Merkel cell carcinoma^[3,4,6,11,12,17,19,20,21,22].

4.2 Superficial Basal Cell Carcinoma

It is the second most common clinical form of this tumor and corresponds to about 17% of cases. Characteristically affects the trunk of male patients. Another characteristic is the greater involvement of younger patients and the presence of multiple injuries. Clinically, it appears as a centrifugal growth plate that leaves the atrophic or cicatricial center. In this form, we can also observe flaking, which is generally thin, (Fig. 5a). Histologically it is characterized by small nests of neoplastic cells in the epidermis, interspersed with healthy skin without a tumor, and the neoplasia in general exhibits retraction artifact and peripheral palisade. The surrounding stroma may have myxoid fibroid areas^[3,4,6,11,17], (Fig. 5b).

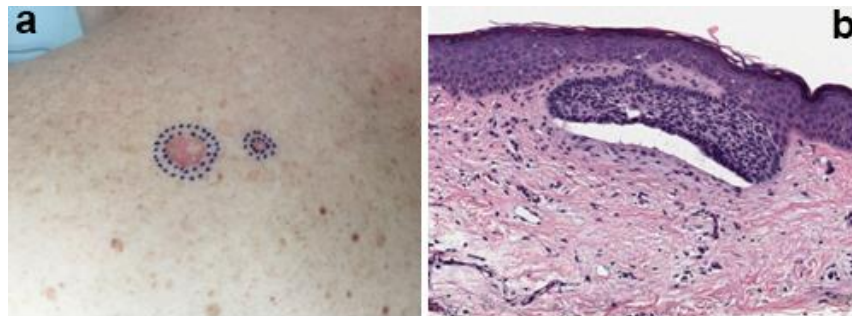


Figure 5. Photo of superficial BCC. a) skin lesion; b) histology.

Source Takita (2019).

Differential diagnosis: histologically, the differential diagnoses are with actinic keratosis, follicular infundibulum tumor, and large cell acanthoma^[3,4,6,11,17].

4.3 Pigmented Basal Cell Carcinoma

It is a name that can be used in all clinical forms of BCC. Its importance derives from recognizing the melanic pigment as a component of clinical forms of any BCC, helping in the differential diagnosis of pigmented tumors^[3,4,6,11,17].

It corresponds to 13.6% of the cases^[23], and clinically what characterizes this variant is its color, which varies from brown to brownish brown, which can be confused with melanoma and other melanocytic or melanin-producing lesions, (Fig. 6a). Microscopically, the nodular and superficial variants of CBC can contain pigment, being categorized as pigmented CBC. Pigmented BCC includes an increased number of benign dendritic melanocytes within the neoplastic cell islands. It can also find melanin within peritumoral macrophages in the adjacent dermis^[3,4,6,11,17], (Fig. 6b).

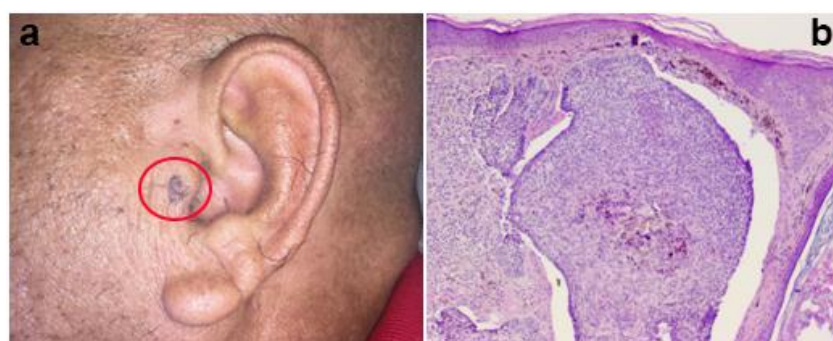


Figure 6. Pigmented Basal Cell Carcinoma. a) skin lesion; b) histology.

Source: Takita (2019).

Differential diagnosis: the histological differential diagnosis includes melanoma, pigmented squamous cell carcinoma, pigmented seborrheic keratosis, pigmented trichoblastoma, porocarcinoma, and matricomamelanocytic^[3,4,6,11,17].

4.4 Infundibulocystic Basal Cell Carcinoma (and with adnexal differentiation)

It is a rare variant of BCC with adnexal differentiation, with a predilection for the periocular region. Clinically, they present as single, papular lesions, with a pearly surface, surmounted by a thin, whitish-pink scale (Fig. 7a). Microscopically, are observed infundibular structures with corneal stoppers in cystic areas, surrounded by nests of basaloid cells in the periphery. The other form would be a basal cell with areas of adnexal, sebaceous, or ductal differentiation^[3,4,6,11,17]. (Fig. 7b).

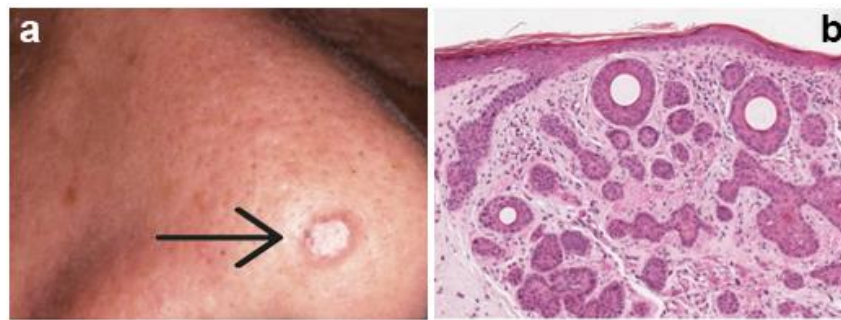


Figure 7 Infundibulocystic Basal Cell Carcinoma. a) skin lesion; b) histology.

Source: Takita (2019).

Differential diagnosis: The histological differential diagnosis of basal cell infundibulocystic carcinoma includes basaloid follicular hamartoma and trichoepithelioma. The BCC with sebaceous differentiation must be differentiated from sebaceoma, sebaceous adenoma, and sebaceous carcinoma^[3,4,6,11,17].

4.5 Fibroepithelial Basal Cell Carcinoma (Pinkus Fibroepithelioma)

It is a rare variant of basal cell carcinoma, most commonly affecting the trunk, in particular, the dorsal region, and can rarely be multiple. Clinically, it usually presents as a flesh-colored nodule. Microscopically, filaments and strands of basaloid cells originate from the epidermis and form anastomosing structures into the fibrotic stroma of the dermis. Basaloid cell islands may be present^[3,4,6,11,17], (Fig.8).

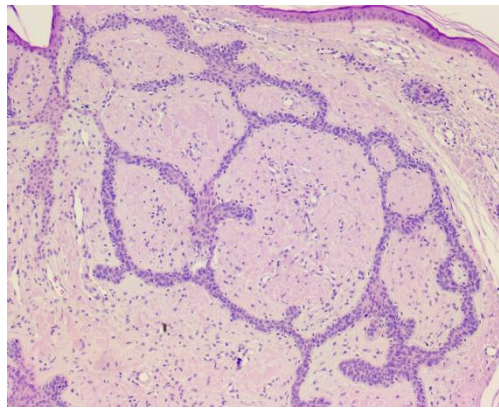


Figure 8. Histology of fibroepithelial BCC(Pinkus tumor).

Source: Takita (2019).

Differential diagnosis: histologically, it must be differentiated from the eccrine syringofibroadenoma, due to the absence of eccrine ductal epithelium and cuticle in the basaloid cell blocks and the predominance of this type of lesion in the trunk instead of the acral region in the BCC^[3,4,6,11,17].

5. High-Risk subtypes:

5.1 Basal squamous cell carcinoma

Also called metatypic carcinoma, it is considered an aggressive variant of BCC, with histological findings of BCC and SCC, with transition zones between both. It usually affects older people, with light skin, in exposed areas. It corresponds to 7.4% of BCCs^[15,16], and clinically presents as a slowly evolving papule or nodule that can ulcerate, present aggressive clinical behavior, with a higher possibility of recurrence and metastasis (Fig. 9a). Microscopically, it presents characteristic changes of basal cell and squamous differentiation in varying degrees^[3,4,6,11,17], (Fig. 9b).

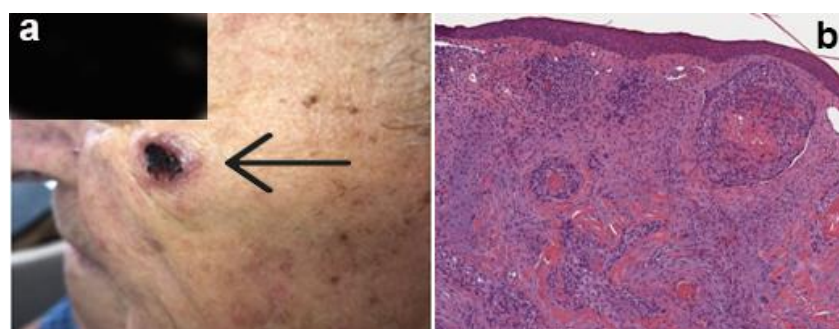


Figure 9. Basal squamous carcinoma. a) skin lesion; b) histology.

Source: Takita (2019).

Differential diagnosis: histologically, it must be distinguished from keratotic BCC (a subtype of nodular BCC) due to the presence of cytologically malignant squamous epithelium and the absence of corneal pearls in the central region of the tumoral nodules. It must also be distinguished from tumors of collision with CBC and CPB^[3,4,6,11,17].

5.2 Sclerodermiform Basal Cell Carcinoma (Morpheaform)

It is an aggressive variant of basal cell carcinoma characterized by thin strands of basaloid cells of imprecise limits, without the presence of a palisade in the periphery, surrounded by an abundant fibrous stroma, sometimes desmoplastic, capable of invading the hypodermis. It corresponds to about 10% of CBCs^[15,16]. Clinically, it presents as a scar pattern plate with ill-defined edges, which rarely ulcerates or bleeds, (Fig. 10a). Microscopically it reveals infiltrating filiform columns of basaloid cells with a thickness of one to five cells in a fibrosclerotic stroma, without cracks or peripheral palisade. There is often overlap or is confused with the infiltrating BCC^[3,4,6,11,17], (Fig. 10b).

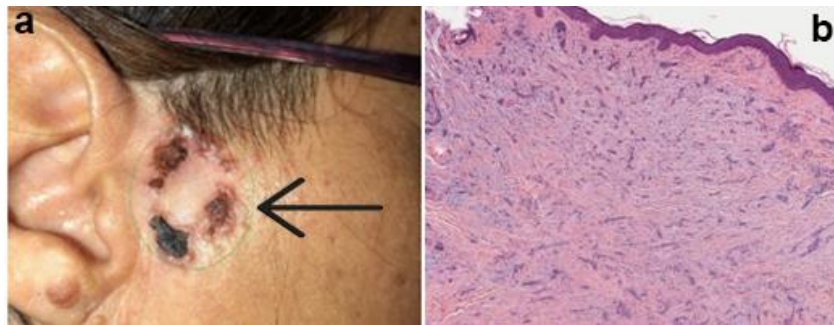


Figure 10. Sclerodermiform Basal Cell Carcinoma. a) skin lesion; b) histology.

Source: Takita (2019).

Differential diagnosis: histologically, it must be distinguished from desmoplastic trichoepithelioma and microcystic adnexal carcinoma, and immunohistochemistry facilitates this distinction. In general, is used a panel of markers where the demonstration of RA +, CK20– and PHLDA–, favors the possibility of trichoepithelioma and CEA +, CK15 +, EMA + and BerEP4–, supports the diagnosis of microscopic adnexal carcinoma^[3,4,6,11,17,21,22].

5.3 Infiltrative Basal Cell Carcinoma

It is an aggressive variant of nodular basal cell carcinoma characterized by narrow strands and nests of basaloid neoplastic cells with irregular and infiltrative growth pattern and corresponds to 7% of cases. Clinically, it presents as a scar pattern lesion, more frequent in the upper trunk, head, and neck, generally more common in patients under 35 years of age. The biopsy should include the deep dermis for a correct diagnosis, (Fig. 11a). Microscopically, it presents irregular nests of basaloid cells, of varying sizes, with tentacle pattern, infiltrating the dermal stroma with a thickness of five to eight cells. Part of infiltrative BCCs, about one-third, mix with a nodular BCC component. Perineural invasion and overlap with sclerodermiform BCC can be observed^[3,4,6,11,17]. (Fig. 11b).

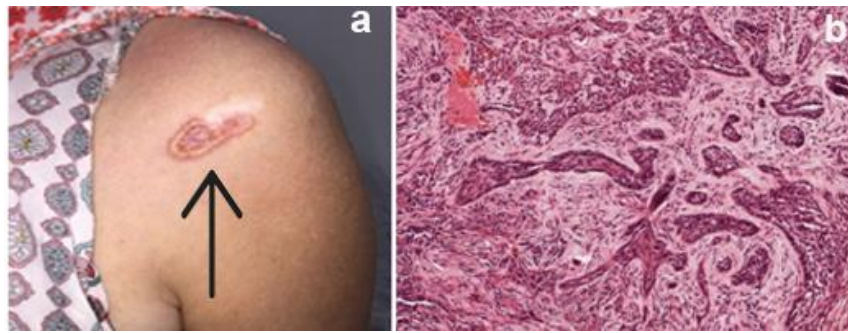


Figure 11. Infiltrative Basal Cell Carcinoma. a) skin lesion; b) histology

Source: Takita (2019).

Differential diagnosis: histologically, it can be confused with sclerodermiform basal cell carcinoma. The presence of perineural neoplastic infiltration favors the diagnosis of infiltrative BCC^[3,4,6,11,17].

5.4 Basal Cell Carcinoma with Sarcomatoid Differentiation

It is a scarce aggressive variant of basal cell carcinoma, with a basaloid epithelial component and sarcomatoid stroma of variable histology. It occurs predominantly in older men, in photo exposed areas of the head and neck, chest and forearms, and the tumors are large, averaging 2.8 cm. Microscopically, it has a basal cell component, and a malignant mesenchymal component made up of undifferentiated pleomorphic cells, osteosarcoma, chondrosarcoma, leiomyosarcoma with or without rhabdomyosarcoma. It generally represents the result of a divergent mesenchymal differentiation^[6,11].

Differential diagnosis: histologically, it is a biphenotypic tumor, and the correct characterization must be focused on the neoplastic mesenchymal component (e.g., undifferentiated pleomorphic, leiomyosarcoma, rhabdomyosarcoma, and others). Immunohistochemical evaluation is essential for definition^[6,11].

5.5 Micronodular Basal Cell Carcinoma

It is a high-risk variant of BCC, rare in its pure form, corresponding to less than 2.6% of BCCs^[24], characterized by small nests of tumor cells, generally smaller than the nodes or blocks of the nodular BCC, which deeply infiltrate the dermis, which may compromise the hypodermis. Clinically, it may present as small papules or plaques with little defined surface and extension, more common in the head and neck. As it profoundly infiltrates the dermis, it can recur after surgery; hence it is considered a high-risk variant of BCC, (Fig. 11a). Microscopically, they are smaller nodules of basaloid cells (less than 0.15 mm in diameter) compared to nodular BCC. There are cracks and peripheral palisades, and the surrounding reticular dermis is fibromyxoid. It can demonstrate perineural and hypodermis infiltration with small satellite nodules in the deep dermis^[3,4,11,17], (Fig. 11b).

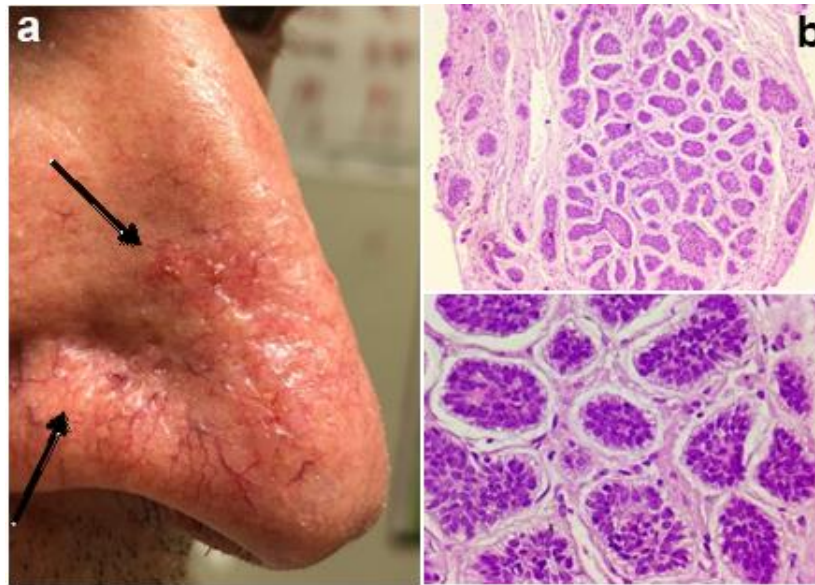


Figure 12. Photo of micronodular BCC

Source: Takita (2019).

Differential diagnosis: histologically, the differential diagnosis includes nodular BCC with focal micronodular architecture, but these tumors are surrounded by a characteristic stroma and present absence of satellite nodules in the neighborhood^[3,4,11,17].

6. Evidence of Inflammation in Carcinogenesis

Inflammation is an essential component of innate immunity, allowing multicellular organisms to restore homeostasis in the face of harmful stimuli or conditions, such as infections with or similar tissue lesions. The inflammatory response depends on four components: inducers, cellular or soluble recognition molecules, inflammatory mediators, and target tissues. When this phenomenon becomes unregulated, it persists, and the cellular response starts to be characterized as chronic inflammation^[25,26,27].

Depending on the origin of the inducing agents, we can divide inflammatory events associated with cancer into extrinsic (for example, chronic inflammation caused by pathogens or environmental agents) and intrinsic (for example, inflammation induced by genetic changes in pre-malignant cells or by necrosis tumor). The presence of leukocyte infiltrate, especially of macrophages associated with the tumor, represents a hallmark of practically all cancers^[25,26,27].

The presence of an inflammatory microenvironment, with high concentrations of reactive oxygen species (ROS) and nitrogen, cytokines, and eicosanoids, leads to the occurrence of direct DNA damage, genetic instability, and epigenetic changes in premalignant cells, favoring the tumor initiation. The inflammatory mediators present in the tumor microenvironment initiate intracellular signaling cascades in tumor cells, culminating in the activation of transcription factors, such as NF- κ B and STAT3^[28,29].

These factors regulate the transcription of genes associated with the inflammatory response, such as cytokines (IL-6, IL-1 β)^[28,30], growth factors (CSF-1), chemokines and their receptors (IL-8, CCL2, CCL20, CXCR4)^[28,31,32,33,34,35,36,37,38,39], matrix metalloproteinases (MMP-2 and MMP-9)^[28,31,40,42,43,44,45],

cyclooxygenases (COX-1 and COX-2)^[28,35,46] and several genes associated with carcinogenesis, representing the point of convergence between inflammation and cancer^[7,25,26,27,28,47,48,49,50,51].

Some authors have reported evidence that suggests a close association between inflammation and cancer^[39,50,52,53,54]. Figure 22 shows, in detail, the signaling pathways associating with inflammation and skin cancer.

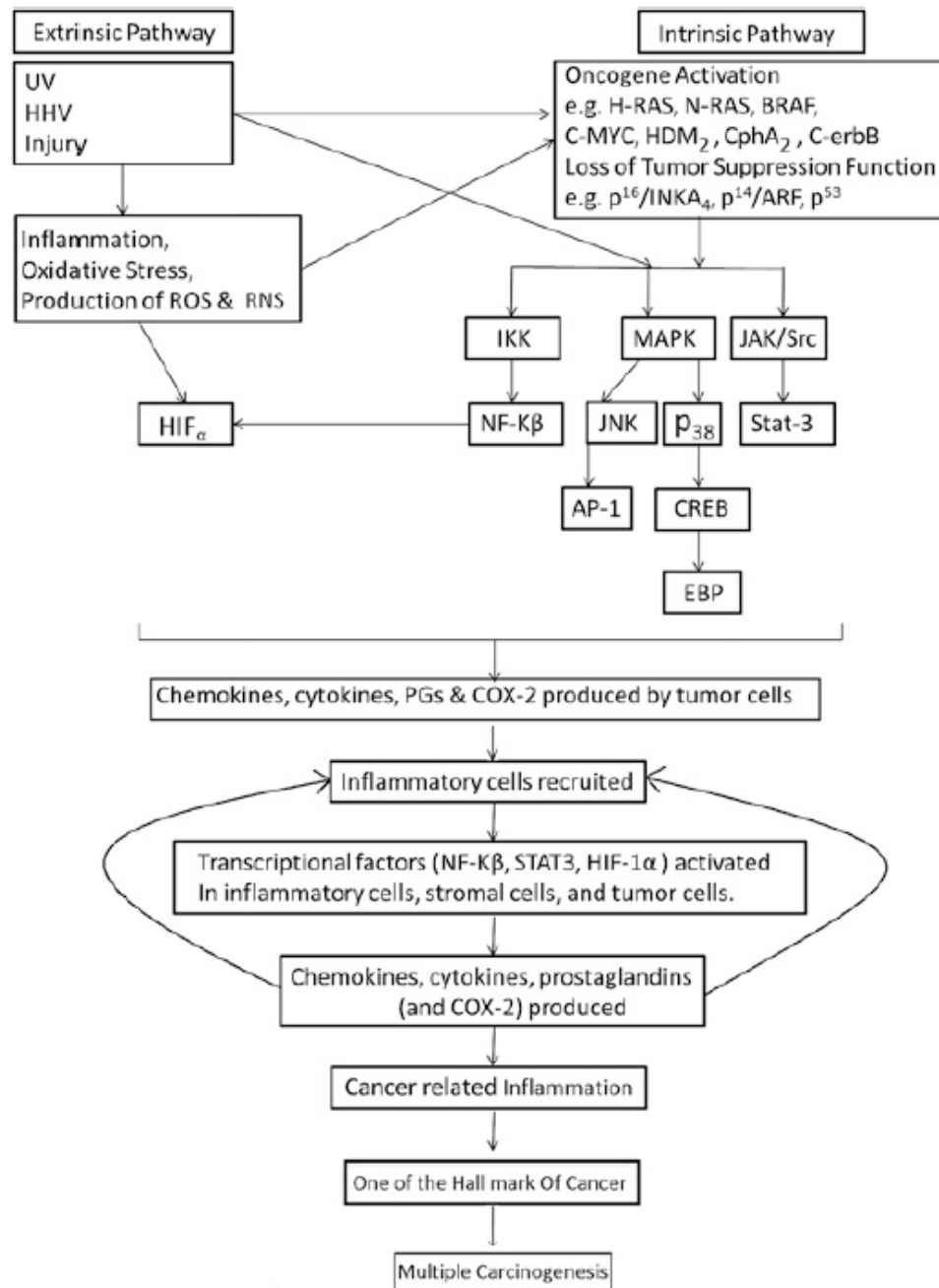


Figure 22. Signaling pathways associated with inflammation and skin cancer.

7. Evidence of inflammation in tumorigenesis of basal cell carcinomas

In the USA alone, it is estimated that 2.8 million new patients are diagnosed each year today, which is a significant public health problem^[53]. One of the characteristics of BCC is the continuous activation of the Hedgehog signaling pathway due to mutations in the tumor suppressor gene patch (Ptch), which induces

inactivation or due to the Smoothed mutation that leads to activation. These mutations were considered a right candidate for a therapeutic target, with direct anti-inflammatory approaches, and clinical trials were performed with anti-inflammatory drugs such as difluoro-dimethyl ornithine, retinoids, non-steroidal anti-inflammatory drugs (NSAIDs), dinucleotide thymidine, vitamin D3, silybin and components of green and black teas^[10].

Another way of signaling inflammation associated with BCC is NF- κ B, which is dependent on I κ B kinase α (IKK α). Jia et al., Demonstrated that nuclear IKK α binds to inflammation-promoting factors; moreover, it appears that it binds to a stem cell marker, LGR5 that activates the STAT3 signaling pathway during tumorigenesis.

By eliminating IKK α , tumor growth, and the EMT process are inhibited by proving that IKK α is an oncogenic transforming factor through a loss of stem cells and activation of inflammation-related genes, this shows that BCC is directly related to the inflammatory tumor microenvironment^[29].

Another pathway related to inflammation in the BCC is the transcription factor SRY pathway related to the HMG-box family (SOX9). In an animal model in rats with BCC, it was seen that SOX9 is expressed in tumor initiation and that its expression is dependent on the Wnt / β -catenin pathway. In this genetic model, the deletion of SOX9 and the constitutive activation of the Hedgehog signaling pathway suppresses the initiation of CBC highlighted by the involvement of SOX9 in the loss of stem cells, remodeling of the extracellular matrix and differentiation of tumor and metastatic development^[56].

In an experimental model using SENCAR rats, in which one the inflammation was induced by UVB radiation, to study the tumor initiation into the skin, it was found that PTK6 (protein tyrosine kinase 6) expression to be increased under the action of UVB. In SENCAR Ptk6 / and Ptk6 -/- mice, exposed to UVB radiation, it was seen that in Ptk6 / mice UVB induces increased inflammation and increased expression of PTK6 in the basal epithelial cells of the epidermis. This exposure was related to a higher frequency of tumors and tumor burden compared to the SENCAR Ptk6 -/- mice. In humans with CPB (squamous cell carcinoma), the activation of PTK6 is quite marked. It appears that PTK6 contributes to inflammation dependent on UVB radiation and the subsequent increase in skin tumorigenesis^[57].

In patients with BCC, there is a constant demand for immune cells related to inflammation that can predict their evolution. Such cells are neutrophils, monocytes, and lymphocytes. In a recent retrospective study of the count of white blood cells in less than 500 patients, They observed that in the group of BCCs, the count of neutrophils and monocytes was reduced in relation to the control group. The neutrophil: lymphocyte ratio was 3.24 in BCC and 3.59 in SCC when compared to 5.06 in the control group^[58].

As non-melanoma skin cancers are strongly associated with excessive UV radiation, there are numerous studies on the association of the risk of skin cancer associated with vitamin D. The endocrine system and vitamin D are associated with inflammation, cell growth, and differentiation^[59].

Vitamin D acts through its binding to the vitamin D receptor (VDR). In a large study reported by Lim et al. Involving about 17,000 cases of BCC compared to more than 250,000 controls, They found 2 single-nucleotide polymorphisms (SNPs) in new loci to be related to the risk of BCC. The study points out that common hereditary variations in VDR are associated with the development of BCC^[60]. Another study by Kaukinen et al., Using an animal skin model, showed that mast cells expressing VDR, are involved in UV immunosuppression mediated by VDR expression of CYP24A1 (a hydroxylase) that inactivates vitamin

D3 metabolites. In healthy skin, over 2.9% of mast cells were CYP24A1+, with a high percentage of CYP24A1+ mast cells in keratoseactinics (AK), CEC, and CBC. The findings of increased CYP24A1+ mast cells in keratinocyte-derived skin cancer require further study^[61]. As in other organs, we can correlate the increased expression of CYP24A1 in the skin with murine models of inflammation and progressive fibrosis^[62].

The tumorigenesis process includes several additional mechanisms, such as neovascularization, tissue invasion, and metastasis. All of these processes involve tissue remodeling, where the urokinase system is highly engaged. Rubina et al. demonstrated that BCC is associated with keratinocyte hyperproliferation, inflammatory cell migration and angiogenesis processes, and observed that the increased expression of urokinase plasminogen activating receptor (uPAR) is present in the tumor stroma surrounding BCC. Therefore, the uPAR system is a molecular network that supports proliferative aggressiveness and tumor cell invasion^[63].

Another molecular system that favors inflammation and tissue remodeling in tumorigenesis is metalloproteinases (MMPs). Its activation is involved in the degradation of the basement membrane in processes such as inflammation, tissue healing, angiogenesis, and carcinogenesis. In BCC, the expression of MMP-1 and MMP-9 has been observed associated with disease progression. Low levels were detected in actinic keratosis (AK), while intense expression was found in different types of BCC^[32].

Several anti-inflammatory compounds support evidence of the association of inflammation with tumorigenesis. naproxen, a known anti-inflammatory compound, shows an anti-proliferative and pro-apoptotic action. Chaudhary et al., using a rat animal model with UVB-induced skin tumorigenesis, he observed that naproxen significantly inhibited both BCC and SCC. They observed inhibition in the number and volume of lesions, and the principal reductions were in BCC type tumors. The effects were associated with decreased expression of PCNA and cyclin D1, increased apoptosis, and inflammation-related molecules (e.g., iNOS, COX-2, nuclear NF- κ B p65). Even residual tumors, after naproxen therapy, had a lower aggressive potential, expression of EMT markers (epithelial-mesenchymal transition, such as N-cadherin, vimentin, Snail, and Twist) and increased expression of E-cadherin^[64].

Regarding therapeutic strategies, we have available Imiquimod, which is a TLR7 agonist (TollLike Receptor-7), which addresses an inflammatory-derived receptor, and which has been approved for the treatment of CPB in situ, and more recently, has been used for treatment superficial BCC with positive clinical results. These results show the success of a therapeutic strategy that reduces inflammation and reduces tumorigenesis^[65].

Currently has been tested in BCC other classic anti-inflammatory compounds such as aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs). Collectively, data from 11 clinical studies showed a 10% risk reduction for BCCs of patients using NSAIDs, while aspirin use had a lesser reduction in risk. This report highlights that in humans, the use of NSAIDs can be used in a high-risk population to reduce the initiation of BCCs^[66].

8. Conclusion

BCC is cancer with multiple clinical and histological facets and can be challenging to differentiate from other cancers and other skin diseases. Therefore, the use of tumor and inflammatory immunohistochemical markers plays an essential role in the differential diagnosis and is necessary for the adoption of the correct therapy in many cases.

Clinical data related to CPNM (non-melanoma skin cancer) show that anti-inflammatory therapeutic approaches can significantly reduce skin carcinogenesis induced by UVB (ultraviolet radiation B).

9. REFERENCES

- [1]. Kim DP, Kus KJB, Ruiz E. Basal Cell Carcinoma Review. *Hematol Oncol Clin N Am* 33. 2019, 13-24. doi: 10.1016/j.hoc.2018.09.004.
- [2]. Instituto Nacional de Câncer “José Alencar Gomes da Silva” (BR). Ministério da Saúde. Estimativa Incidência de Câncer no Brasil. Rio de Janeiro: INCA; 2018. doi: 10.32635/2176-9745.RBC.2018v64n1.115
- [3]. Elder David E. et al. WHO Classification of Skin Tumors; 4th Edition; Lyon 2018: 26-34.
- [4]. Lupi O, Ribeiro RC, Hoff PM. Câncer Cutâneo. 1. Ed. Rio de Janeiro: Atheneu, 2019.
- [5]. Montagna E, Lopes OS. Bases moleculares do carcinoma basocelular. *Anais Brasileiros de Dermatologia*. 2017; 92(4):518-21. <http://www.anaisdedermatologia.org.br/detalhe-artigo/102786/Bases-moleculares-do-carcinoma-basocelular->
- [6]. Vasef AM, Auerbach A, et al. *Diagnostic Pathology Molecular Oncology*. 2th Edition; Philadelphia, PA: Elsevier; 2020:776-779.
- [7]. Ribeiro PL, Filho JBS, Abreu KD, Brezinski MS, Pignatelli CC. Você conhece esta síndrome? Síndrome de Gorlin-Goltz. *Anais Brasileiros de Dermatologia*. 2016; 91 (4): 541-3. <http://www.anaisdedermatologia.org.br/detalhe-artigo/102521/Voce-conhece-essa-sindrome-->
- [8]. Marzuka, AG, Book, SE. Basal Cell carcinoma: Pathogenesis, Epidemiology, Clinical Features, Diagnosis, Histopathology and Management. *Yale Journal of Biology and Medicine*. 88 (2015), p. 167-179. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4445438/>
- [9]. Tang JY, Azterbaum M, Athar M, Barsanti F, Cappola C, Estevez N, Hebert J, Hwang J, Kim A, Lu Y, So PL, Tang X, Kohn MA, McCulloch CE, Kopelovich L, Bickers DR, Epstein Jr EH. Basal Cell Carcinoma Chemoprevention with Nonsteroidal Anti-inflammatory drugs in Genetically Predisposed PTCH1+/- Humans. *Cancer Prev Res (Phila)*. 2010; 3(1): 25-34. DOI: 10.1158/1940-6207.CAPR-09-0200
- [10]. Tilley C, Deep G, Agarwal R. Chemopreventive Opportunities to Control Basal Cell Carcinoma: Current Perspectives. *Molecular Carcinogenesis*. 54; 688-697, 2015. doi: 10.1002/mc.22348. Epub 2015 Jun 5
- [11]. Busam KJ. *Dermatopatologia*. 2ª Edição; Rio de Janeiro: Elsevier, 2018:397-406.
- [12]. Cameron MC, Lee E, Hibler BP, Baker CA, Mori S, Cordoval M, Nehal KS, Rossi AM. Basal Cell Carcinoma: epidemiology, pathophysiology; clinical and histological subtypes; and disease

- associations. Journal of the American Academy of Dermatology, Volume 80, Issue 2, February 2019, Pages A38. doi: 10.1016/j.jaad.2018.03.060. Epub 2018 May 18
- [13]. Takita LC, Sacht GL. Carcinoma Basocelular. In: Takita LC, Sanguenza MA. Patologia de Tumores Cutâneos. Abordagem prática com correlações clínicas. São Paulo: Livraria Livromed Paulista; 2020.
- [14]. Pele – Carcinoma Basocelular – (5ª Edição – 2019). SBP, 2019. Disponível em: <<http://www.sbp.org.br/mdlhisto/pele-carcinoma-basocelular/>>. Acesso em: 30/09/2019.
- [15]. Chinem, VP, Miot, HA. Epidemiologia do carcinoma Basocelular. Anais Brasileiros de Dermatologia. 2011;86(2):292-305. doi: 10.1590/S0365-05962011000200013
- [16]. Nasser, N. Epidemiologia dos carcinomas basocelulares em Blumenau, SC, Brasil, de 1980 a 1999. Anais Brasileiros de Dermatologia. 2005;80:363-8. <http://www.scielo.br/pdf/abd/v80n4/v80n4a06.pdf>
- [17]. Hoang MP. Immunohistochemistry in Diagnostic Dermatopathology. 1th Edition. New York, NY: Cambridge University Press; 2017.
- [18]. Ishi LA, Pereira IC, Schellini SA, Marques MEA, Padovani CR. Carcinoma Basocelular de pálpebra – fatores relacionados com a recidiva. Anais Brasileiros de Dermatologia 2004, 79(4): 423-430. doi: 10.1590/S0365-05962004000400004
- [19]. Crowson AN. Basal Cell carcinoma: biology, morphology and clinical implications. Modern Pathology, 2006, 19, S127- S147. doi: 10.1038/modpathol.3800512
- [20]. Takita LC, Gdla V, Loro LS, Sanabria BD, Freitas CAF, Abreu AC, Sobrinho CA, Ramalho RT. Basal cell carcinoma in the labial filter: surgical treatment and reconstruction with bilateral perialar advancement flap in ascending. International Journal for Innovation Education and Research. 2019; 7(8): 402-406. doi: 10.31686/ijer.Vol7.Iss8.1701
- [21]. Sunjaya AP, Sunjaya AF, Tan ST. The use of BEREPA immunohistochemistry staining for detection of basal cell carcinoma. Journal of Skin cancer. 2017, 1-10. doi: 10.1155/2017/2692604
- [22]. Ramezani M, Mohamadzaheeri E, Khazaei S, Najafi F, Vaisi-Raygani A, Rhbar M, Sadeghi M. Comparison of EMA, CEA, CD10 and Bcl-2 Biomarkers by Immunohistochemistry in Squamous Cell Carcinoma and basal cell carcinoma of the skin. Asian Pac J Cancer Prev, 2016, 17 (3), 1379-1383. doi: 10.7314/apjcp.2016.17.3.1379
- [23]. Mantese, SAO, Berbert, ALCV, Gomides, MDA, Rocha, A. Carcinoma Basocelular – Análise de 300 casos observados em Uberlândia – MG. Anais Brasileiros de Dermatologia. 2006;81:136-42. doi: 10.1590/S0365-05962006000200004
- [24]. Bernard, P, Dupuy, A, Sasco, A, Brun, P, Duru, , Nicoloyannis, N, et al. Basal cell carcinomas and actinic keratoses seen in dermatological practice in France: a cross-sectional survey. Dermatology. 2008;216:194-9. doi: 10.1159/000112925
- [25]. Sousa, R.B.; Cunha, F.Q. Inflamação e Câncer. In: HOFF, P.M.G., Editor. Tratado de Oncologia. São Paulo: Atheneu; 2013: v.1. cap.32, p. 431-446.
- [26]. St.Clair, JM, Bar-Sagi, D. The role of inflammation in cancer. In: LaFond, RE, Editor. Cancer: the outlaw cell. New York: Oxford University Press; 2012: cap. 12, p: 151-164.

- [27]. Rizzo, MBS, Lepique, AP. Inflamação e Câncer. In: Saito, RF., et al. Ed. Fundamentos de oncologia molecular. São Paulo: Atheneu; 2015. Cap. 15, p: 281-299.
- [28]. Fernandes JV, Cobucci RNO, Jatoba CAN, Fernandes TAAM, Azevedo JWV, Araujo JMG. The role of the mediators of inflammation in cancer development. *Pathol. Oncol. Res.* 2015, 21(3): 527-534. doi: 10.1007/s12253-015-9913-z
- [29]. Jia J, Shi Y, Yan B, Xiao D, Lai W, Pan Y, Jiang Y, Chen L, Mao C, Zhou J, Xi S, Ya Cao, Liu S, Tao Yy. LGR5 expression is controlled by IKKa in basal cell carcinoma through activating STAT3 signaling pathway. *Oncotarget*, 2016, 7(19):27 280 – 27294. DOI: 10.18632/oncotarget.8465
- [30]. Ciurea ME, Cernae D, Georescu CC, Cotoi OS, Patrascu V, Parvanescu H, Popa D, Parvanescu V, Ciurea RN, Mercut R. Expression of CXCR4, MMP-13 and β -catenin in different histological subtypes of facial basal cell carcinoma. *Rom J Morphol Embryol* 2013, 54(4): 939-951. <http://www.rjme.ro/RJME/resources/files/540413939951.pdf>
- [31]. Pittayapruek P, Jitlada M, Prapapan O, Komine M, Ohtsuki M. Role of matrix metalloproteinases in Photoaging and Photocarcinogenesis *Int. Journal of Molecular Science.* 2016, 17, 868. doi: 10.3390/ijms17060868
- [32]. Kuznetsova EV, Snarskaya ES, Zavalishina LE, Tkachenko SB. Immunohistochemical study of the specific features of expression. Of matrix metalloproteinases 1, 9 in the photoaged skin, the foci of actinic keratosis and basal cell carcinoma. *ArkhPatol.* 2016; 78(6): 17-22. DOI: 10.17116/patol201678617-22
- [33]. Bridge JA, Lee JC, Daud A, Wells JW and Bluestone JA. Cytokines, chemokines and other biomarkers of response of checkpoint inhibitor therapy in skin cancer. *Front. Med.* 2018, 5: 351. doi: 10.3389/fmed.2018.00351
- [34]. Salan AI, Marasecu PC, Camen A, Cuica EM, Matei M, Florescu AM, Padureanu V, Margaritescu C. The prognostic value of CXCR4, α -SMA and WASL in upper lip basal cell carcinomas. *Rom J Morphol Embryol*, 2018,59(3): 839-849. <http://www.rjme.ro/RJME/resources/files/590318839849.pdf>
- [35]. Sivrikoz ON, Uyar B, Dag F, Tasli F, Sanal SM. CXCR-4 and COX-2 Expression in Basal Cell Carcinomas and well-differentiated Squamous Cell Carcinoma of the Skin; Their relationship with tumor invasiveness and Histological Subtype. *Turk Patoloji Derg* 2015, 31: 30-35. DOI: 10.5146/tjpath.2014.01279
- [36]. Castillo JM, Knol AC, Nguyen JAM, Khammari A, Saint-Jean M, Dreno B. Immunohistochemical markers of advanced basal cell carcinoma: CD56 is associated with a lack of response to vismodegib. *Eur J Dermatol*, 2016; 26(5): 452-9. <https://link.springer.com/article/10.1684/ejd.2016.2826>
- [37]. Xu CZ, Wang PH, Yan XJ, Wang T, Chen D, Zhang ZJ, Shi RJ. Expression of CXCR4 is associated with progression and invasion in patients with nasal-surface basal cell carcinoma. *Journal Otorhinolaryngol Rela Spec.* 2013 75(6): 332-41. doi: 10.1159/000357027
- [38]. Chen GS, Yu HS, Lan CCE, Chow KC, Lin TY, Kok, If, Lu MP, Liu CH, Wu MT. CXCR chemokine receptor CXCR4 expression enhances tumorigenesis and angiogenesis of basal cell

- carcinoma. *British Journal of Dermatology*. 2006 154:910-918. DOI: 10.1111/j.1365-2133.2006.07150.x
- [39]. Mantovani, A.; Savino, B.; Locati, M. et al. The chemokine system in cancer biology and therapy. *Cytokine Growth Factor Rev*, Oxford, 2010, 21(1): 27-39. DOI: 10.1016/j.cytogfr.2009.11.007
- [40]. Gozdzińska A, Wojas-Pelc A, Drag J, Brzewski P, Jaskiewicz J, Pastuszcak M. Expression of metalloproteinases (MMP-2 and MMP-9) in basal cell carcinoma. *Mol Biol Rep* 2016, 43:1027-1033. doi: 10.1007/s11033-016-4040-9
- [41]. El-Khalawany MA, Abou-Bakr AA. Role of Cyclooxygenase-2, Ezrin and Matrix metalloproteinases-9 as predictive markers for recurrence of basal cell carcinoma. *Journal of Cancer Research and Therapeutics*. 2013 9(4): 613-617. doi: 10.4103/0973-1482.126456
- [42]. Ciazynska M, Bednarski IA, Wodz K, Kolano P, Narbutt J, Sobjanek M, Wozniacka A, Lesiak A. Proteins involved in cutaneous basal cell carcinoma development. *Oncology Letters*. 2018, 16: 4064-4072. doi: 10.3892/ol.2018.9126
- [43]. Ribeiro RIMA, Junior PCB, Cardoso SV, Candelori I, Espindola FS, Cassali D, Loyola AM. Expressão de metaloproteinases de matriz e de seus inibidores teciduais em carcinoma basocelulares. *Bras Patol Med Lab*, 2008; 44(2): 115-21. Doi: 10.1590/S1676-24442008000200008
- [44]. Mohian N, Jewett BS, Baker SR, Varani J. Matrix Metalloproteinase Expression in Normal Skin Associated with Basal Cell Carcinoma and in Distal Skin from the Same Patients. *Arch Facial Plast Surg*. 2005; 7: 238-243. DOI: 10.1001/archfaci.7.4.238
- [45]. Zhu L, Kohda F, Nakahara T, Chiba T, Tsuji G, Hachisuka J, Ito T, Tu Y, Moroi Y, Uchi H. Aberrant expression of S100A16 and matrix metalloproteinase 9, but not S100A2, S100A4 and S100A7, is associated with epidermal carcinogenesis. *Journal of Dermatological Science* 72, 2013: 311-319.
- [46]. Karahan N, Baspinar S, Bokurt KK, Ibrahim MC, Kapucuoglu N. Increased expression of COX-2 in recurrent basal cell carcinoma of the skin: A pilot study. *Indian Journal of Pathology Microbiology*. 2011 54(3): 526-531. DOI: 10.4103/0377-4929.85086
- [47]. Correa MPD, Ferreira AP, Gollner AM, Rodrigues MF, Guerra MCS. Expressão de marcadores de proliferação celular e apoptose em carcinoma basocelular. *Anais Brasileiros de Dermatologia* 2009, 84(6): 606-614. Doi: 10.1590/S0365-05962009000600006
- [48]. Chiacchio ND, Cuce LC. Carcinoma Basocelular: estudo comparativo dos três tipos histológicos mais frequentes em relação à proliferação celular. *Anais Brasileiros de Dermatologia*. 1997, 72(5): 427-431. <https://pesquisa.bvsalud.org/portal/resource/pt/sms-2949>
- [49]. Lima JSB, Miola AC, Marques MEA, Miot HA. Patterns of proliferation and apoptosis in the different subtypes of basal cell carcinoma adjacent epidermis and recurrent forms. *An Bras Dermatol*. 2019, 94(1): 108-10. Doi: 10.1590/abd1806-4841.20198165
- [50]. Maru GB, Gandhi K, Ramchandani A, Kumar G. The role of Inflammation in Skin Cancer. *Inflammation and Cancer, Advances in Experimental Medicine and Biology* 816, Springer Basel 2014. DOI: 10.1007/978-3-0348-0837-8_17

- [51]. Neagu M, Constantin C, Caruntu C, Dumitru C, Surcel M, Zurac S. Inflammation: A key process in skin tumorigenesis (Review). *Oncology Letters*, 17: 4068-4084, 2019. doi: 10.3892/ol.2018.9735
- [52]. Puizina-Ivic N, Sapunar D, Marasovic D, Miric L. An overview of Bcl-2 expression in histopathological variants of basal cell carcinoma, squamous cell carcinoma, actinic keratosis and seborrheic keratosis. *CollAntropol*, 2008 oct;32 Suppl 2:61-5. PMID: 19138009
- [53]. Aggarwal, B.B.; Vijayalekshmi, R.V.; Sung, B. Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res*, Philadelphia, 2009, 15(2): 425-430. DOI: 10.1158/1078-0432.CCR-08-0149
- [54]. Grivennikov, S.; Greten, F.; Karin, M. Immunity, inflammation, and cancer. *Cell*, Cambridge, 2010, 140(6): 883-899. doi: 10.1016/j.cell.2010.01.025
- [55]. Ghita, MA, Caruntu, C, Rosca, AE, Kaleshi, H, Caruntu, A, Moraru, L, Docea, AO, Zurac, S, Boda, D, Neagu, M, *et al*: Reflectance confocal microscopy and dermoscopy for in vivo, non-invasive skin imaging of superficial basal cell carcinoma. *Oncol Lett*. 2016, 11:3019-3024. doi: 10.3892/ol.2016.4354
- [56]. Larsimont, JC, Youssef, KK, Sanchez-Danes, A, Sukumaran, V, Defrance, M, Delatte, B, Liagre, M, Baatsen, P, Marine, JC, Lippens, S. *et al*: Sox9 controls self-renewal of oncogene targeted cells and links tumor initiation and invasion. *Cell Stem Cell* 17: 60-73, 2015. DOI: 10.1016/j.stem.2015.05.008
- [57]. Chastkofsky, MI, Bie, W, Ball-Kell, SM, He, YY, Tyner, AL. Protein tyrosine kinase 6 regulates UVB-induced signaling and tumorigenesis in mouse skin. *J Invest Dermatol* 135: 2492-2501, 2015. doi: 10.1038/jid.2015.166. Epub 2015 Apr 30
- [58]. Baykan, H, Cihan, YB, Ozyurt, K. Roles of white blood cells an subtypes as inflammatory markers in skin cancer. *Asian Pac J Cancer Prev*. 16: 2303-2306, 2015. DOI: 10.7314/apjcp.2015.16.6.2303
- [59]. Lupu, M, Caruntu, A, Caruntu, C, Papagheorghe, LML, Ilie, MA, Voiculescu, V, Boda, D, Constatin, C, Tanase, C, Sifaki, M, *et al*. Neuroendocrine factors: The missing link in non melanoma skin cancer (Review). *Oncol Rep*. 38: 1327-1340, 2017. doi: 10.3892/or.2017.5817
- [60]. Lin, Y, Chahal, hs, Wu, W, Cho, HG, Ransohoff, KJ, Dai, H, Tang, JY, Sarin, KY, Han, J. Association between genetic variation within vitamin D receptor-DNA binding sites and risk of basal cell carcinoma. *Int J Cancer*. 140: 2085-2091, 2017. DOI: 10.1002/ijc.30634
- [61]. Kaukinen A, Siiskonen, H, Plkonen, J, Harvima, IT. Immunoreactivity to CYP24A1, but not vitamin D receptor, is increased in mast cells of keratinocyte skin cancers. *Eur J Dermatol*. 27: 590-598, 2017. DOI: 10.1684/ejd.2017.3132
- [62]. Weidenbusch, M, Rodler, S, Song, S, Romoli, S, Marschner, JA, et al. Gene expression profiling of the Notch-AhR-IL22 axis at homeostasis an in response to tissue injury. *Biosci Rep*. 37: BSR20170099, 2017. DOI: 10.1042/BSR20170099
- [63]. Rubina KA, Sysoeva VY, Zaorujko EI, Tsokolaeva ZI, Kurdina MI, Parfyonova YV and Tkachuk VA. Increased expression of uPA, uPAR, and PAI-1 in psoriatic skin and in basal cell carcinomas. *Arch Dermatol Res* 309:433-442, 2017. DOI: 10.1007/s00403-017-1738-z

- [64]. Chaudhary SC, Waseem M, Rana M, Xu H, Kopelovich L, Elmets CA and Athar M. Naproxen inhibits UVB-induced basal cell and squamous cell carcinoma development in Ptch^{+/-}/Skh-1 hairless mice. *PhotochemPhotobiol*, 2017, 93(4):1016-1024. DOI: 10.1111/php.12758
- [65]. Papakostas D and Stockfleth E. Topical treatment of basal cell carcinoma with the immune response modifier imiquimod. *Future Oncol*. 2015, 11:2985-2990. DOI: 10.2217/fon.15.192
- [66]. Muranushi C, Olsen CM, Green AC and Pandeya N. Can oral nonsteroidal anti-inflammatory drugs play a role in the prevention of basal cell carcinoma? A systematic review and metaanalysis. *J AmAcadDermatol*. 2016, 74:108-119. DOI: 10.1016/j.jaad.2015.08.034