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Malignant Transformation in Skin is Associated with the Loss of T-Cadherin Expression in Human Keratinocytes and Heterogeneity in T-Cadherin Expression in Tumor Vasculature

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1. Introduction

A tumor is an abnormal mass of cells, the growth of which exceeds that of the normal tissue. Although most of the skin tumors retain a resemblance to the normal tissues from which they arise, they can show variations in their structure which cause difficulties in establishing pathological diagnosis. In contrast to benign skin tumors, which in most cases remain at the site of their origin and form compact mass of tumor cells, malignant tumors are composed of cells with the ability to invade the basement membrane and metastasize to other organs through blood and lymphatic vessels. Moreover, malignant tumors are often characterized by a more rapid growth and less differentiation, which histologically is characterized by a higher mitotic index and cellular and nuclear pleomorphism (Quinn & Perkins, 2010). Differentiation between benign and malignant skin tumors is one of important questions in terms of diagnostics, prognosis and treatment of the skin lesions.

Recently, a variety of molecular markers were shown to be promising in correlation with aggressive and invasive behavior of skin cancers. These involve aberrant expression of p53 (Verdolini et al., 2001), increased expression of transcription factors (Keehn et al., 2004), metalloproteinases (MMPs) (Verdolini et al., 2001), and proliferation markers mib1, Ki-67 (Oh & Penneys, 2004), stem cell markers c-kit, p63 (Laskin & Miettinen, 2003), increased phosphorylation of regulatory proteins and up-regulation of receptors of growth factors (Weigelt et al., 2005).

Tumor growth and invasiveness is accompanied by altered cell-cell communications. Thus, aggressive cancers are associated with decreased expression of E-cadherin which correlates with increased expression of desmosomal junction protein desmoglein (Kurzen et al., 2003) and N-cadherin (Gloushankova, 2008; Berx & van Roy, 2009).

T-cadherin, a non-classical member of cadherin family, was also suggested to play a role in cancer progression (Andreeva & Kutuzov, 2010; Philippova et al., 2009).

2. T-cadherin structure and intracellular signaling

T-cadherin is an atypical member of the cadherin superfamily. While possessing the general extracellular structure of classical cadherins, T-cadherin lacks transmembrane and cytoplasmic domains and is anchored to the plasma membrane by a glycosylphosphatidylinositol (GPI) moiety (Ranscht & Dours-Zimmermann, 1991). Since transmembrane and cytoplasmic domains of classical cadherins are generally recognized to be crucial in maintaining stable cell-cell contacts (Gumbiner, 2005), it is considered that the main function of T-cadherin is not cell-cell adhesion (Rubina et al., 2005a; Rubina & Tkachuk, 2004). Like other GPI-anchored proteins, T-cadherin is located in lipid rafts/caveolae (Philippova et al., 1998). Lipid rafts are cholesterol and sphingolipid rich domains of plasma membrane, which contain GPI-anchored proteins and signal transduction molecules such as Src-family kinases (Brown & London, 2000; Maxfield, 2002).

Indeed, T-cadherin was shown to be involved in regulation of cell adhesion, migration, proliferation and survival via activation of intracellular signaling. By using dominant negative and constitutively active forms of Rho, Rac and Cdc42 it was shown that Rho GTPases act downstream of T-cadherin and the activation of Rac1 and Cdc42 GTPases results in increased phosphorylation of LIMK1 kinase, actin and microtubule cytoskeleton rearrangements, activation of endothelial cell migration and increased permeability of endothelial cell monolayer (Philippova et al., 2005; Semina et al., 2009). Overexpression of T-cadherin in endothelial cells led to higher phosphorylation levels for phosphatidylinositol-3-kinase (PI3K) target Akt and mTOR target $p70^{S6K}$ involved in survival pathway in endothelial cells, but lower levels for p38MAPK (death pathway) (Joshi et al., 2005). In line with that, it was shown that T-cadherin mediated activation of PI3K/Akt/GSK3β signaling which protects endothelial cells from oxidative stress-induced apoptosis (Joshi et al., 2005). The effects of T-cadherin on Akt activation and survival require T-cadherin interacting partner Grp78, which is also known to be up-regulated in cancers (Andreeva et al., 2010; Philippova et al., 2008). High molecular weight adiponectin activates NF-kB and inhibits endothelial cell apoptosis suggesting that T-cadherin binding to adiponectin could prevent apoptosis of endothelial cells in tumor vessels (Adachi et al., 2006). Overexpression of T-cadherin in human aortic smooth muscle cells and in HUVECs increases cell proliferation (Ivanov et al., 2004). However, T-cadherin overexpression in HUVECs also results in an increased number of multinuclear cells, whereas its downregulaion results in increased amount of cells with multiple centrosomes (Andreeva et al., 2009). Stimulation of vascular endothelial cells and T-cadherin overexpressing HEK293 cells with plasma low density lipoproteins demonstrated the T-cadherin-induced signaling involving phospholipase C and IP3 formation, intracellular Ca^{2+} mobilization, activation of tyrosine kinases Erk 1/2, and nuclear translocation of NF-kB (Kipmen-Korgun et al., 2005; Rubina et al., 2005b).

However, in contrast to endothelial cells, overexpression of T-cadherin in C6 glioma (Huang et al., 2003) hepatocellular carcinoma cells (Chan et al., 2008), in immortalized keratinocytes (Mukoyama et al., 2005) and in p53(-/-) mouse embryonic fibroblasts (Chan et al., 2008) suppresses proliferation by delaying the G_2/M phase progression. In hepatocellular carcinoma cells T-cadherin expression also increases sensitivity to TNFα-induced apoptosis (Chan et al., 2008). Hence, in different studies T-cadherin was shown to be involved in regulation of proliferation, apoptosis and angiogenesis in normal tissues and tumor growth.

3. T-cadherin mediates homophilic interaction and vessel repulsion in angiogenesis

It is worth noting that in most experimental studies, the main attention is usually paid to the expression of T-cadherin in endothelial cells of the vessels while the role of T-cadherin expression by stromal cells in neoangiogenesis is rarely considered. In contrast, we used the Matrigel model, where Matrigel plugs containing L929 fibroblasts (control or overexpressing T-cadherin) where injected subcutaneously into nu/nu mice. In this settings, migrating endothelial cells, naturally expressing T-cadherin, contacted with T-cadherin positive fibroblasts and this interaction resulted in suppressed blood vessel growth. This effect of T-cadherin was dependent upon the concentration of T-cadherin expressing cells injected into the Matrigel. Moreover, small vessels and capillaries which invaded the Matrigel plug with high level of T-cadherin, did not express T-cadherin. Conceivably, high expression of T-cadherin inhibited the growth of the blood vessels. Furthermore, T-cadherin overexpression in the stroma regulated qualitative composition of blood vessels infiltrating the tissue either by negative guiding of T-cadherin expressing vascular endothelial cells or by downregulation of T-cadherin expression in the growing vessels, or both (Rubina et al., 2007).

It was shown that the general mechanism of T-cadherin mediated repulsion could involve homophilic T-cadherin interaction and contact inhibition as it was revealed for the growth of axons in the embryonic nervous system (Fredette et al., 1996). The same mechanism was shown to be responsible for regulation of the trajectory of the growing vessels. The first set of evidence came from in vitro experiments utilizing immobilized N-terminal EC1 domain of T-cadherin (Ivanov et al., 2004), which was responsible for homophilic T-cadherin interaction of contacting cells (Rubina et al., 2007). In vitro in Boyden chamber, ring aorta and capillary tube assays, we have shown that migration of endothelial cells, which endogenously express T-cadherin (Philippova et al., 2003), was inhibited by immobilized EC1 domain.

Thus, the most likely mechanism of T-cadherin-mediated suppression of blood vessel ingrowth is the interaction between T-cadherin molecules on endothelial and surrounding cells. This interaction leads to initiation of intracellular signaling cascades, which presumably are similar to ephrin's signaling, followed by cell-cell repulsion.

4. T-cadherin and tumor growth and vascularization

It has been proposed that T-cadherin functions as a tumor suppressor factor and its downregulation due to allelic loss or hypermethylation in the promoter region of the gene or some other reasons is related to tumor growth and metastasis in certain cancers (Takeuchi et al., 2002b; Andreeva & Kutuzov, 2010). Downregulation of T-cadherin was shown to be associated with malignant phenotype and tumorigenecity in breast (Riener et al., 2008), lung (Sato et al., 1998), and gallbladder cancers (Adachi et al., 2009). However, in other cancers such as ovarian, endometrial (Widschwendter et al., 2004; Suehiro et al., 2008) and osteosarcoma (Zucchini et al., 2004) T-cadherin decreased expression correlated positively with patient survival. T-cadherin overexpression was found to be a common feature of human invasive hepatocellular carcinomas (Riou et al., 2006) and high grade astrocytomas, where it was associated with malignant transformation of astrocytes. Hetezygosity for NF1 (neurofibromatosis 1) tumor suppressor resulting in reduced attachment and spreading and increased motility also coincided with upregulated T-cadherin expression (Gutmann et al., 2001).

Data on non-melanoma skin cancers and related premalignant lesions are also contradicting. In normal skin T-cadherin is expressed in keratinocyte basal cell layer (Zhou et al., 2002). In actinic keratosis T-cadherin expression is pronounced on the atypical keratinocytes, while in Bowen disease expression of T-cadherin varies and is in general weaker than in normal skin (Pfaff et al., 2010). Expression of T-cadherin is reduced in psoriasis (Zhou et al., 2003), is absent in invasive cutaneous squamous cell carcinoma due to aberrant methylation and gene deletion (Takeuchi et al., 2002a) and is down-regulated in basal cell carcinoma of the skin (Takeuchi et al., 2002b).

While in some studies the authors investigated the correlation between the hypermetylation of T-cadherin promoter or allelic loss, the others addressed the effect of T-cadherin re-expression on the malignant properties of cancer cells upon injection of cells in vivo in mouse models. Melanoma cells (Kuphal et al., 2009), hepatocellular carcinoma cells (Chan et al., 2008) and human breast carcinoma cells (Lee et al., 1998) showed a reduced tumor growth upon re-expression of T-cadherin. The transfection of mammary gland cells with cDNA of T-cadherin resulted in suppression of the cell proliferation in culture, which was also accompanied by transformation of the cancer cells from the invasive to the normal phenotype (Lee, 1996). The overexpression of T-cadherin in the neuroblastoma cells led to the suppression of invasion of the cells and the loss of their ability to respond to the addition of epidermal growth factor (EGF) with increased proliferation (Takeuchi et al., 2000). The overexpression of T-cadherin in the cells of glioma C6 was accompanied by the decrease of cell migration and suppression of the growth and proliferation in those cells due to blockade of the cell cycle on the stage G_2 (Huang et al., 2003). In immortalized keratinocyte cell lines derived from squamous cell carcinoma forced over-expression of T-cadherin resulted in decreased cell proliferation (Mukoyama et al., 2005).

These in vivo and in vitro data suggest that T-cadherin could be an endogenous negative regulator of keratinocyte proliferation. However, proliferating basal keratinocytes of the epidermis also express T-cadherin, leading to the conclusion that the role of T-cadherin in regulation of tumor cell growth and invasion is more complex.

Angiogenesis is necessary for tumor growth, invasion and metastases, therefore it has prognostic value and can be a therapeutic target. Angiogenesis is the process in which endothelial cells divide and migrate to form new capillaries, which support the continued growth of tumor through blood flow (Hasan et al., 2002; Sasano et al., 1998). Cancer-induced angiogenesis in general results from increased expression of angiogenic factors by tumor and/or stromal cells such as VEGF-A or decreased expression of anti-angiogenic factors, or a combination of both events (Hasan et al., 2002). Numerous authors reported that angiogenesis plays an important role in tumor progression and metastasis of the great majority of human solid tumors (Hasan et al., 2002; Offersen et al., 2002; Rubin et al., 1999; Vieira et al., 2004). During tumor angiogenesis, a certain sequence of events occurs resulting in directional migration of endothelial cells through the basement membrane and perivascular stromal cells toward angiogenic stimuli produced by tumor cells. In normal angiogenesis after endothelial cell migration and proliferation mural cells (smooth muscle cells and pericytes) enable stabilization of the nascent vessels. However, the newly formed tumor vessels are usually thin-walled capillaries or sinusoids with little more than an endothelial lining stabilized by a basement membrane and are susceptible to spontaneous hemorrhage and thrombosis (Carmeliet, 2000; Jain & Carmeliet, 2001; Yancopoulos et al., 2000).

Increasing evidence supports the essential role of VE and N-cadherin in the assembly of the vascular network. The adhesive properties of these cadherins are important for their

angiogenic function, as far as they control both endothelial cell–cell interactions and the interaction of endothelial cells with stroma. The application of antibody against N-terminal repeat of VE-cadherin established this cadherin as a possible target for inhibiting angiogenesis in tumors (Cavallaro et al., 2006).

It is quite possible that T-cadherin affects carcinogenesis not only due to its aberrant expression in cancer cells, but also because it affects tumor neovascularization. Thus, in normal blood vessels T-cadherin is expressed in endothelial and mural cells (smooth muscle cells and pericytes) (Ivanov et al., 2001). However, as shown in numerous studies, T-cadherin expression is altered in tumor vessels: in Lewis carcinoma lung metastasis and F9 teratocarcinoma, PC-3 prostate cancer, in A673 rhabdomyosarcoma the expression of T-cadherin is upregulated on endothelial cells of the blood vessels penetrating the tumor (Riou et al., 2006; Wyder et al., 2000), while no T-cadherin could be detected in the blood vessels of B16F10 melanoma lung metastasis (Wyder et al., 2000). Using mouse mammary tumor virus (MMTV)-polyoma virus middle T (PyV-mT) transgenic model with inactivated T-cadherin gene it was shown that T-cadherin deficiency limits mammary tumor vascularization and reduces tumor growth (Hebbard et al., 2008).

In tumor neovascularization of hepatocellular carcinoma (HCC) T-cadherin is also upregulated in intratumoral capillary endothelial cells, whereas in surrounding tumor tissue as well as in normal liver no T-cadherin could be detected (Adachi et al., 2006). The increase in T-cadherin expression in endothelial cells of HCC was shown to correlate with tumor progression (Adachi et al., 2006). The involvement of T-cadherin in melanoma angiogenesis was demonstrated using an in vitro tumor spheroid model in co-culture with endothelial cells where T-cadherin upregulation in endothelial cells potentiated intratumoral angiogenesis (Ghosh et al., 2007). These data indicate that the contradictory results on tumor progression could be due to the complex cancer, stromal and endothelial cell intracellular interactions inside the growing tumor. The possible mechanism underlying the function of T-cadherin in angiogenesis could be the regulation of the trajectory of the growing blood vessels, thus T-cadherin acts as a navigating receptor (Rubina et al., 2007).

A diversity of navigating receptors has been already identified and shown to be involved in regulation of angiogenesis during embryogenesis and regeneration. These include semaphorins and their receptors (plexins and neuropilins), neutrins and their receptors (DCC/neogenine and Unc5), slit-ligands and their receptors Robo, and ephrins and their receptors (Adams et al., 1999; Weinstein, 2005). It is also known that ephrins and their receptors are navigation molecules regulating the trajectory of migration and differentiation of the cells in cardiovascular system (Adams et al., 1999); they have also been linked to the regulation of tumor angiogenesis (Ogawa et al., 2000).

To address the influence of T-cadherin overexpression in tumor cells on the ingrowth of the blood vessels into the tumor we used in vivo model of chorioallantoic membrane. For that the melanoma B16F10 cells overexpressing T-cadherin were injected under the chorioallantoic membrane in chick embryo, thus creating the microenvironment with high content of T-cadherin. This resulted in the reduction of the amount of blood vessels growing into the tumor with high expression of T-cadherin in comparison to the control (Yurlova et al., 2010). Presumably, the homophilic interaction and “repulsion” between molecules of T-cadherin on the surface of endothelial cells and tumor cells occurred at the contact of migrating endothelial cells which endogenously express T-cadherin with the tumor cells of melanoma, thereby resulting in the suppression of angiogenesis.

5. Stroma plays an active role in tumor growth and progression

In normal tissues stromal fibroblasts are responsible for the synthesis, deposition and remodeling of the extracellular matrix, as well as for the production of the soluble paracrine factors that regulate (promote or inhibit) cell proliferation, morphology and migration, survival and apoptosis (Klopp et al., 2011; Tlsty & Coussens, 2006). Tumor fibroblasts are derived, in part, from mesenchymal stem cells that may be recruited regionally or from circulating populations from the bone marrow (Mishra et al., 2008; Spaeth et al., 2008). Tumor fibroblasts isolated from malignant tissues exhibit altered phenotypes, mostly because of the aberrant production of the extracellular matrix proteins and growth factors (Bauer et al., 1979; Knudson et al., 1984; Tlsty & Coussens, 2006), disorganized patterns of growth, and enhanced proliferation (Rasmussen & Cullen, 1998; van den Hooff, 1988). Such phenotypes promote tumor progression (Klopp et al., 2011).

Tissue combination experiments using normal human prostatic epithelial cells with stromal cells obtained from prostatic adenocarcinoma demonstrated an interaction that limited growth potential of the epithelial cells while re-establishing their ability to form ductal structures resembling prostatic intraepithelial neoplasia. Engrafting of the stromal cells isolated from tumors together with immortalized human prostatic epithelial cells led to tumor formation exceeding by 500 fold the weight of control grafts (Olumi et al., 1999). Remarkably, isolation of pure human epithelial cell populations from these tumors and subsequent grafting into animals demonstrated that the epithelial cells were then able to form tumors while tumor fibroblasts presence and activity was no longer necessary (Olumi et al., 1999). Histological analysis of these tumors showed their characteristic features of malignant neoplasms with enhanced cell proliferation, reduced apoptosis, active angiogenesis, and genomic instability. Tumor fibroblasts isolated from human tumors also facilitate the growth of human breast and ovarian cancers when co-injected into immunosuppressed mice (Orimo et al., 2005).

These studies demonstrate that tumor stromal cells can produce oncogenic signals that can transform normal epithelial cells and induce them towards malignant state, thus establishing an active role of stromal cells in tumorigenic processes. Reciprocally, when placed in co-culture, tumor cells can directly induce stromal cells to convert into α–smooth muscle actin positive cells and express vimentin and stromal derived factor 1 (SDF-1), common to cancer associated fibroblasts. Transforming growth factor β (TGF–β) often produced by tumor cells was shown to induce conversion of adjacent stromal cells into α–smooth muscle actin expressing cells (Mishra et al., 2008; Spaeth et al., 2009; Tlsty & Coussens, 2006).

Thus, stromal cells together with cancer cells regulate tumor neoangiogenesis, in part, by local changes in the balance between soluble and insoluble molecules that elicit either pro- or antiangiogenic effects (Cavallaro et al., 2006; Takeuchi & Ohtsuki, 2001; Wyder et al., 2000). Mesenchymal stromal cells are known to secrete different proangiogenic factors, such as vascular endothelial growth factor (VEGF-A), fibroblast-derived growth factor (FGF), platelet-derived growth factor (PDGF), and SDF-1 (Efimenko et al., 2010; Rubina et al., 2009). These cytokines promote endothelial and smooth muscle migration and proliferation at the tumor site, facilitating angiogenesis (Kinnaird et al, 2004; Potapova et al., 2007). Other growth factors responsible for mesenchymal stromal cell effects on tumor vasculature include hepatocyte growth factor (HGF), cyclooxygenase, insulin-like growth factor 1 (IGF-1), PDGF-a, and TGF–α (Beckermann et al., 2008).

6. T-cadherin expression in precancerous lesions and malignant neoplasm of the skin

To define the role of T-cadherin in the pathogenesis of skin lesions we performed a comparative study of T-cadherin expression in normal skin samples, in non-melanoma skin cancer and related premalignant lesions. Cryosections of human skin biopsies from healthy donors, patients with keratoacanthoma in growth and stabilization stages, patients with keratosis, patients with superficial, nodular and infiltrative types of basal cell carcinoma, patients with basosquamous cell carcinoma and patients with squamous cell carcinoma were immunostained with antibodies against T-cadherin and vascular cell markers and analysed using fluorescent microscope.

6.1 Immunofluorescent staining

Human skin biopsies from 6 healthy donors, 10 patients with keratoacanthoma, 3 patients with keratosis, 30 patients with basal cell carcinoma, 5 patients with basosquamous cell carcinoma and 5 patients with squamous cell carcinoma were obtained from Dermatology Department of First Moscow State Medical University. Consequent cryosections of skin biopsies (7μm thick) were fixed in 4% paraformaldehyde (PRS Panreac, Spain) for 10 min. After several washes with phosphate buffer saline (PBS, Sigma-Aldrich, USA) sections were incubated in PBS/0.1% bovine serum albumine (BSA, Sigma-Aldrich, USA) containing 10% normal donkey serum (Sigma-Aldrich, USA) to block non-specific binding of antibodies. This was followed by incubation in a mixture of primary antibodies against T-cadherin (rabbit anti-human, ProSci, USA) and endothelial cell markers - vWF (Von Willebrand factor, mouse anti-human, BD Biosciences, USA) or CD31 (mouse anti-human, BD Biosciences, USA), or marker of smooth muscle cells and pericytes - α–actin (rabbit anti-human, Epitomics, USA) for 1 hour and subsequent extensive washing in PBS. Then sections were incubated in a mixture of secondary antibodies Alexa488-conjugated donkey anti-mouse and Alexa594-conjugated donkey anti-rabbit or Alexa488-conjugated donkey anti-rabbit and Alexa594-conjugated donkey anti-mouse (Molecular Probes, USA) (1μg/ml in PBS). Cell nuclei were counterstained with DAPI (Molecular Probes, USA). Sections were mounted in Vectashield mounting media (Vector Laboratories Inc., USA). For negative controls mouse or rabbit non-specific IgGs were used in appropriate concentration. Images were obtained using Zeiss Axiovert 200M microscope equipped with CCD camera AxioCam HRc and Axiovision software (Zeiss, Germany) and further processed using Adobe PhotoShop software (Adobe Systems, USA).

6.1.1 Normal skin

In normal skin the strongest T-cadherin expression was found in basal keratinocytes, stromal cells and in all blood vessels located in the underlying derma as observed by staining with antibody against endothelial marker vWF and marker of smooth muscle cells and/or pericytes - α–actin (Fig.1).

This data are in line with the previous observations (Takeuchi et al., 2002b). And yet, for the first time we have identified T-cadherin expression in hair follicles and sebaceous glands (Fig.1). In contrast to other studies (Zhou et al., 2002; Pfaff et al., 2010), we have found T-cadherin expression in the suprabasal layers of epidermal keratinocytes, although weaker than in the basal layer.

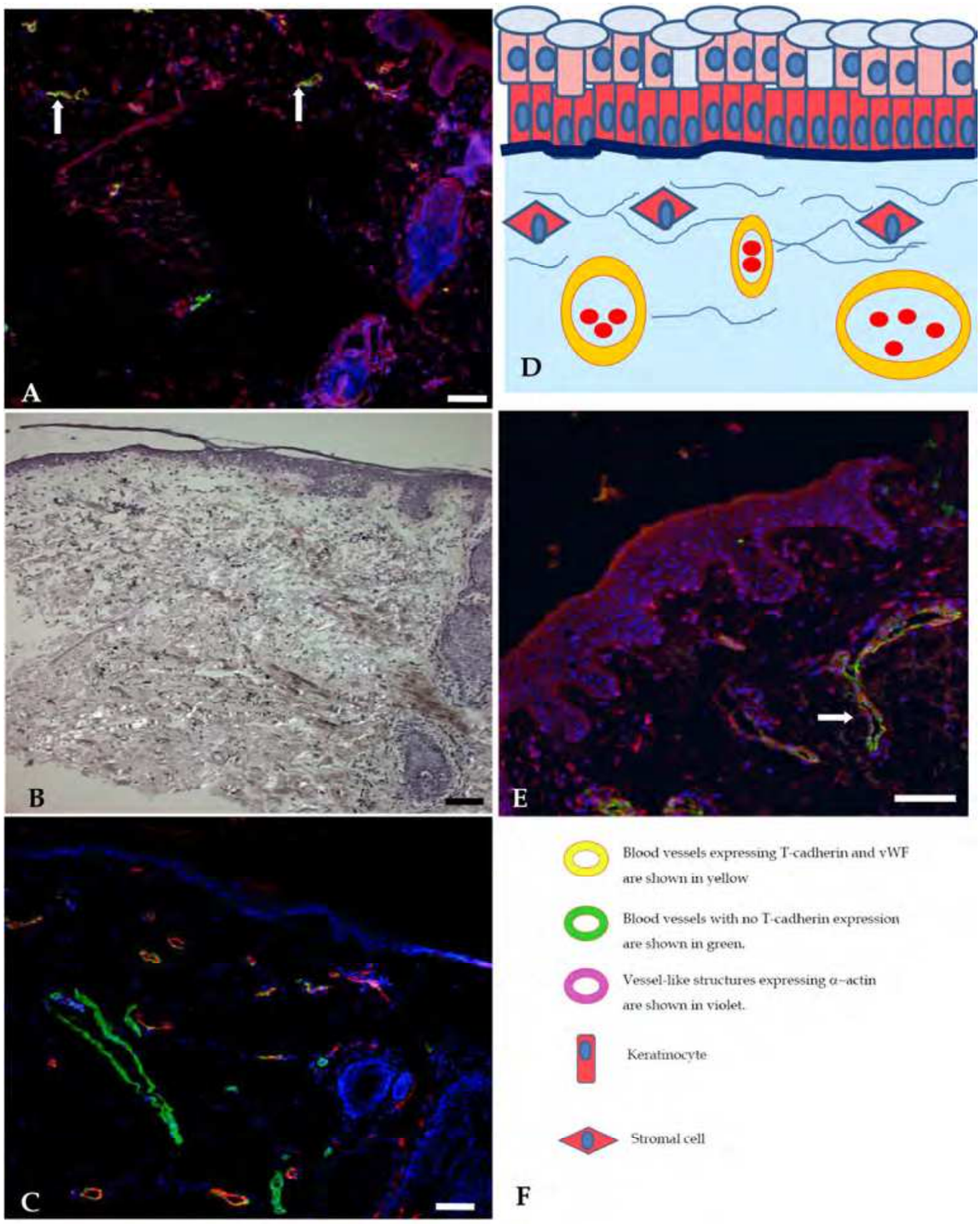


Fig. 1. Double immunofluorescent staining of normal skin samples with antibodies against T-cadherin (red) and vWF (green) (A, E) or vWF (red) and α–actin (green) (C). Figures A, B, C represent parallel frozen sections of the same sample. T-cadherin expression was detected in basal keratinocytes, suprabasal layers, stromal cells and in hair follicles and sebaceous glands. Nuclei were counterstained with DAPI (blue). Figure B depicts phase contrast image. Uniform

expression of T-cadherin in small and large blood vessels was noted (yellow), colocalization of T-cadherin and vWF is showed by the arrow. Stabilized vessels were located in derma and were double positive for vWF and α–actin; stromal cells were also α–actin-positive (C). Bars, 100 μm. Figure D represents the diagram explaining strong T-cadherin expression in basal cell layer (red) and stromal cells, moderate T-cadherin expression (pink) in suprabasal layers and T-cadherin expression in all vWF-positive blood vessels (yellow). F figure legend.

Premalignant epithelial lesions are conditions that have certain clinical and histopathological features and are associated with an increased risk of cancer development (Quinn and Perkins, 2010). Premalignant lesions frequently have many histopathological changes in common with invasive cancers; however, this doesn't imply that the premalignat lesions will change into neoplastic process. Therefore, it is important to identify the diagnostic markers which will allow better accuracy in diagnostics of premalignant lesions and cancer and their treatment.

6.1.2 Psoriasis

Psoriasis is a chronic condition that causes keratinocytes proliferate much faster that in normal skin and move to the skin surface forming sharply demarcated erythematous plaques or thick patches (Godic, 2004). Such pathology reflects the abnormal epidermal keratinocyte proliferation and differentiation and delayed apoptosis. Histological characteristics of psoriasis are hyperkeratosis, parakeratosis, acanthosis of the epidermis, tortuous and dilated capillary vessels and an inflammatory infiltrate composed mainly of lymphocytes, which is located in the upper dermis. The underlying mechanism of increased keratinocyte growth remains controversial. It is considered to be genetically determined and have a strong autoimmune component implicating activated T-lymphocytes and excessive production of inflammatory cytokines (Godic, 2004). However, psoriasis is unique because it exhibits excessive but controlled keratinocyte proliferation. Recent study demonstrated that there is downregulation of T-cadherin expression in epidermal keratinocytes in psoriatic samples compared to normal skin. The immunostaining against T-cadherin in psoriasis vulgaris as shown in this paper is restricted to the keratinocyte basal cell layer (Zhou et al., 2003). In contrast, our results indicate that T-cadherin expression in psoriatic skin is comparable to normal skin (Fig.1 and Fig.2). Our data have been acquired at a fixed exposure period and the intensity of the immunifluorescent staining in both types of samples was the same. In psoriatic skin T-cadherin expression was found in all keratinocyte cell layers with a stronger expression in basal keratinocytes than in hyperproliferating suprabasal layers, also in stromal cells and in all blood vessels located in the underlying derma. Strikingly, in contrast to normal skin samples, in psoriatic skin the abnormal location of blood vessels within the epidermal layer was also found (Fig.1 and Fig.2). Noteworthy, these vessels, as verified by endothelial marker vWF, also uniformly expressed T-cadherin (Fig.2).

6.1.3 Actinic Keratosis (AK)

AK is a common sun-induced skin lesion. Actinic keratosis is usually characterized as scaly or keratotic papules with a diffuse erythematous base, usually less than 1-2 cm in diameter. Historically, AK has been described as a pre-cancerous lesion (Quinn and Perkins, 2010). Many authors consider these lesions as pre-malignant epithelial tumors that have the potential to develop into squamous cell carcinoma (SCC) (Epstein, 2004; Jorizzo et al., 2004; Yu et al., 2003). However, a number of studies indicate that progression of AK to invasive SCC may be rather exception than a rule and that AKs can undergo spontaneous regression

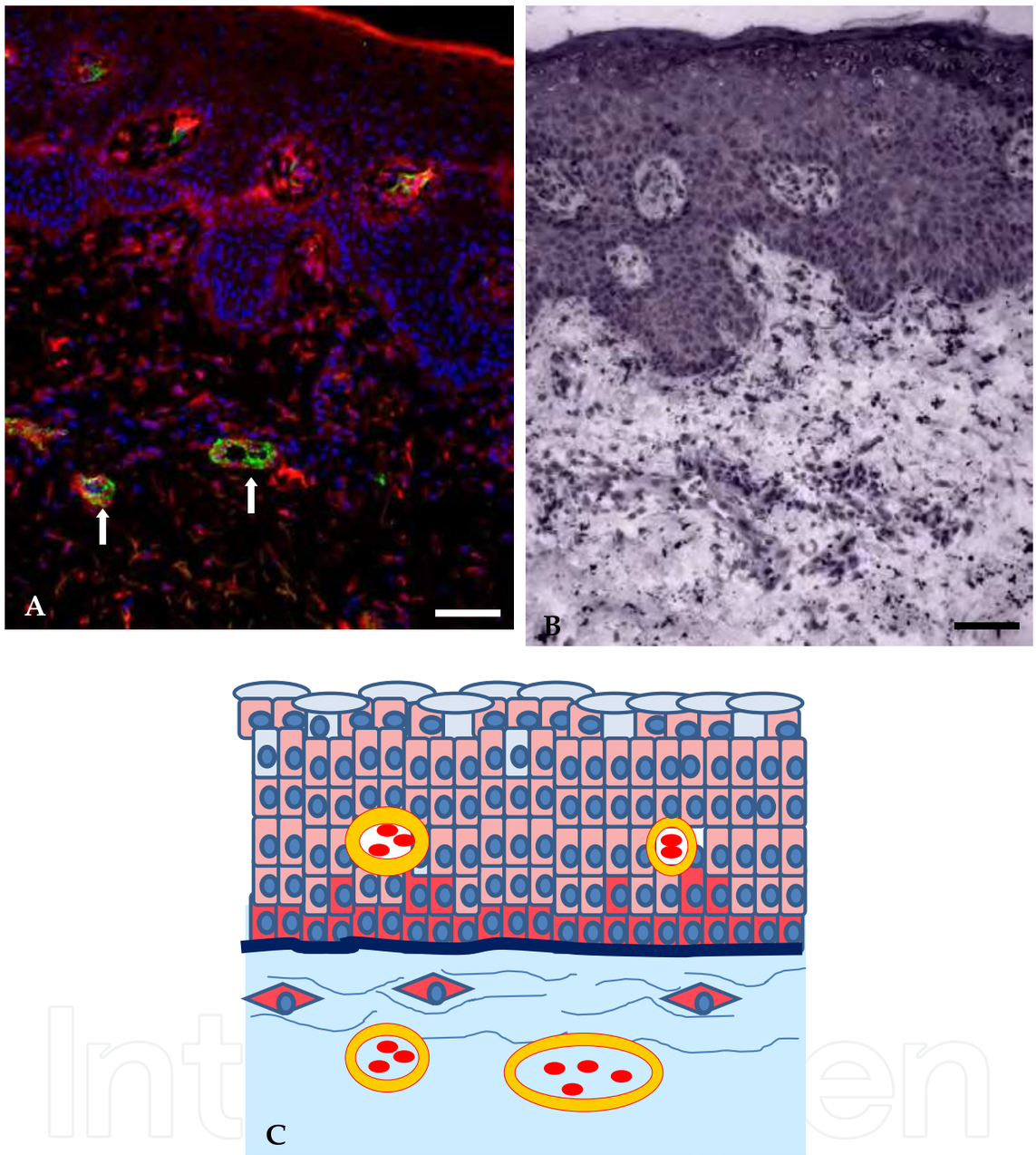


Fig. 2. Double immunofluorescent staining of psoriatic skin sample with antibodies against T-cadherin (red) and vWF (green) (A). Nuclei were counterstained with DAPI (blue). Figure B represents hematoxylin staining of the parallel section. Strong T-cadherin expression was found in basal keratinocytes, in hyperproliferating suprabasal layers, stromal cells and blood vessels located in the underlying derma and within the epidermal layer. Uniform expression of T-cadherin in small and large blood vessels was observed (yellow), colocalization of T-cadherin and vWF is showed by the arrows. Bars, 100 μm. The diagram (C) explaining strong T-cadherin expression in basal cell layer (red), moderate T-cadherin expression in suprabasal layers and stromal cells (pink) and T-cadherin expression in all and all vWF-positive blood vessels (yellow).

(as cited in Quinn & Perkins, 2010). Other authors have stated that there is no patho-biological difference between AK and SCC and that AK itself represents SCC variant (Ackerman & Mones, 2006; Freeman et al., 1984; Lebwohl et al., 2004). Without treatment, AK can develop into invasive SCC and has the potential to metastasise and cause death.

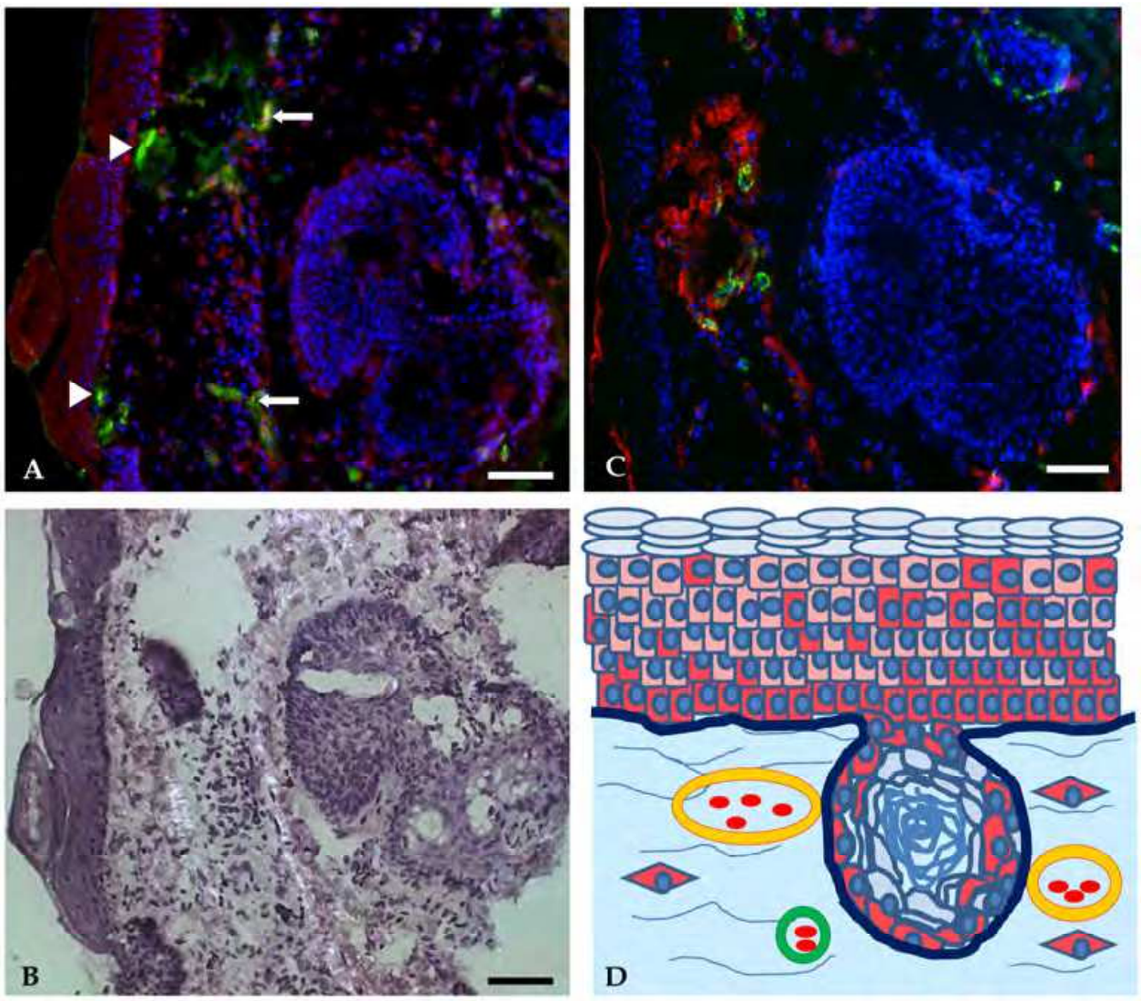


Fig. 3. Double immunofluorescent staining of actinic keratosis sample with antibodies against T-cadherin (red) and vWF (green) (A) or vWF (green) and α–actin (red) (C). Nuclei were counterstained with DAPI (blue). Figure B represents hematoxylin staining of the parallel section. T-cadherin expression was observed in basal keratinocytes, including suprabasal layers, with a more pronounced staining in the basal cell layer. Not all blood vessels as detected by vWF staining were positive for T-cadherin. Colocalization of T-cadherin and vWF is shown by the arrows, blood vessels which do not express T-cadherin - by arrowheads. Stabilized vessels were located in derma and were double positive for vWF and α–actin; (C). Bars, 100 μm. The diagram (D) explaining strong T-cadherin expression in basal cell layer (red), moderate T-cadherin expression in suprabasal layers and stromal cells (pink). Blood vessels expressing T-cadherin and vWF are shown in yellow, blood vessels with no T-cadherin expression are shown in green.

In AK the boundary between unaffected and affected epidermis is sharp. The affected zone grows under the normal epidermis and around the ductal epithelium. Histologically, AK is characterized by the presence of atypical keratinocytes at the epidermal basal cell layer, which in advanced lesions may extend into the entire epidermis (Röwert-Huber et al., 2007). There is epidermal hypertrophy with hyperkeratosis and parakeratosis. The basement membrane is intact but basaloid cells may form multiple buds. Within the epidermis there may be a simple dysplasia or a range of abnormalities. The underlying papillary vessels are irregularly increased. There is degeneration of dermal collagen and deposition of material staining like elastin in the upper half of the dermis (Quinn & Perkins, 2010). In addition to the epidermal changes, a common feature of AK is the presence of a chronic inflammation in the papillary dermis of the abnormal epidermis (Pinkus et al., 1963).
Figure 3 presents the hematoxylin and immunofluorescent stainings of AK sections with antibody against T-cadherin, vWF and α–actin. The lesion is characterized by the presence of atypical keratinocytes at the epidermal basal cell layer and loss of orderly maturation of keratinocytes. The affected zone has grown under the epidermis and is separated from it by the cleft. T-cadherin is uniformly expressed in all layers of keratinocytes, including suprabasal layers, with a slightly increased staining in the basal cell layer (Fig.3), which correlates with literature data (Pfaff et al., 2010). T-cadherin expression was also verified in the dermal blood vessels (in endothelial and mural cells) and in the stromal cells, in the vicinity of atypical keratinocytes. However, not all blood vessels which were vWF positive expressed T-cadherin, which puts AK in line with malignant skin lesions such as squamous cells carcinoma (Fig.6).

6.1.4 Keratoacanthoma (KA)

Keratoacanthoma (KA) is a low-grade malignancy skin lesion with rapid growth, followed by a slow spontaneous resolution. KA is composed of keratinizing squamous cells originating in pilosebaceous follicles and histopathologically resembles squamous cells carcinoma (SCC) (Quinn & Perkins, 2010). However, it is well known that the morphological similarity between KA and SCC contrasts with their different biological behavior.
Histologically, the squamous keratinocytes in KAs are enlarged, pale, eosinophilic, and often have a hyalinized or "glassy"-appearing cytoplasm. Inflammatory infiltrates are present in the underlying papillary dermis. While superficially infiltrative and mitotically active, especially in early lesions, the cells of KA generally show no pronounced atypia or cellular pleomorphism of conventional SCC. Atypical mitoses are not found in KA. Additionally, stromal desmoplasia is usually absent unlike invasive SCC, and the nests are typically rounded and sharply demarcated from the surrounding stroma (Cassarino et al., 2006b).
SCC is a malignant tumor with the potential to grow, metastasize and cause death, while KA usually undergoes regression, thus representing a self-limiting or "biologically benign" variant of SCC (Zalaudek et al., 2009). KA progression could be divided into 3 phases: growth, stabilization and involution. The first phase is characterized by a rapid increase in size within a few weeks or months followed by stabilization and spontaneous resolution over 4-6 months. However, occasionally KA may enlarge up to 5 cm and become locally aggressive (Quinn & Perkins, 2010). Lesions typically begin as firm skin papules that progress to nodules with a central crateriform ulceration or keratin plug that may project like a horn. The histological features vary with the stage of evolution. The early lesion is composed of a mass of rapidly proliferating squamous cells. The marginal cells aggressively invade the surrounding derma, while those in the center keratinize to form a core of keratin that communicates with the surface. Resolution occurs through maturation of the hyperplastic cell masses and lesion

opening to the surface. When the horn is finally shed, the irregular epithelium under the lesion is formed. KA leaves a residual scar, if not excised (Quinn & Perkins, 2010).
Figure 4 and Figure 5 represents KA in the stage of growth and stabilization, correspondingly. As a whole, our histological data indicate that the cells in KA are mature and the epithelium exhibit differentiation from the basal layer to the surface keratinocytes.

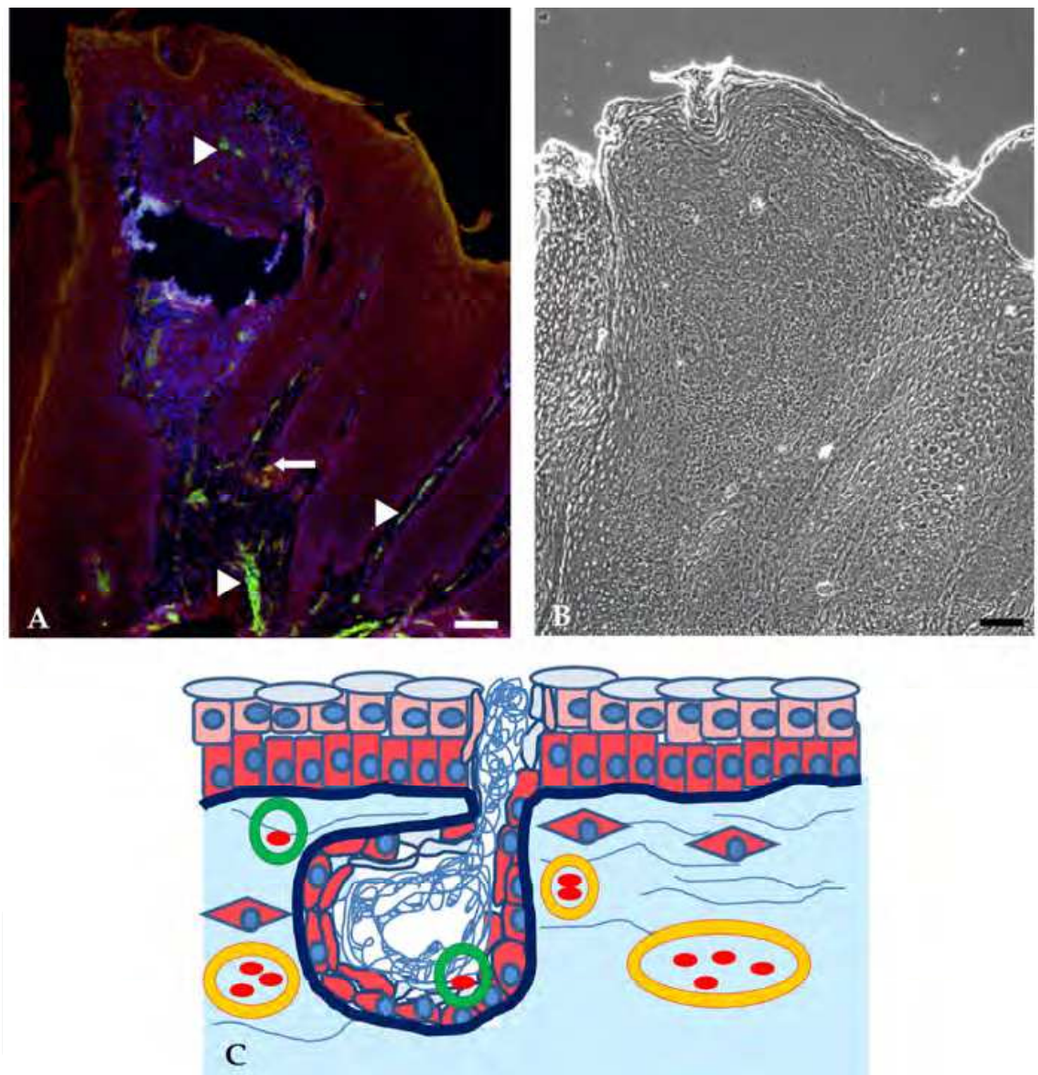


Fig. 4. Double immunofluorescent staining of keratoacanthoma at the stage of growth with antibodies against T-cadherin (red) and vWF (green) (A). Nuclei were counterstained with DAPI (blue). Figure B depicts phase contrast image of the parallel section. T-cadherin expression was verified in all keratinocytes. Part of the blood vessels showed no T-cadherin expression, at the same time some of the blood vessels were found among keratinizing squamous cells at the site of the future pearl (A). Colocalization of T-cadherin and vWF is shown by the arrow, blood vessels which do not express T-cadherin are marked by arrowheads. Bars, 100 μm. The diagram shows strong (red) and moderate (pink) T-cadherin expression in keratinocytes. Blood vessels expressing T-cadherin and vWF are shown in yellow, blood vessels with no T-cadherin expression are shown in green.

However, abnormal or premature keratin production (dyskeratosis) is observed resulting in individually keratizing cells or formation of keratin pearls (Fig.5). The stroma is vascular and infiltrated (Fig.4 and Fig.5). In KA T-cadherin expression was verified in all keratinocyte layers (Fig.4 and Fig.5). At stabilization stage of KA, T-cadherin expression was detected in all the surrounding blood vessels as verified by immunofluorescent staining with antibody against T-cadherin, endothelial marker vWF and mural cell marker – α–actin (Fig.5). However, part of the blood vessels in KA at the growth stage did not express T-cadherin (Fig.4). Noteworthy, is the abnormal location of blood vessels within the epidermal hypertrophied layer and among keratinizing squamous cells at the site of the future pearl (Fig.4). The abnormal vessel location and down-regulated T-cadherin expression in KA at the growth stage most probably reflects the rapid and locally aggressive behavior of the tumor, while at stabilization stage, T-cadherin expression in keratinocytes and blood vessels resembles their expression in the normal skin samples.

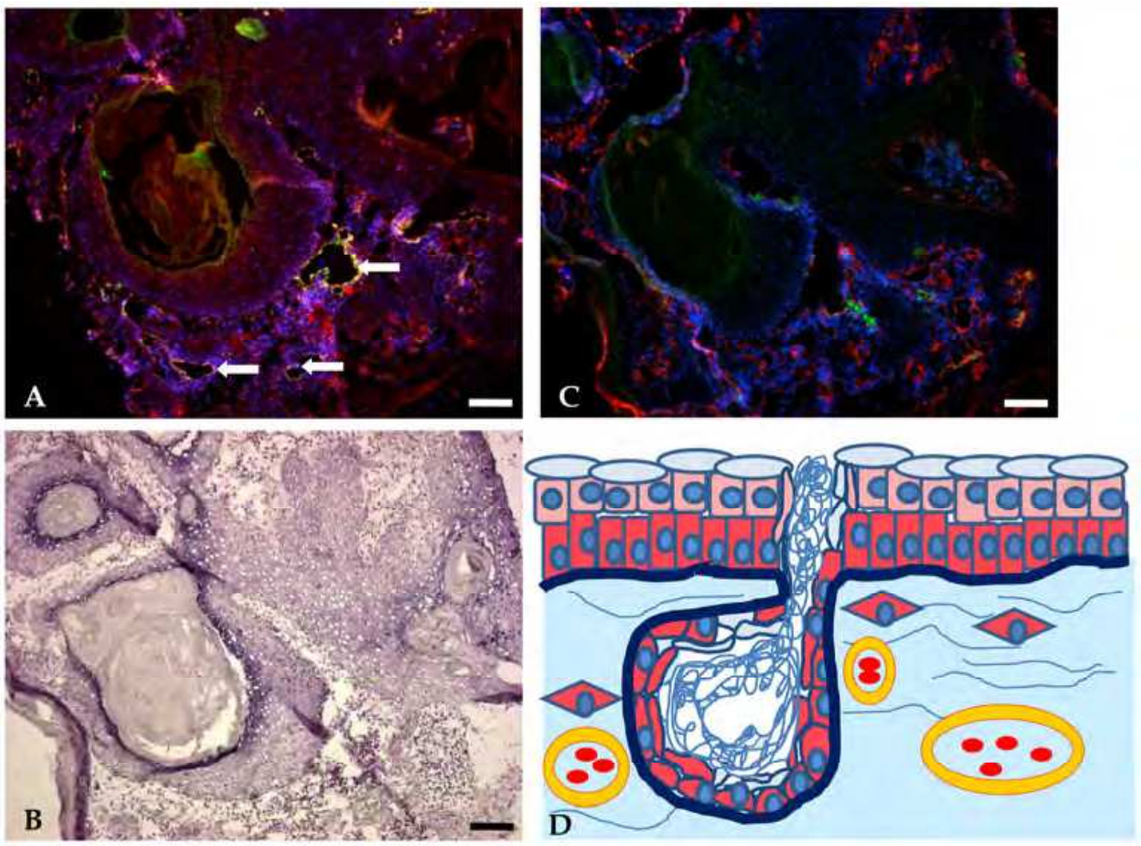


Fig. 5. Double immunofluorescent staining of keratoacanthoma at stabilization stage with antibodies against T-cadherin (red) and vWF (green) (A) or vWF (green) and α–actin (red) (C). Nuclei were counterstained with DAPI (blue). Figure B represents hematoxylin staining of the parallel section. T-cadherin expression was verified in all keratinocytes. Most of the blood vessels showed colocalization of vWF and T-cadherin expression, as shown by the arrows (A). Stabilized vessels were located in derma and were double positive for vWF and α–actin. Bars, 100 μm. The diagram shows strong (red) and moderate (pink) T-cadherin expression in keratinocytes. Blood vessels expressing T-cadherin and vWF are shown in yellow.

6.1.5 Basal Cell Carcinoma (BCC)

BCC is the most common malignant tumor of the skin composed of cells originating from the basal cell layer of the epidermis and its appendages, namely BCCs arise from the hair follicle bulge stem cell or from the interfollicular epidermis (Quinn & Perkins, 2010; Wang et al., 2011). The typical BCC progresses slowly and rarely metastases. The early tumors are usually small, translucent or pearly and covered by thin epidermis. The more advanced tumors show a variety of forms. Some tumors grow at a very slow rate and they are in practical terms benign. This is true for many superficial lesions and some of the nodular types of BCCs (Quinn & Perkins, 2010). BCCs are truly invasive in only a small proportion of cases. Then the tumors show no tendency to grow as rounded masses, have no palisade or organized stroma, and penetrate the dermis and deeper structures, destroying them as they grow. Such tumors are almost always ulcerated, usually from an early stage (Quinn & Perkins, 2010).

In the present study we examined T-cadherin expression in superficial, nodular and infiltrative samples of BBC. In superficial BCC, expression of T-cadherin was prominent in tumor cells and in the surrounding stroma. The majority of vessels around the tumor aggregates coexpressed markers of endothelial cells vWF and T-cadherin, however, blood vessels with no expression of T-cadherin were also noted (Fig. 6).

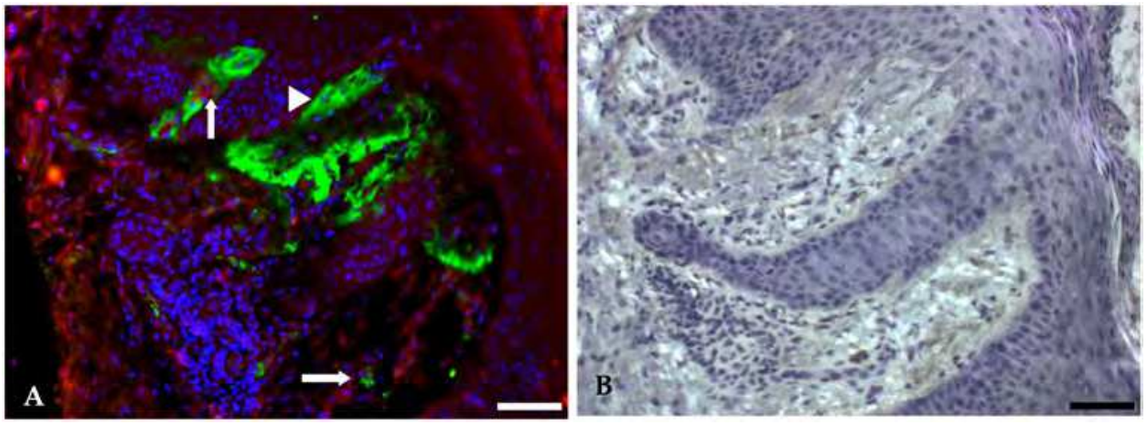


Fig. 6. Double immunofluorescent staining of superficial BCC with antibodies against T-cadherin (red) and vWF (green) (A). Nuclei were counterstained with DAPI (blue). Figure B shows hematoxylin staining of the parallel section. T-cadherin expression was observed in tumor cells and in the surrounding stroma. Not all blood vessels as detected by vWF staining were positive for T-cadherin. Colocalization of T-cadherin and vWF is shown by the arrows, blood vessels which do not express T-cadherin - by arrowhead. Bars, 100 μm.

The nodular BCC samples demonstrated "classic" features of basalioma, including large tumor nests with a smooth palisaded border and stromal retraction. In nodular BCC the expression of T-cadherin was heterogeneous: some tumor nests were strongly positive for T-cadherin expression (Fig. 7), while weak or undetectable expression of T-cadherin occurred in some tumor nests or individual cells within these nests (Fig. 7). These results coincide with the results obtained by other authors (Buechner et al., 2009), but are in contrast to data obtained by Takeuchi and colleagues (Takeuchi et al., 2002). Most of the blood vessels coexpressed endothelial cells marker vWF and T-cadherin. However, in some samples of nodular BCC, the aberrant expression of vessel markers and T-cadherin was revealed: in part of vWF-positive vessels T-cadherin expression was lost; while structures, morphologically resembling

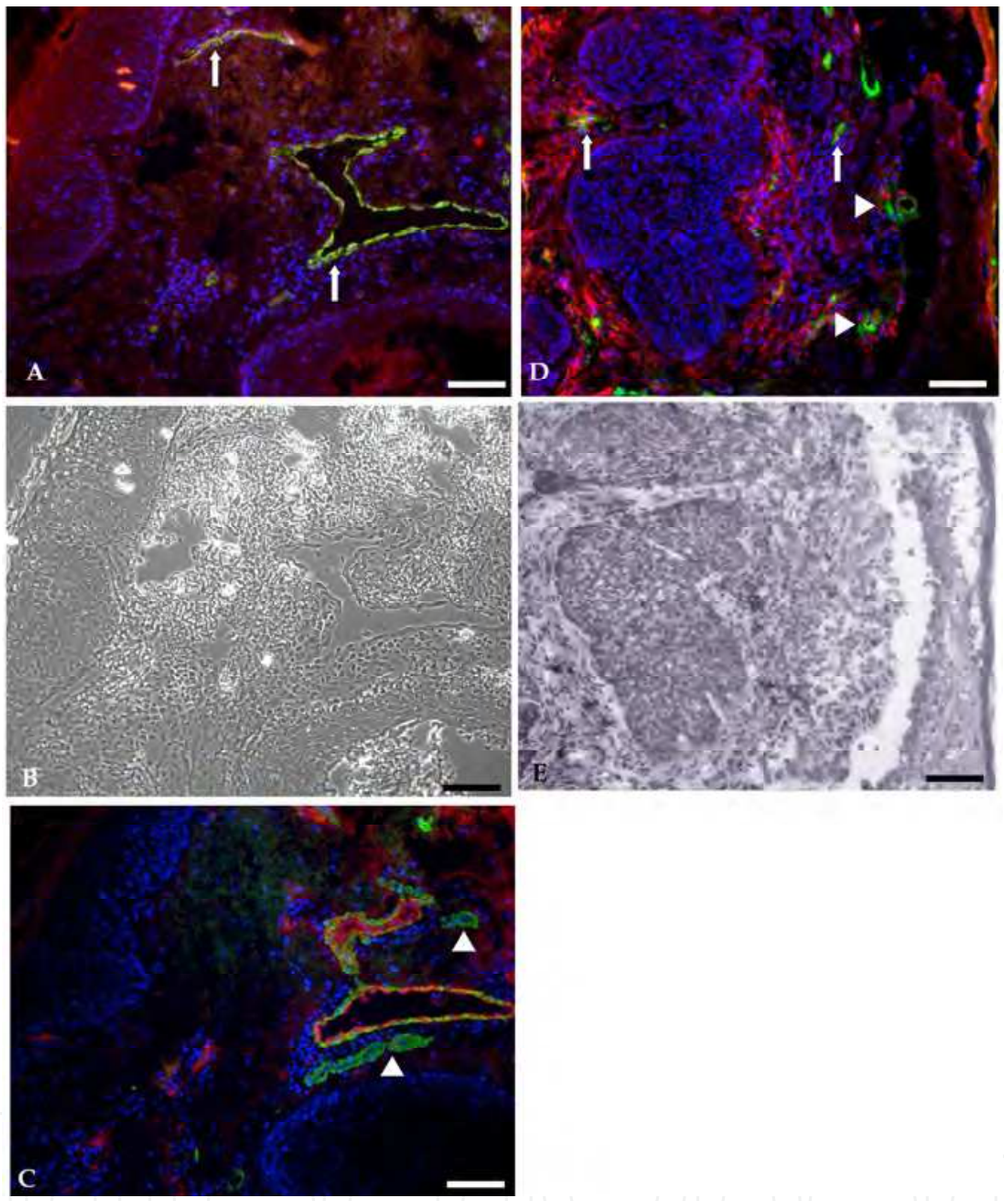


Fig. 7. Double immunofluorescent staining of nodular BCCs with antibodies against T-cadherin (red) and vWF (green) (A, D) or vWF (red) and α–actin (green) (C). Nuclei were counterstained with DAPI (blue). Figure E shows hematoxylin staining the parallel section of the same sample shown in Figure D; Figure B reflects phase contrast image of the parallel section of the same sample shown in Figures A and C. Some tumor nests were T-cadherin positive (A), while other nodules or individual cells within them demonstrated weak T-cadherin expression (D). Most of the blood vessels coexpressed endothelial cells marker vWF and T-cadherin as shown by the arrows in A and D. However, in some samples, the aberrant expression of vessel markers and T-cadherin was revealed: in part of vWF-positive vessels T-cadherin expression was lost (arrowhead pointing to the vessels in A and D); while some samples structures, morphologically resembling blood vessels and expressing α–actin but vWF-negative were observed (arrowhead in C). Bars, 100 μm.

blood vessels and expressing α–actin were vWF-negative (Fig. 7). In samples of infiltrating BCC, nests of variable size with irregular borders were detected. There was frequently little palisading and sometimes no stromal retraction. Tumor cells and cells of the surrounding stroma expressed T-cadherin, while in the blood vessels located among the stromal cells, aberrant vessel markers and T-cadherin was marked: in part of vWF-positive vessels T-cadherin expression was lost (Fig. 8). While T-cadherin expression was present in keratinocytes in 90% of the samples, in the vessels surrounding BCC nests, its expression was lost in part of the blood vessels.

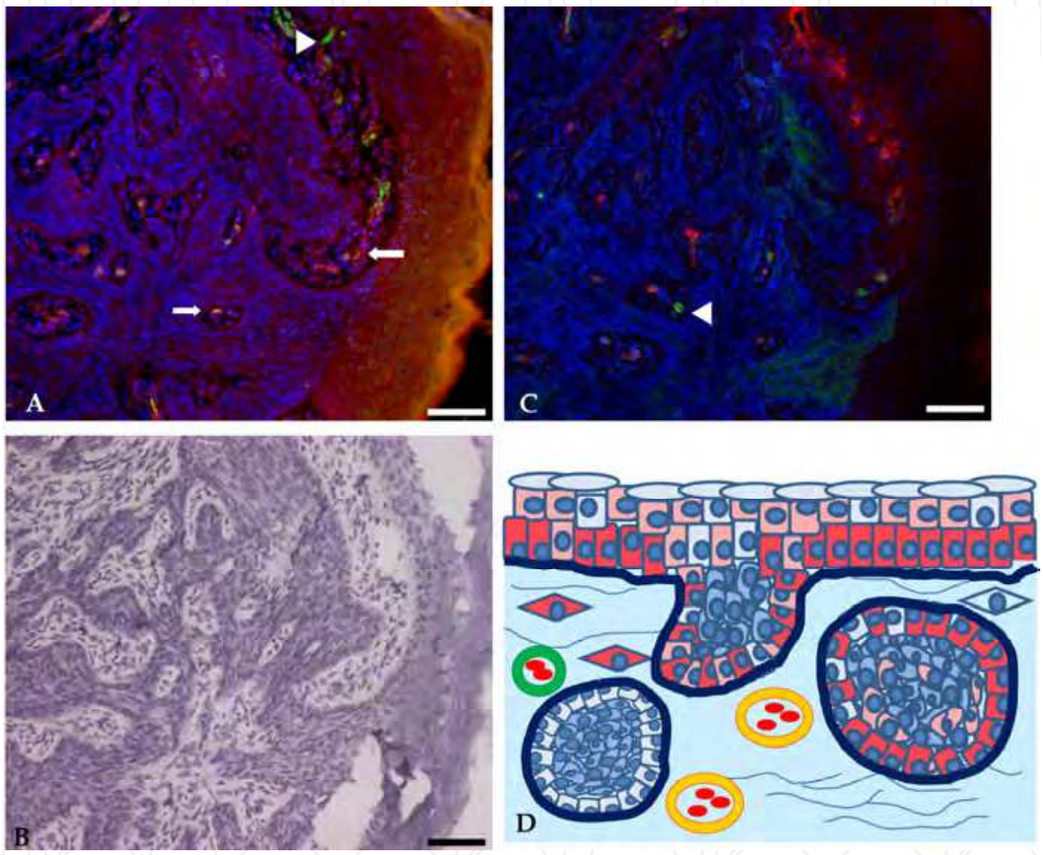


Fig. 8. Double immunofluorescent staining of infiltrating BCC sample with antibodies against T-cadherin (red) and vWF (green) (A) or vWF (red) and α–actin (green) (C). Nuclei were counterstained with DAPI (blue). Figure B shows hematoxylin staining of the parallel section. T-cadherin expression was observed in tumor cells and in the surrounding stroma. In part of vWF-positive blood vessels located among the stromal cells T-cadherin expression was noted (arrows in A). However, in some vessel-like structures aberrant expression of vessel markers and T-cadherin was observed: in part of vWF-positive vessels T-cadherin expression was not detected (arrowheads in A); while in some samples, structures, morphologically resembling blood vessels and expressing α–actin were demonstrated to be vWF-negative (arrowheads in C). Bars, 100 μm. The diagram shows strong T-cadherin expression in red and moderate - in pink. Some of the tumor cells in BCC nests retain T-cadherin expression, while in the others T-cadherin is lost. Blood vessels expressing T-cadherin and vWF are shown in yellow, blood vessels with no T-cadherin expression are shown in green.

6.1.6 Squamous Cell Carcinoma (SCC)

A SCC of the skin is a malignant neoplasm of epidermal keratinocytes and its appendages. Cutaneous SCCs include many subtypes with different clinical behaviors, ranging from indolent to aggressive tumors with significant metastatic potential (Cassarino et al., 2006a; Cassarino et al., 2006b). Various classifications of SCC were proposed basing upon the malignant potential of SCC variants with low, intermediate or high metastatic rate (Cassarino et al., 2006a; Cassarino et al., 2006b; Yanofsky et al., 2011). According to the latest classification, histopathologically SCC can be divided into three separate categories including: actinic or solar keratoses (AKs) and SCC *in situ* (Bowen's disease), - common precursors of SCC arising from excessive sun exposure; invasive SCC (SCCI), clear-cell SCC, spindle cell (sarcomatoid) SCC, and SCC with single cell infiltrates - tumor subtypes emerging from invasive progression of AKs and SCC *in situ*; *de novo* SCC, lymphoepithelioma-like carcinoma of the skin (LELCS), and verrucous carcinoma (VC) - very rare variants of SCC with no direct correlation to sun exposure or actinic neoplasms (Yanofsky et al., 2011).

SCCIs are often referred to as conventional SCCs. SCCI are subdivided into three histological grades based on their associated degree of nuclear atypia and keratinization (well-differentiated, moderate and poorly-differentiated SCCI). The majority of SCCI's arising from AKs, are well-differentiated tumors, containing slightly enlarged cells with hyperchromatic nuclei, which produce large amounts of keratin, resulting in the formation of keratin pearls. These tumors are associated with a very low malignant potential. The histological and cytopathological changes seen in the individual cells of AK and SCCI are identical. Both show atypical keratinocytes with loss of polarity, nuclear pleomorphism, disordered maturation and increased numbers of mitotic figures; many of them atypical and pleomorphic. In contrast to AK, SCCI are characterized by the presence of infiltrative cells passing through the basement membrane into the dermis. This infiltrate can be difficult to detect at the early stages of invasion, however, additional indicators such as full thickness epidermal atypia or the involvement of hair follicles can be used to facilitate the diagnosis. Later stages of invasion are characterized by the formation of nests of atypical tumor cells in the dermis often with inflammatory infiltrate (Yanofsky et al., 2011).

In contrast to well-differentiated SCCI, in poor-differentiated tumors, cells are characterized by enlarged, pleomorphic nuclei with high degree of atypia and frequent mitosis. Keratin production in these cells is markedly reduced. Poorly-differentiated SCCI show deep infiltration of the underlying dermis and subcutaneous tissues. These SCCI demonstrate a much more aggressive clinical behavior, with an increased rate of metastasis and recurrence. A third, moderately-differentiated subtype of SCCI shares the features of both well-differentiated and poor-differentiated tumors (Yanofsky et al., 2011). It is thought that poorly differentiated tumors have a higher rate of metastasis (Dinehart et al., 1997; Dinehart & Pollack, 1989; Lund et al., 1984). Another essential component in assessing the malignant potential of a tumor is the presence of perineural and perivascular spread. Invasion of capillaries and nerves reflects a more aggressive tumor behavior and correlates with an increased rate of metastases, local recurrence and disease-specific death (Yanofsky et al., 2011). The accurate microscopy diagnostics between these variants is critically important for prognosis and the treatment of SCCI (Yanofsky et al., 2011).

In our study in moderate-to-poorly-differentiated SCCI samples tumor cells deeply invaded the underlying dermis (Fig.9). Occasionally, some atypical cells in isolated tumor nests and stromal cells exhibited week T-cadherin staining. However, in basaloid cells of most of the tumor nests T-cadherin expression was down-regulated. The activated stroma expressed α–actin.

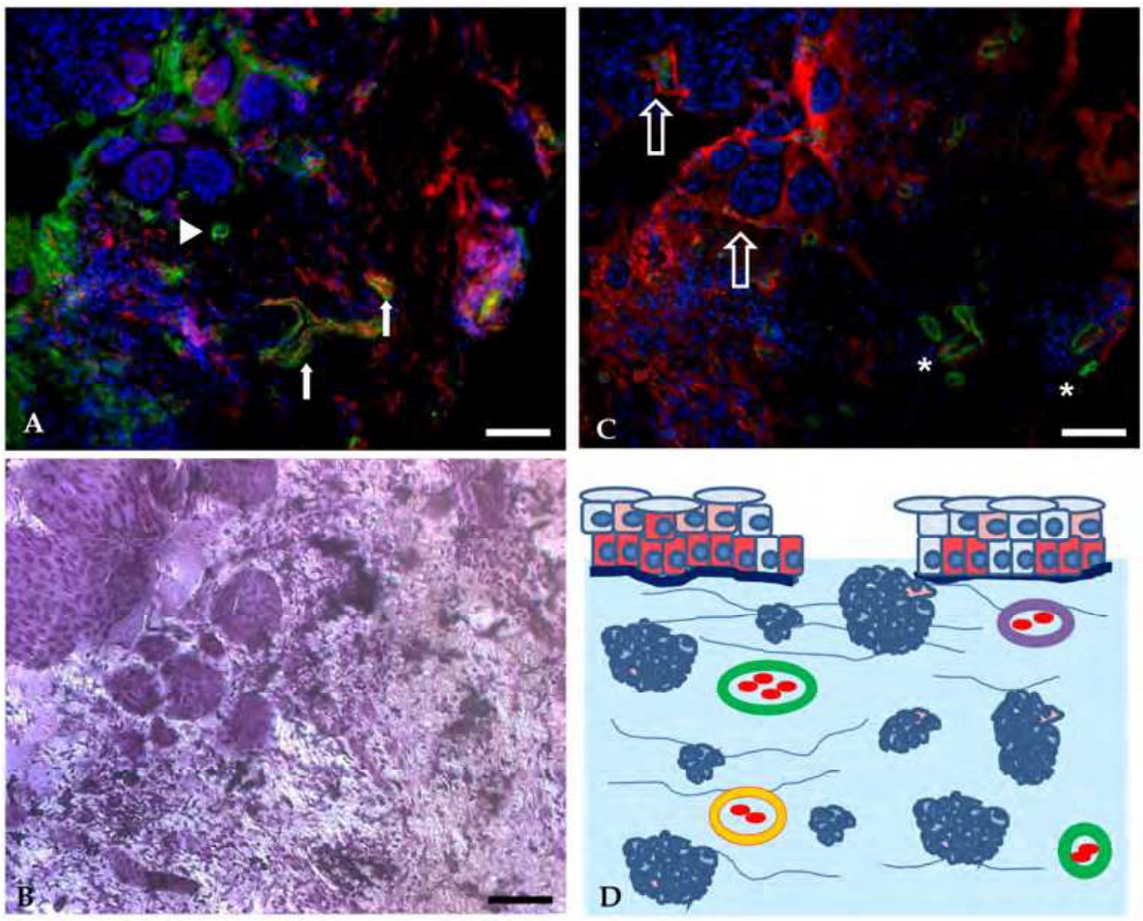


Fig. 9. Double immunofluorescent staining of moderate-to-poorly-differentiated SCCI sample with antibodies against T-cadherin (red) and vWF (green) (A) or CD31 (red) and α–actin (green) (C). Nuclei were counterstained with DAPI (blue). Figure B shows hematoxylin staining of the parallel section. Some atypical cells in isolated tumor nests and stromal cells exhibited T-cadherin staining (A), however, basaloid cells in most of the tumor nests show no T-cadherin expression (A). Vessel-like structures, which do not express CD31 but exhibit α–actin are noted (asterisk in C), moreover, CD31-positive areas, morphologically different from vessels are also present (empty arrows in C). Bars, 100 μm. The diagram marks strong T-cadherin expression in red, and moderate - in pink. In most tumor cells growing in small aggregates T-cadherin expression is absent. Blood vessels expressing T-cadherin and vWF are shown in yellow, blood vessels with no T-cadherin expression are shown in green. Vessel-like structures expressing α–actin are shown in violet.

This data correlate with results obtained by other authors (Mykoyama et al., 2005; Pfaff et al., 2010; Takeuchi et al., 2002b; Zhou et al., 2003) and indicate that T-cadherin loss due to aberrant methylation of the T-cadherin gene or its deletion correlates with SCC invasive phenotype and potentially more aggressive tumor behavior.

However, our results demonstrated that in SCCI not only T-cadherin expression was lost in atypical keratinocytes. Among other abnormalities the aberrant expression of vessel markers and T-cadherin was noted: in part of vWF-positive vessels T-cadherin expression was lost; at

the same time, we observed vessel-like structures, which did not express vWF but bear T-cadherin or α–actin. Strikingly, CD31/vWF-positive areas, morphologically different from vessels were also noted (Fig.9).

6.1.7 Basosquamous Cell Carcinoma (BSCC) or metatypical basal cell carcinoma

The term basosquamous cell carcinoma is used for tumors that exhibit the features of both BCC and SCC (Garcia et al., 2009). BSCC is not widely discussed in the literature and little attention has been paid to this subtype in recent comprehensive reviews of cutaneous SCC (Cassarino et al., 2006a; Cassarino et al., 2006b). The importance of diagnostics of these tumors is based on the fact that BSCC pathological pattern is associated with a more aggressive behavior and a significantly higher incidence of metastasis than BCC or SCC (Banks et al., 1992; Farmer & Helwig, 1980; Smith & Irons, 1983; Winzenburg et al., 1998). The diagnosis of BSCC is currently based on histological criteria, initially proposed by Wain and coauthors (Wain et al., 1986). BSCCs are characterized by exaggerated nuclear to cytoplasmic ratio of the tumor nests which results in their basaloid appearance. Atypical mitotic figures can be readily visualized (Zbären et al., 2004; Boyd et al., 2011). The cells are larger with a larger paler nucleus than in the classic BCC and have a more eosinophilic cytoplasm (Quinn & Perkins, 2010). The BSCC is characterized by cell aggregates lacking classical palisading of BCC and embedded in a dense and profound fibrous stroma. The surrounding stroma is fibrotic with occasional deposits of hyaline basement membrane in the form of the extracellular material adjacent to tumor aggregates (Sarbia et al., 1997; Zbären et al., 2004).

Figure 10 presents representative patterns of immunostaining of BSCC with antibodies against T-cadherin, endothelial cell marker vWF and smooth muscle/pericyte cell marker α–actin. Tumor cells formed aggregates of different size, which generally lacked T-cadherin expression; however, in some cells at the periphery of these aggregates T-cadherin expression was still observed (Fig. 10). Tumor masses were surrounded by stroma expressing T-cadherin (Fig.10). The majority of vessels around the tumors aggregates coexpressed markers of endothelial cells - vWF and T-cadherin or vWF and α–actin (Fig. 10), thus resembling capillaries and stable blood vessels of the normal skin (Fig. 10). However, structures morphologically resembling blood vessels and expressing T-cadherin or α–actin, but lacking expression of classical endothelial marker vWF was noted (Fig. 10). Alternatively, vWF-positive vessels with no expression of T-cadherin were observed (data not shown).

To summarize, the obtained data confirm the fact that the initially occasional loss of T-cadherin expression in keratinocytes and blood vessels of pre-malignant lesions but subsequently progressive down-regulation of T-cadherin expression in tumor cells, appearance of blood vessels aberrantly expressing T-cadherin and endothelial/mural cell markers of more aggressive tumors correlate with the malignant transformation of the skin neoplasms.

7. Conclusion

The presented data support the statement that the loss of T-cadherin expression in epidermal keratinocytes is biologically relevant to malignant transformation of normal epidermal cells into cancer and correlates with the literature data. It has been proposed that T-cadherin expression may contribute to maintenance of tissue integrity in resting

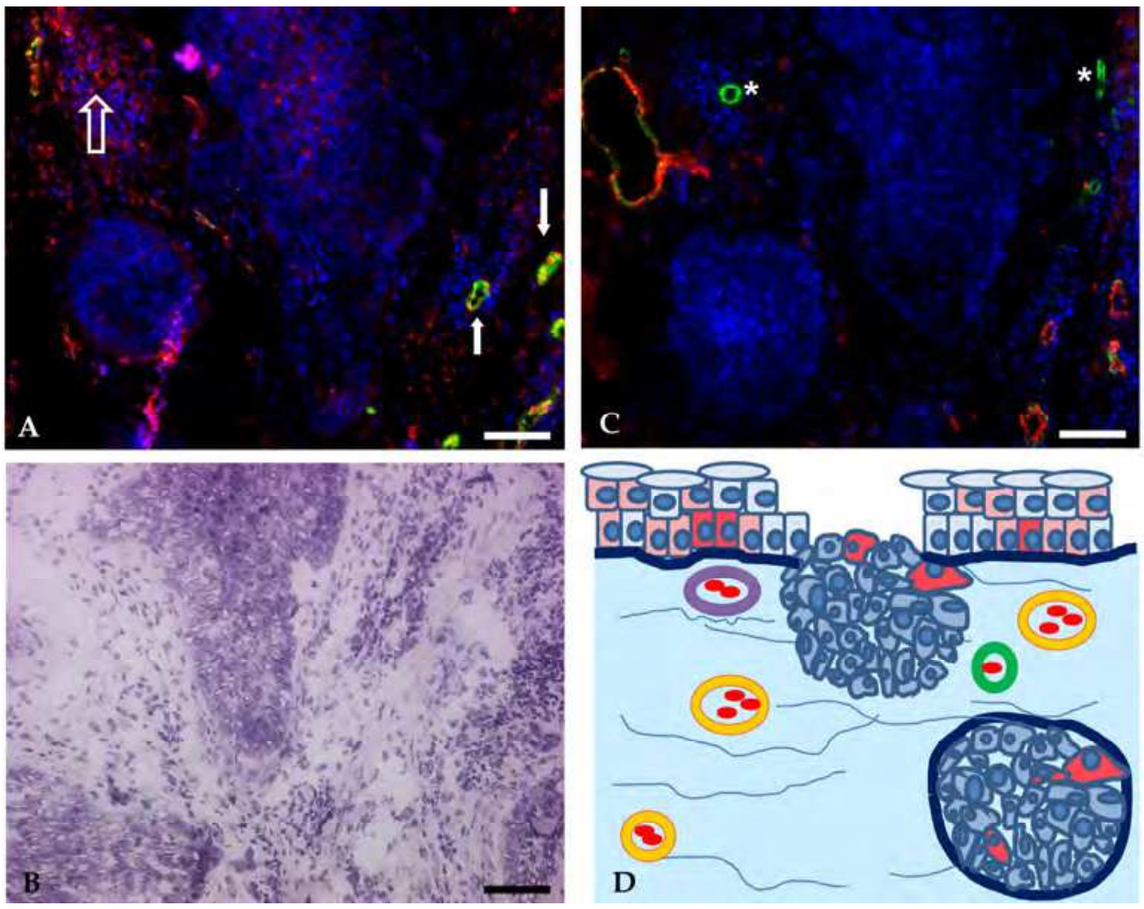


Fig. 10. Double immunofluorescent staining of BSCCs sample with antibodies against T-cadherin (red) and vWF (green) (A) or CD31 (red) and α–actin (green) (C). Nuclei were counterstained with DAPI (blue). Figure B shows hematoxylin staining of the parallel section. Tumor cells formed aggregates of different size, which generally lacked T-cadherin expression, however, in some tumor nests or in cells at the periphery of tumor aggregates T-cadherin expression is still observed (A). The majority of vessels around the tumor aggregates coexpressed markers of endothelial cells - vWF and T-cadherin (arrows in A) or vWF and α–actin (C). However, aberrant expression of vessel markers and T-cadherin could be seen: vessel-like T-cadherin positive structures with no expression of vWF are marked by empty arrow in B and α–actin vessel-like structures with no expression of CD31 by asterisk in C. The diagram marks strong T-cadherin expression in red, and moderate - in pink. In most tumor cells growing in small aggregates T-cadherin expression is absent. Blood vessels expressing T-cadherin and vWF are shown in yellow, blood vessels with no T-cadherin expression are shown in green. Vessel-like structures expressing α–actin are shown in violet.

conditions by preventing cell dislocation (Ivanov et al, 2003), that's why T-cadherin expression is well marked in the basal layer of keratinocytes attached to the basal membrane and bordering with underlying derma.

In the normal skin proliferation takes place in the basal layer of keratinocytes which correlates with the maximal T-cadherin expression in these cells. Interestingly, upon maturation epidermal keratinocyte are moved from the basal cell layer towards skin surface

not crossing the layer with the maximal T-cadherin expression. In pre-malignant skin lesions such as KA at stabilization stage, psoriasis, AK and superficial basalioma, which demonstrate slow or controlled growth and, in most cases, where keratinocytes maintain interactions with the basal membrane, the pattern of T-cadherin expression partly resembles that in the normal skin. Upon tumorigenesis in some BSCCs, SCCs, and in some cases of BCC, when tumors are characterized by a higher proliferative, invasive and metastatic potential, keratinocytes tend to grow in smaller cell aggregates and down-regulate T-cadherin expression. It is tempting to speculate that T-cadherin acts as a tumor suppressor in the normal skin and pre-malignant lesions by restricting keratinocyte proliferation and migration and by enhancing their homophilic interactions within the cell layer. In cancer, aggressive behavior of tumor cells correlates with the loss of T-cadherin expression.

In normal skin samples and in pre-malignant lesions such as psoriasis, KA at stabilization stage and superficial BCC all blood vessels uniformly express endothelial cells marker vWF and T-cadherin. Although AK in some papers is regarded as premalignant skin lesion, we revealed that in AK not all vWF-positive blood vessels expressed T-cadherin. This puts AK in line with malignant skin lesions such as SCC where T-cadherin is partly lost from the blood vessels. In KA at the growing stage part of the blood vessels do not express T-cadherin and grow into the layer of hypertrophied and rapidly proliferating keratinocytes, which reflects the aggressive behavior of this tumor at the stage of the fast growth. In cancer samples such as BSCC, BCC or SCC we observed heterogeneity in the expression of vascular markers (vWF and smooth muscle/pericyte cell marker α–actin) and T-cadherin. Thus, aberrant expression of classical vascular markers and heterogeneity in T-cadherin expression in tumor vasculature correlates with the histological features and invasive behavior of more aggressive tumors such as BSCC, BCC or SCC.

We propose that high expression of T-cadherin in normal tissue and in benign tumors prevents the excessive ingrowth of blood vessels that also express T-cadherin. During the tumor transformation, expression of T-cadherin on vascular endothelial cells is disturbed, and this causes abnormality in vascularization of tumor nodules and surrounding stroma.

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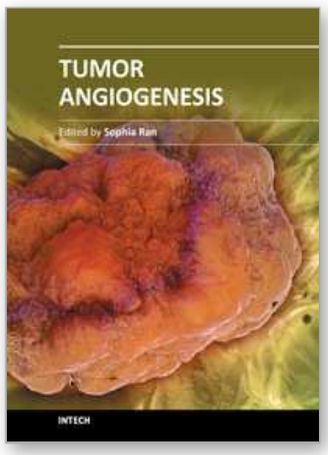
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Tumor Angiogenesis

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Tumor angiogenesis is the main process responsible for the formation of new blood vessels that promote tumor growth and metastasis. This process is driven by potent pro-angiogenic factors that are predominant in the tumor environment and are produced by both malignant cells and the host cells recruited to the tumor site. Tumor environment is characterized by the imbalance between pro-angiogenic and anti-angiogenic factors, which drives the construction of numerous but structurally defective vessels. These poorly perfused and abnormal vessels significantly contribute to the tumor pathology not only by supporting the expansion of the tumor mass but also by promoting chronic inflammation, enhancing thrombosis, impeding drug delivery, and disseminating tumor cells. These problems associated with tumor vasculature continue to attract great attention of scientists and clinicians interested in advancing the understanding of tumor biology and development of new drugs. This book complies a series of reviews that cover a broad spectrum of current topics related to the pathology of tumor blood vessels including mechanisms inducing new vessels, identification of new targets for inhibition of tumor angiogenesis, and potential clinical use of known and novel anti-angiogenic therapies. The book provides an update on tumor angiogenesis that could be useful for oncologists, cancer researchers and biologists with interests in vascular and endothelial cell behavior in the context of cancer.

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