Review Article

Tumor-suppressor Genes, Cell Cycle Regulatory Checkpoints, and the Skin

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Abstract

The cell cycle (or cell-division cycle) is a series of events that take place in a cell, leading to its division and duplication. Cell division requires cell cycle checkpoints (CPs) that are used by the cell to both monitor and regulate the progress of the cell cycle. Tumor-suppressor genes (TSGs) or antioncogenes are genes that protect the cell from a single event or multiple events leading to cancer. When these genes mutate, the cell can progress to a cancerous state. We aimed to perform a narrative review, based on evaluation of the manuscripts published in MEDLINE-indexed journals using the Medical Subject Headings (MeSH) terms "tumor suppressor's genes," "skin," and "cell cycle regulatory checkpoints." We aimed to review the current concepts regarding TSGs, CPs, and their association with selected cutaneous diseases. It is important to take into account that in some cell cycle disorders, multiple genetic abnormalities may occur simultaneously. These abnormalities may include intrachromosomal insertions, unbalanced division products, recombinations, reciprocal deletions, and/or duplication of the inserted segments or genes; thus, these presentations usually involve several genes. Due to their complexity, these disorders require specialized expertise for proper diagnosis, counseling, personal and family support, and genetic studies. Alterations in the TSGs or CP regulators may occur in many benign skin proliferative disorders, neoplastic processes, and genodermatoses.

Keywords: Basal cell carcinoma (BCC), Cell cycle checkpoints (CPs), cyclins, Familial melanoma, Genetic counseling, Gorlin syndrome, Laryngotracheal stenosis, Arthropathy, Prognathism, and short stature syndrome (LAPS), Melanoma, Myhre syndrome (MS), Neurofibromatosis type 1 (NF-1), Oncogenes, Sézary syndrome (SS), Skin, Tumor suppressor genes (TSGs), Squamous cell carcinoma (SCC), Von Hippel-Lindau (VHL), Werner syndrome (WS)

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Introduction

Review objectives

To learn how to define a tumor-suppressor gene (TSG) or antioncogene

A TSG is a gene that protects a cell from proceeding toward cancer. When this gene is mutated to cause a loss or reduction in its function, the cell can progress to a cancerous state, usually in combination with other genetic changes.

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To learn how to define CPs

There are many "points" in the cell cycle regulation systems that control cellular transit through the eukaryotic cell cycle; these specific points are termed CPs.

TSGs encode proteins that normally serve as a brake on cell growth. When such genes are mutated, the brake may be lifted, resulting in runaway cell growth known as cancer. In contrast, oncogenes are genes that encode proteins involved in normal cell growth. When such genes are mutated, they may also cause cancer but they do so by activating the growth-promoting signals. Cancer therapies that target oncogenes usually seek to block or reduce their action, while those aimed at TSGs seek to restore or increase their action. In this review, we aim to compile current data on TSGs and the skin.

The cell cycle or cell-division cycle

The cell cycle is a series of events that take place in a cell,

leading to its division and duplication.[1,2] In cells with a nucleus (eukaryotes), the cell cycle may be divided into the following three phases: 1) the interphase, during which the cell grows, accumulating nutrients needed for mitosis and duplicating its DNA, 2) the mitosis (M) phase, during which the cell begins dividing itself into two distinct cells, often called "daughter cells," and 3) the final phase, cytokinesis, where the new cell is completely divided.[1,2] The cell-division cycle is thus the vital process via which a single-celled fertilized egg develops into a mature organism as well as the process by which hair, skin, blood cells, and some internal organs are renewed.[1,2] The cell cycle is controlled by numerous mechanisms ensuring proper cell division. Many cells reside in a resting or quiescent state, but can be stimulated by external signals to reenter the cell cycle.[1,2] These external growth-promoting signals are specifically growth factors that bind to the cell surface receptors [Figure 1]. Most growth factors induce the expression of genes that are referred to as early and delayed response genes. The activation of early response genes occurs in response to the growth factor receptor-mediated signal transduction, resulting in phosphorylation and activation of the transcription factor proteins that are already present in the cell. Many of the induced early response genes themselves encode transcription factors, which then activate the expression of delayed response genes. In the context of the cell cycle, these delayed response genes encode proteins of the G_1 cyclin-dependent kinases (CDKs).[1,2]

The complexity of the cell cycle

The complexity of cell cycle regulation is also reflected in the plethora of alterations leading to aberrant cell proliferation and cancer development.[1,2] CDKs respond to the previously described growth factor signals and are largely responsible for pushing cells through the cell cycle. Due to their pivotal role in cell division, nature has evolved elaborate mechanisms to regulate the activity of CDKs.[3] Cyclins are CDK binding partners that are required for kinase activity and their protein levels are directly linked to the cell cycle stage. A variety of other CDK regulators including phosphorylation events, natural inhibitors, and complex stability are currently known. Phosphorylation of CDK substrates results in diverse outcomes, including changes in gene expression, formation of prereplicative complexes, and breakdown of the nuclear envelope.[3] One example of the importance of the cell cycle regulator molecules and the skin is cyclin D1; this molecule specifically localizes to the cytoplasms of keratinocytes during skin differentiation and regulates cell-matrix adhesion.[4] Cyclin D1 seems to be downregulated in specific skin cancers, especially in squamous cell carcinoma (SCC) by an altered TSG such as the gene Deleted in Liver Cancer 1 (DLC1).[5]

Regulation of the eukaryotic cell cycle

Cell cycle regulation directs processes crucial to cell survival, including detection and repair of genetic damage as well as the prevention of uncontrolled cell division.[6] In the skin, uncontrolled cell division can occur in diseases such as psoriasis, skin cancers, and genodermatoses. The molecular events that control the cell cycle are almost impossible to reverse.[6] To be specific, there are many "parts" to the systems that control transit through the eukaryotic cell cycle. These "parts" include the following:

1. mechanisms to control the timing of events so that each individual process is turned on and off at an appropriate time;
2. Controls to ensure that events occur in a linear, irreversible direction;
3. Redundancy, or backup systems, to ensure that the cell cycle functions properly even in the context of some malfunctioning parts; and
4. Adaptable system control so that the cell cycle events may be modified in the context of different cell types and/or environmental conditions.[6]

Many of the most important discoveries about the

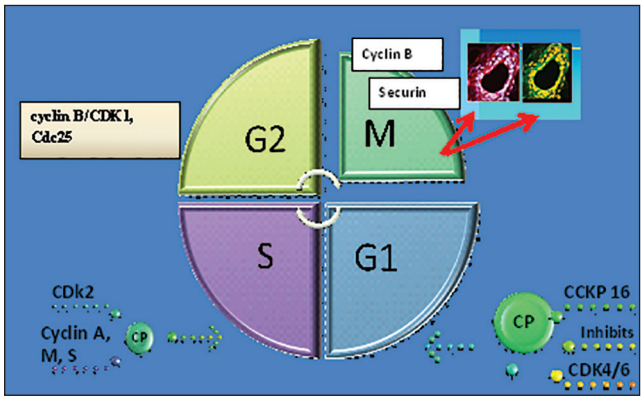

Figure 1: Displays a simplistic diagram of the cell cycle consisting of four distinct phases: Gap1 (G1)-phase, synthesis (S)-phase, Gap2 (G2)-phase (collectively known as interphase), and mitosis (M)-phase. The M-phase is itself composed of two tightly coupled processes: mitosis, in which the cell's chromosomes are divided between the two daughter cells, and cytokinesis (two cells, red arrows), in which the cell's cytoplasm divides in half, forming distinct cells. Growth factors, nutrients, cell size, and DNA damage can act as possible restriction points. CPs are control mechanisms that ensure the fidelity of cell division in eukaryotic cells. In G_1, the (restriction CP) main player is CDK inhibitor p16 (CCK p16). This protein inhibits CDK4/6 and safeguards it so that that it can no longer interrelate with cyclin D1 to cause cell cycle progression. The second CP is located at the termination of G_2 phase; this CP involves an activating phosphatase known as Cdc25, which under favorable circumstances removes the inhibitory phosphates present within the mitosis promoting factor (a term for the cyclin B/CDK1 complex). Metaphase or spindle phase or mitosis phase CPs require cyclin B, which harbors a destruction box (D-box) and breaks down securin; the breakdown of securin then allows progression of the cell cycle. Many other CPs are present in the cell cycle but are not shown here.

mechanisms that control events of the cell cycle were elucidated using yeast models, which are single cell eukaryotes. Within the yeast models, pertinent discoveries were attained by mutating genes encoding components of cell cycle control systems. These genes were thus identified as cell division cycle (CDC) genes. Much of the control of the progression through the phases of a cell cycle is exerted at specific checkpoints.[6] There are many such checkpoints in a given cell, but the two of the most critical are:

1. Those that occur at the close of a G_1 phase (prior to S-phase entry) and
2. Those at the close of a G_2 phase, preceding mitosis.[6]

For example, CPs have been shown to be downregulated in a large proportion of basal cell carcinomas (BCCs).[7] In addition, 14-3-3σ IkappaB kinase α (IKK-α), one of the two catalytic subunits of the IκB kinase (IKK) complex involved in nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), functions as a specific CP modulator of epidermal development and differentiation.[7]

Other possible disruptions in skin cell cycle regulation and their association with skin cancers

Reduced DNA repair has been linked to an increased risk of cutaneous malignant melanoma, but insights into the molecular mechanisms of that link are scarce. In the skin, the INK4a/ARF cyclin-dependent kinase inhibitor 2A (CDKN2A) locus encodes two proteins that regulate two of the most important tumor-suppressor pathways represented by tumor protein p53 and retinoblastoma susceptibility gene (pRB). Loss of either $p16^{INK4a}$ or $p19^{ARF}$ was recently reported to reduce the ability of mouse cells to repair ultraviolet (UV) induced DNA damage and to induce a UV-mutator phenotype, as suggested by the actions of specific regulating genes. In other examples, loss of either $p16^{INK4a}$ or p19 (ARF) was recently reported to reduce the ability of mouse cells to repair UV-induced DNA damage. These events led to a UV-mutator phenotype and have been suggested to play an important role in the genesis of skin melanomas.[8]

Roles of cyclins and CDKs in cell cycle regulation in the skin

Two key classes of regulatory molecules, cyclins and CDKs influence a cell's progress through the cell cycle and this is especially important in case of skin cancers.[9,10] Many of the genes encoding cyclins and CDKs are conserved among all eukaryotes; however, more complex organisms classically have more elaborate cell cycle control systems that incorporate more individual components. Operationally, cyclins on the skin form the regulatory subunits and CDKs form the catalytic subunits of an activated heterodimer. Thus, cyclins have no catalytic activity and CDKs are inactive in the absence of a partner cyclin. When activated by a bound cyclin, CDKs perform a biochemical phosphorylation that activates or inactivates target proteins and orchestrates coordinated entry into the next phase of the cell cycle, especially on the skin. Specific cyclin-dependent kinase complex (cyclin-CDK) combinations determine the specific downstream proteins targeted.[9,10] CDKs are constitutively expressed in skin cells; in contrast, cyclins are synthesized at specific stages of the cell cycle in response to molecular signals. Four different classes of cyclins have been defined, based on the stage of the cell cycle in which they bind and activate CDKs in the skin. These four classes are G_1-cyclins, G1/S cyclins, S cyclins, and M cyclins [Figure 1].[9,10] Although CDKs are inactive unless bound to a cyclin, there is more to the activation process than just the interaction of the two parts of the complex. When cyclins bind to CDKs, they alter the conformation of the CDKs. The conformational change allows exposure of a domain that is the specific site of phosphorylation; the phosphorylation is then performed by another kinase called a CDK-activating kinase (CAK). Following CAK phosphorylation, the cyclin-CDK complex is fully active, especially in the skin.[9,10]

Other roles of CDKs and cell cycle regulators in the skin

In addition to the control of CDK kinase activity by cyclin binding and CAK phosphorylation in the skin, control of CDK activity may occur via interfaces with inhibitory proteins or by inhibitory phosphorylation procedures. Thus, there is a significant control on the overall activity of each CDK. One of the inhibitory kinases that phosphorylates CDKs is called Wee1.[9,10] The Wee1 inhibiting phosphorylations are in turn removed through the action of a phosphatase called Cdc25. The action of these two regulatory enzymes on CDK activity is very important relative to M-CDK activity at the start of mitosis particularly in the skin. Proteins that bind to and inhibit cyclin-CDK complexes are called CDK inhibitory proteins or cyclin-dependent kinase inhibitors (CKIs).[9,10] Mammalian cells express two classes of CKIs. These are termed:

1. CDK-interacting proteins (CIPs) or CDK inhibitory proteins; and
2. INK4s, for inhibitors of kinase 4.

The CIPs bind and inhibit cyclin-dependent kinase 1 (CDK1), cyclin-dependent kinase 2 (CDK2), cyclin-dependent kinase 4 (CDK4), and cell division protein kinase 6 (CDK6) complexes, while the INK4s bind and inhibit only the CDK4 and CDK6 complexes. There are at least three CIP proteins in mammalian cells; these are identified as p21 / WAF1 / CIP1 (gene symbol = CDKN1A), $p27^{Kip1}$ (gene symbol = CDKN1B), and $p57^{Kip2}$ (gene symbol = CDKN1C). The expression of each of these CIPs is controlled by specific events that

may have happened during the cell cycle, particularly in the skin. For example, $p21^{Cip1}$ expression is induced in response to DNA damage.[9,10] The induction is in turn affected by the action of the tumor-suppressor protein (TSP) p53. INK4 is a TSG protein and is associated with several genes including p16INK4a and p14ARF, and with several other proteins like the Harvey rat sarcoma viral oncogene homolog (HRAS). The INK4 proteins are identified by their molecular weights, which are as follows: Cyclin-dependent kinase 4 inhibitor B (p15INK4B), p16INK4A), cyclin-dependent kinase 4 inhibitor C (p18-INK4C), and p19INK4. The p16INK4A protein is also a TSG since loss of its function leads to cancer particularly in the skin. All the INK4 proteins contain four tandem repeats of a sequence of amino acids that were first identified in ankyrin and are thus referred to as ankyrin repeats.[9,10] An alternative model of the cell cycle response to DNA damage has also been proposed, known as the postreplication checkpoint model. As noted above, p53 plays an important role in triggering control mechanisms at both G1/S and G2/M checkpoints.

TSGs and the skin

TSGs can induce skin cancers as a result of a loss of their normal function, i.e., these proteins suppress the development of cancer.[1-5] A recent review documented 716 human TSG (637 coding and 79 noncoding genes), 628 mouse TSG, and 567 rat TSG.[1-7] Since a single normal allele will express the wild-type TSG, the majority of human TSGs are recessive; specifically, both alleles must be defective for the cell to be susceptible to tumor development. TSGs act as cell cycle repressors and/or promoters of apoptosis through 1) interruption of the cell cycle, 2) prevention of cell division, 3) halting of the cell cycle if DNA damage is not yet repaired, 4) induction of apoptosis if DNA damage cannot be repaired, and 5) promotion of cell adhesion and contact inhibition. All of these actions prevent tumor cell progression, invasion, and metastasis.

Functions of TSGs

TSGs (or more precisely the proteins for which they code) have 1) a dampening or repressive effect on the cell cycle, 2) promote apoptosis, and 3) occasionally perform both functions. The functions of TSPs fall into several categories. First, TSPs repress genes that are vital for continuing the cell cycle. If these genes are not expressed, the cell cycle will not continue, thereby effectively inhibiting cell division. Second, TSPs decouple the cell cycle due to DNA damage.[11] If there is a damaged DNA in the cell, TSPs prevent the cell from dividing. If the DNA damage can be repaired, the cell cycle is allowed to continue. Third, if the damage cannot be repaired, TSPs initiate apoptosis (programmed cell death) to remove the threat the cell poses to the greater good of the organism. Fourth, some TSPs are involved in cell adhesion and prevent tumor cells from dispersing, block loss of cellular contact inhibition, and inhibit metastasis.[1-10] Fifth, DNA restoration proteins are typically classified as TSPs as well as mutations in such genes that raise the risk of cancer; examples include mutations in hereditary nonpolyposis colorectal cancer (HNPCC), multiple endocrine neoplasia type 1 (MEN-1 syndrome), tumor protein 53 [TP53(p53)], breast cancer 1, early onset (BRCA1) and breast cancer 2, early onset (BRCA2), adenomatous polyposis coli (APC), and retinoblastoma protein (RB1). Further, increased mutation rates resulting from the decreased DNA repair lead to an increased inactivation of TSGs and the activation of oncogenes.

All-trans retinoic acid (ATRA) and the skin

All-trans retinoic acid (ATRA) has been used for the treatment and prevention of a number of epithelial cancers. In the SCL-1 skin cell line of human squamous cell carcinoma (SCC), a group of authors recently showed that ATRA inhibited the expression of the cyclin D1/CDK4 and cyclin E/CDK2 complexes, and also increased the expression of the cyclin-dependent kinase inhibitors p21 and p27.[12] ATRA has been shown to suppress signal transducer and activator of transcription 3 (STAT3) signaling during skin carcinogenesis.

Epigenetic regulation in the melanoma TSG p16INK4A protein

p16INK4A protein has also been shown to be of importance in epigenetic regulation in melanoma via microRNAs (miRNAs).[13] miRNAs are short, noncoding ribonucleic acid (RNA) molecules that function as specific epigenetic regulators of the transcriptome. miRNAs are involved in a broad spectrum of physiological and pathological processes, including cancer-related functions such as proliferation, cell cycle regulation, migration, invasion, immune evasion, and drug resistance. These functions are primarily regulated in melanoma through four molecular deregulated pathways, including the rat sarcoma/mitogen-activated protein kinases (RAS/MAPK) pathway, microphthalmia-associated transcription factor (MITF) pathway, p16INK4A-CDK4-RB pathway, and phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)-protein kinase B (Akt) pathway.[13]

Putative therapeutic role of TSGs in skin cancer

The documentation of genes involved in chemotherapeutic responses is critical for predicting tumor responses and treating drug-resistant cancer patients. A group of genes commonly lost or inactivated in cancer are TSGs, which can thus stimulate the initiation and progression

via cell proliferation and cell migration/invasion particularly in the skin.[11] Lately, the increasing evidence suggests that TSG also plays an important role in the response of cancers to a variety of chemotherapeutic drugs.[14] Phosphatase and tensin homologue deleted on chromosome 10 (PTEN) was identified as a TSG through mapping of homozygous mutations occurring in multiple sporadic tumor types, and in patients with cancer predisposition syndromes including Cowden syndrome.[14] Since that time, PTEN has appeared as one of the most frequently mutated or deleted genes in human cancers, including human skin cancers. In particular, damage of PTEN function through mutation or deletion has been detected in up to 70% of melanoma cell lines and epigenetic silencing of PTEN has been witnessed in 30-40% of malignant melanomas.[14,15]

The retinoblastoma susceptibility gene (pRB), the p53, and the p21^{Cip1} TSG in the skin

Other examples of importance in the skin are the proteins encoded by the pRB and the p53 proteins; these protein genes are both TSGs. The function of pRB is to act as a brake, preventing cells from exiting G_1; the function of p53 is to inhibit progression from S-phase to M-phase.[16] One major function of the p53 protein, which is active as a homotetrameric transcription factor, is to serve as a component of the checkpoint that controls whether cells enter and pass through S-phase.[16] The action of p53 is induced in response to DNA damage. Under normal circumstances, p53 levels remain very low due to its interaction with a member of the ubiquitin ligase family, mouse double minute 2 homolog (MDM2). MDM2 was isolated as an amplified gene in the tumorigenic mouse cell line 3T3DM.[16] In response to DNA damage, for example, as a result of UV irradiation or γ irradiation, cells activate several kinases including checkpoint kinase 2 (CHK2) and ataxia telangiectasia mutated (ATM) protein. One phosphorylation target of these kinases is p53. ATM also phosphorylates MDM2. When p53 is phosphorylated, it is released from MDM2 and can carry out its transcription activation functions. One target of p53 is the cyclin inhibitor p21^{Cip1} gene.[16] Activation of p21^{Cip1} leads to increased inhibition of the cyclin D1-CDK4 and cyclin E-CDK2 complexes, thereby halting progression through the cell cycle either prior to S-phase entry or during S-phase. As a consequence of p53-induced synthesis of p21 expression, there is a convergence of the roles of p53 and pRB (as outlined above) in the regulation of cyclin-CDK complexes.[16] In either case, the aim is to allow the cell to repair its damaged DNA prior to replication or mitosis. Given our limited knowledge of the functions of pRB and p53, it is still easy to understand how the loss of function of either protein can lead to aberrant cell cycle progression and the potential for the development of cancer. In addition, a spontaneous SCC has been shown to be induced by somatic inactivation of retinoblastoma and transformation-related protein 53 (TRP53) TSG.[16] TSGs associated with skin conditions include p53, pRB, and genes leading associated with Wilms tumor, neurofibromatosis type I (NF-1), and von Hippel-Lindau (VHL) syndrome.[16]

Inherited mutations of TSGs (germline mutations)

Inherited abnormalities of TSGs have been found in some familial cancer syndromes particularly in the skin.[17] These are genetic imperfections that are passed from parents to children. Hereditary mutations are present in individual eggs or sperm that join during fertilization. Because the mutation is present at the zygotic stage, it exists in all cells of the body including reproductive cells. A hereditary mutation is a major factor in 5-10% of all cancers.[17] They cause certain types of cancer to run in families. There are many examples of inherited TSG mutations and more are being discovered every year.[17]

Acquired mutations of TSGs in the skin

Most cancers are caused by DNA changes that happen during the person's lifetime. These are termed acquired, sporadic, or somatic mutations. An acquired mutation can be caused by things in the environment such as exposure to radiation and/or toxins.[18] However, for most acquired mutations no specific cause can be established. Unlike inherited mutations, acquired mutations begin in one cell of the body and are found only in the descendants of the parent cell. They are thus not in every cell of the body.[18] Because they are not in the reproductive cells, acquired mutations cannot be passed on to following generations.[18]

TSG mutations have been found in many skin cancers

As previously noted, most of these mutations are acquired and not inherited.[19] For example, abnormalities of the TP53 gene (which codes for the p53 protein) have been found in more than half of human cancers. Abnormalities of the p53 gene can be inherited in Li-Fraumeni syndrome (LFS), which increases the risk of developing various types of cancers. An alteration associating this TSG with melanomas has been recently described.[19] The TSG PTEN acts by opposing the action of PI3K, which is essential for antiapoptotic, protumorogenic Akt activation. Other examples of TSGs associated with human cancers include VHL, APC, cluster of differentiation 95 (CD95), suppression of tumorigenicity 5 (ST5), Yippee-like 3 (YPEL3), suppressor of tumorigenicity protein 7 (ST7), and suppressor of tumorigenicity 14 protein (ST14).

Some specific examples of mutated TSGs leading to pathologic skin conditions

Activated intracellular signaling pathways based on mutations in oncogenes and TSGs play a vital role

in a variety of malignant tumors.[20] In dermatology, such mutations have been recognized in melanoma, BCC, and SCC. Discovery of these associations has led to new, targeted therapies.[20] Treatment advances have been particularly impressive in 1) melanoma, with small molecule inhibitors directed against the mutated serine/threonine-protein kinase B-Raf (BRAF) oncogene; and 2) BCCs, with inhibitors directed against the hedgehog (Hh) signaling pathway. Novel sequencing technologies, specifically using next generation sequencing, have allowed a better and more comprehensive understanding of malignant tumors. To be specific, these studies confirmed the pathogenic roles for BRAF and microtubule-associated protein (MAP) kinase pathways in melanoma.[20] Simultaneously, a series of further molecules associated with melanoma genesis including ERBB4, GRIN2A, GRM3, PREX2, RAC1, and TP53 have been characterized.[20]

TSG patched (PTCH) homolog 1 protein, the nevoid BCC syndrome, and basal cell nevus syndrome (BCNS) or Gorlin syndrome in the skin

Gorlin syndrome is a rare genodermatosis. BCC comprises the majority of nonmelanoma skin cancers. Dermatologists and other health professionals should incorporate family history into clinical practice to identify patients who may be at increased risk for BCNS.[20] BCNS is an autosomal dominant disorder that disposes to BCCs of the skin, ovarian fibromas, and medulloblastomas [Table 1].[20] Additional manifestations include palmoplantar pits, jaw cysts, and bony deformities like kyphoscoliosis and frontal bossing.[20] Other alterations include rib abnormalities (splaying, synostosis, bifid, and cervical ribs), vertebral anomalies (block vertebrae, hemivertebrae, spina bifida occulta, and kyphoscoliosis), and shortening of the metacarpal and the small flame lucency in phalanges. Further abnormalities described in the reproductive system are uterine fibromas in females and cryptorchidism and hypogonadism in males.[20] Additional findings in BCNS include mesenteric cysts, renal calculi, cardiac fibromas, and a tendency to develop various other neoplastic lesions such as melanomas, neurofibromas, and rhabdomyosarcomas. The five primary BCNS diagnostic criteria include multiple BCCs, odontogenic keratocysts, palmar and plantar pits, flare calcifications, and a positive family history. The six minor criteria include congenital skeletal anomalies (ribs, vertebra), macrocrania, cardiac or ovarian fibromas, medulloblastomas, lymphomesenteric cysts, and congenital malformations (i.e., cleft lip/palate, polydactyly, or eye anomalies).[20] The presence of two major or one major and two minor criteria is considered diagnostic of BCNS. In the 1990s, a link between aberrations of the Hh signaling pathway and BCCs in mice was confirmed. At about the same time, multiple studies connected this pathway in humans with both sporadic BCCs and an autosomal dominant genetic syndrome predisposing to multiple BCCs. The Hh signaling pathway has been identified as important to normal embryonic development in living organisms and is involved in processes including cell proliferation, differentiation, and tissue patterning. In contrast to other hereditary disorders associated with cancer, BCNS often features widespread birth defects. BCNS is caused by mutations in PTCH, which is a TSG. The PTCH gene is mapped to human chromosome 9q22.3.[21] Clinical findings are variable in 9q deletions and duplications involving PTCH, thus influencing individual predisposition to the benign and the malignant tumors reported in BCNS [see Table 1].[21] Moreover, the majority of mutations in sporadic BCCs and in Gorlin syndrome are believed to involve PTCH.[21] Loss of heterozygosity at this chromosomal location (primarily in hereditary tumors) suggests that the gene is homozygously inactivated and normally functions as a TSG.[21] Cytogenetic BCNS studies may show intrachromosomal insertions; thus, cytogenetic analyses are important in providing accurate genetic counseling.[21] Early diagnosis and treatment of this syndrome is important to reduce the severity of complications including cutaneous and cerebral malignancies, and oromaxillofacial deformation and destruction due to jaw cysts. Since BCNS transmission is autosomal dominant, any child of an affected family is at 50% risk of carrying the affected gene. Regular follow-up is necessary for assessing progression of BCCs. Vismodegib is the first-in-class smooth muscle inhibitor, approved for the treatment of locally advanced or metastatic BCCs.[21] Tazarotene (Tazorac, Allergan, Irvine, California, USA) is a topical retinoid with relative specificity for retinoic acid receptor beta (RAR-β) and retinoic acid receptor gamma (RAR-γ) receptors, and has shown good clinical results in BCC applications. Surgical management is also recommended in selected lesions.

TSG VHL binding protein 1 (VBP1) and the skin

VHL [Online Mendelian Inheritance in Man (OMIM) number 193300] disease is a hereditary cancer syndrome, characterized by the development of various tumors including renal, pancreatic, retinal, and central nervous system (CNS) cerebellar hemangioblastomas, pheochromocytomas, and renal clear cell carcinomas, and ear, nose, and throat adenomas.[22-24] The title VHL disease was first utilized in 1936 and has been in common use since the 1970s. VHL disease is also considered a neurocutaneous disorder, associated with NF-1, the tuberous sclerosis complex, incontinentia pigmenti, Sturge-Weber syndrome, hypomelanosis of Ito, and linear nevus sebaceous syndrome.[22-24] VHL is inherited in an autosomal dominant manner and caused by germline

Table 1: TSG and the skin

Gene ID, name, synonyms, and gene type	Diseases	Description
2272, fragile histidine triad (FHIT), (FRA3B); protein coding; also, 51741[(WW domain containing oxidoreductase WWOX)]; protein coding	Kaposi sarcoma, the most common cancer in human immunodeficiency virus (HIV) positive individuals, is caused by endothelial transformation mediated by the Kaposi sarcoma herpes virus (KSHV)-encoded G-protein-coupled receptor (vGPCR)	TSGs genes FHIT and WWOX are also deleted in primary effusion lymphoma (PEL) cell lines.
7128, (TNFAIP3), (TNFA1P2; tumor necrosis factor); protein coding	SS, a disseminated, leukemic form of cutaneous T-cell lymphoma; also in BCC	TSG TNFAIP3 (A20) is frequently deleted in SS.
5325, (PLAGL1), (ZAC; pleiomorphic adenoma gene-like 1); protein coding	BCC	Potential TSGs; *ZAC* expression is present in normal skin, with a high expression level in basal keratinocytes and a lower, more heterogeneous expression in the first suprabasal layers of the epidermis. ZAC is a zinc finger transcription factor that induces apoptosis and cell cycle arrest in multiple cell lines. The ZAC gene is involved in keratinocyte differentiation and its expression is lost in BCCs.
5727, (PTCH), (PTCH1; BCNS|HPE7); protein coding	Gorlin syndrome is an autosomal dominant disorder that predisposes to multiple lesions, including BCCs of the skin, ovarian fibromas, and medulloblastomas.	BCCs of the skin represent the most common type of cancer in humans. The majority of these tumors display aberrant activation of the Sonic Hedgehog (Shh)/ PTCH pathway, triggered by mutations in the PTCH TSGs, which encode a transmembrane receptor of SHH. Also, heterozygous mutations in PTCH incite BCC-like features in human organotypic skin cultures.
7157, (TP53), (TRP53; tumor protein p53); protein coding	BCC and SS	TP53 has been implicated with polymorphisms and lack of expression in BCCs, suggesting a crucial role for its expression in tumor suppression of BCCs.
8643, (PTCH2), (PTC2; patched 2); protein coding	The nevoid basal cell carcinoma syndrome (NBCCS) as well as in sporadic basal cell carcinomas	Mutations of TSGs in the human patched gene 2 (PTCH2) have been identified in individuals with NBCCS.
5925, (RB1), (pp110; retinoblastoma); protein coding; also, 7157, (TP53), (TRP53; tumor protein p53); protein coding	SCC, a cancer of the epidermis	Cancerous tissues from 30 patients with SCCs were confirmed for loss of heterozygosity in 4 TSGSs (p16, RB1, E-cadherin, and p53) at loci 9p21, 13q21, 6q22, and 17p13, respectively, utilizing microsatellite markers amplified by PCR. P16 is also associated with aggressive behavior of penile carcinomas. The p53 TSGs pathway is disrupted in most oral SCCs due to either an abnormality in p53 itself or loss of expression of p53 regulatory factors.
4851, (NOTCH1), (TAN1); protein coding	Bowen's disease, SCCs and solar keratoses: the Notch signaling pathway may play contrasting roles in cancer. It can be oncosuppressive or protumoral, contingent on the cellular and tissue setting.	The Notch 1 gene is a member of the Notch family, which undergoes downregulation upon exposure to UV. In UV-related squamous cell photocarcinogenesis, Notch 1 downregulation could perform a TSGs suppressor function via its receptor. In contrast, Notch 1 is upregulated in sun-protected SCCs.
4763, (NF-1), (WSS; Neurofibromin 1); Protein coding	NF1 is an inherited, autosomal dominant human disease.	The NF1 TSGs is a modifier of carcinogen-induced pigmentation and papilloma formation in experimental studies on C57BL/6 mice. NF1 patients heterozygous for mutations in the NF1 gene are predisposed to develop benign peripheral nerve sheath tumors, learning disabilities, bone abnormalities, certain malignant tumors, and pigmentation defects. Pigmentation defects include patches of hyperpigmented skin called café au lait macules, found in all NF1 patients by 5 years of age, axillary and inguinal freckling, and altered patches of retinal melanocytes termed Lisch nodules.
2131, (EXT1), (EXT1; Exostosin 1); Protein coding	WS (also known as adult progeria) is a rare, autosomal recessive, progeroid syndrome, which is characterized by the appearance of premature aging and associated skin cancer development	Epigenetic loss of the familial TSG exostosin-1 (EXT1) disrupts heparan sulfate synthesis and repair in WS cancer cells. WS is specifically caused by loss of function mutations of the werner syndrome (WRN) gene, a RecQ family member with both helicase and exonuclease activities. However, despite its putative tumor-suppressor function, little is known about the contribution of WRN to human sporadic malignancies.
4089, (CDKN2A), (DPC4|JIP|SMAD4); Protein coding	MS is a developmental disorder characterized by reduced growth, generalized muscular hypertrophy, facial dysmorphism, deafness, cognitive deficits, joint stiffness, and skeletal anomalies.	SMAD4 has been established as a TSG and is somatically mutated in some cancers (including skin cancers). The mutations may occur as a result of germline loss-of-function lesions and deletions of the gene. A restricted spectrum of mutations in the SMAD4 TSGs underlies MS.

mutations in the VHL TSG. Many patients with VHL may develop endolymphatic sac tumors, which can cause tinnitus or deafness. The diagnosis of VHL may be made in a patient with a family history of VHL, based on a single retinal or cerebellar hemangioblastoma, renal cell carcinoma or pheochromocytoma, and possibly, multiple pancreatic cysts. Renal and epididymal cysts are not sufficient to establish a diagnosis of VHL.[22-24] In order to confirm a VHL diagnosis in the absence of a family history of VHL, the presence of two or more retinal or cerebellar hemangioblastomas, or one hemangioblastoma and one visceral tumor are required. Studies of the natural history of VHL had shown a life expectancy of less than 50 years before surveillance protocols were developed.[22-24] Annual assessments (physical and ophthalmologic examinations) should begin in infancy. Imaging of the abdominal organs and the brain and spine should be done in teenagers and adults. Renal cysts and tumors should be monitored by computed tomography every 6 months. Mutation analysis has allowed presymptomatic identification of affected family members; those found not to have inherited the gene do not need to be monitored. VHL disease is characterized by marked phenotypic variability and age-dependent penetrance. VHL gene mutations have been reported in more than 900 disease kindreds (http://www.umd.be/VHL/W_VHL, Last access on January, 20, 2014). Many functions have been assigned to the abnormal VHL normal TSG product (pVHL), including targeting the alpha subunits of the heterodimeric transcription factor hypoxia-inducible factor (HIF) for destruction.[22-24] HIF, also known as prefoldin 3, is a chaperone protein that normally binds to VHL protein and transports it from perinuclear granules to the nucleus or cytoplasmic sites inside the cell. HIF is also involved in transporting normal nascent polypeptides to cytosolic chaperonins for posttranslational folding [see Table 1].[22-24] A second protein often damaged in VHL disease is VBP1. VBP1 is a 197–amino acid heterohexamer, comprising two prefoldin-α and four prefoldin-β subunits; it is a member of the prefoldin-α subunit family.[22-24] It is ubiquitously expressed in tissues and is located in the cell in both the nucleus and cytoplasm. The VBP1 gene is located at human locus Xq28. Clinical VHL disease is often a complex multisystem disorder that needs management from multiple medical specialties. Coordinating the medical care of VHL families can be challenging, but is vital to prevent avoidable morbidity and mortality.[22-24] Recommended screening includes searching for retinal angioma by performing annual ophthalmic examinations, beginning in infancy or early childhood.[22-24] In addition, CNS, and ear, and nose and throat screenings are needed, with magnetic resonance imaging (MRI) scans of the head every 12-36 months, beginning in adolescence. Screening for renal cell carcinoma and pancreatic tumors via MRI (or ultrasound) examination of the abdomen every 12 months starting at 16 years is recommended. Testing for pheochromocytoma is recommended, by performing annual blood pressure monitoring and 24-h urine studies for catecholamine metabolites.[22-24] Finally, more intense surveillance (e.g., annual measurement of plasma normetanephrine levels and adrenal imaging) beginning at 8 years should be considered in families at high-risk for pheochromocytoma. Early diagnosis of VHL complications improves the prognosis of each patient. All VHL patients and at-risk relatives should enter into a comprehensive screening program in childhood (unless VHL is excluded by molecular genetic testing).

Familial melanoma (FM) syndrome and the skin

Originally titled familial atypical multiple mole melanoma (FAMMM) syndrome, with initial descriptions of increased hyperdiploidy observed as an *in vitro* phenomenon in cultured skin fibroblasts from high-risk and affected subjects. The FAMMM genotype was described as complex, in that it predisposed a patient not only to melanoma (cutaneous and intraocular malignant melanoma) but also to other types of cancer including lung, pancreas, and breast.[25] After recognizing this entity, attention was initially focused on cancer surveillance and management programs for patients at increased risk for the several forms of hereditary malignant melanoma.[25] Genetic analysis performed long ago in some families with clinical and pathologic verifications of the FM syndrome had shown some at-risk members in these families, with a segregation ratio of about 0.47 (consistent with an autosomal dominant mode of inheritance). Some obligate gene carriers who lacked any FM phenotypic manifestations were observed, and the rate of penetrance for the FM gene was calculated to be 0.93. The melanocytic lesions or "moles" in this syndrome had shown to be mainly histologic compound nevocellular nevi with varying degrees of dysplasia of the melanocytes, an increased occurrence of fibroplasia, and chronic inflammation within the papillary dermis. Of further interest were findings of variation in the degree of dysplasia in "moles" between and within families affected by FM. These observations, when coupled with recent reports by others, are consistent with an autosomal dominant gene showing variable expressivity. About 5-10% of melanomas may be genetic in origin and about 2% of melanomas can be unambiguously attributed to pathogenic germline mutations in CDKN2A.[25] Recently another high penetrance gene, CDK4, was found to be responsible for melanoma development in some families. CDKN2A is a dominantly inherited gene that is associated with mutations in the TSG CDKN2A/p16 [Table 1].[25] CDKN2A can also be altered after exposure to UV radiation. Specifically, UV light can induce distinct alterations in genes related to cell cycle regulation and DNA damage responses; these same genes are also reported to be dysregulated in patients with familial

melanoma.[25] Thus, some authors have suggested that CDKN2A needs to be monitored for personalized prevention strategies in high-risk populations.[25] Presently, genetic testing is widely used for identifying individuals with hereditary colorectal cancer and hereditary breast/ovarian cancer, but genetic testing of CDKN2A in the framework of melanoma prevention is not part of the routine practice. However, there are now several laboratories in the United States and in other countries that offer CDKN2A testing. The likelihood of detecting a CDKN2A mutation depends greatly on the population being studied, which may be a result of differences in penetrance associated with 1) variations in melanoma predisposition phenotypes (e.g., light skin, red hair) and 2) the local amount/intensity of UV radiation exposure. Notably, in geographical areas with high baseline rates of melanoma, there is greater probability of having multiple family members with melanoma (and individuals with multiple primary melanomas) caused by reasons other than a CDKN2A mutation. Still, melanoma penetrance in CDKN2A mutation carriers is also higher in areas with higher baseline rates of melanoma, indicating a potential interaction between CDKN2A and other predisposing factors for melanoma in these areas.[25] Finally, there is growing awareness among the public about the genetic basis of cancer and the availability of pertinent testing. Management of these patients is difficult as one cannot be certain which moles require biopsy and then, following histological study, which will require wider excision. Studies of the FM syndrome should deal carefully with its natural history, including the patient's lifelong susceptibility to multiply malignant melanomas and the possibility that cancer of other anatomic sites may be integral components of this hereditary cancer syndrome. Dermatologists and other health specialists should include family history and risk assessment in clinical practice to identify patients who may be at increased risk for familial melanoma.[25] About 3-5% of all patients with melanoma will develop additional primary melanomas in their lifetime. In recognizing new familial melanoma genes using next generation sequencing, a small number of new high penetrance genes have been discovered. Such research has identified the lineage including the specific oncogene microphthalmia-associated transcription factor (MITF) as a susceptibility gene both in melanoma families and the general population, as well as the discovery of telomere maintenance as a key pathway underlying melanoma predisposition.

TSG tumor necrosis factor, alpha-induced protein 3 (TNFAIP3) (A20) is frequently deleted in Sézary syndrome (SS) in the skin

SS is a disseminated form of cutaneous T cell lymphoma (CTCL). It often presents with erythroderma, the presence of greater than 1000 Sézary cells in the peripheral blood, lymphadenopathy, and pruritus. Complete remission is rare in patients with SS. According to the original description (Sézary, 1949), the syndrome is characterized by generalized, intensely pruritic, edematous and pigmented erythroderma, lymphadenopathy, and large cerebriform cells in the circulating blood. In many cases, a fatal outcome was common 18-40 months after diagnosis. Other symptoms and signs included palmar and plantar hyperkeratoses with painful fissures, dystrophic nails, patchy pigmented involvement of mucous membranes, leonine facies, alopecia, and night sweats or chills with normal or subfebrile body temperatures. The histopathology of Sézary skin lesions usually reveals irregular acanthosis with mixed hyperkeratosis and parakeratosis, intercellular epidermal edema with foci of frank spongiosis, small cavities containing abnormal mononuclear cells (analogous to the Pautrier's microabscess of mycosis fungoides) and a dermal mononuclear cell infiltrate of variable intensity. In all tissues including the peripheral blood, Sézary stressed the presence of the peculiar cerebriform cells with large, highly irregular, and convoluted nuclei. In 1961, Taswell and Winkelmann confirmed the presence of intracytoplasmic periodic acid-Schiff (PAS) positive granules, an added diagnostic feature of Sézary cells. Later, the cells were found to have an equally characteristic ultrastructural appearance, quite similar to that of mycosis fungoides cells, by Lutzner and Jordan in 1968 and Brownlee and Murad in 1970. The Sézary treatment is aimed at the clearance of skin disease, minimization of reappearance, prevention of disease progression, and safeguarding of the quality of life. Other considerations include control of symptom severity including pruritus and patient age/comorbidities. Overall, for the limited patch and plaque disease, patients currently have an excellent prognosis using topical formulations, such as corticosteroids and nitrogen mustard. The extended disease with widespread patches/plaques often requires phototherapy. Current Sézary therapy (especially for those with significant skin compromise) includes combined immunomodulatory therapy, using targeted biologic agents, and/or total skin electron beam therapy followed by nonablative allogeneic stem cell therapy. Other treatments such as extracorporeal photopheresis, alpha interferon, retinoids, antibiotics, and/or topical steroids have been utilized. Medications such alemtuzumab, mogamulizumab, and/or others have been utilized; however, in many cases fatality may occur secondary to sepsis due to secondary immunotherapy.

Mycosis fungoides (MF) and TSGs in the skin

MF is the most common clinical presentation of primary cutaneous CTCL.[26] The CTCL entities comprise MF, presenting with patches, plaques, and/or tumors

without a significant leukemic component; and SS, classically presenting with erythroderma and leukemic CTCL cells.[26] MF comprises the majority of CTCL cases. MF patients frequently present with early phase disease, typically associated with a favorable prognosis and survival of 10-35 years; however, over 25% may progress to the advanced stage of the disease, with a median survival less than 4 years and a median survival of a few months in patients with lymph node involvement. SS classically presents as advanced MF disease with erythroderma, lymphadenopathy, and CTCL leukemia [see Table 1].[26] The Bunn and Lamberg staging system (1979) comprises stages IA-IIA (early stage disease) and IIB-IVB (progressive stage disease), and provides prognostic CTCL information. Notably, some tumor stage (IIB) patients have a worse prognosis than erythrodermic stage patients (III). Further, plaque stage (IB) folliculotropic MF may have a worse outcome than tumor stage (IIB) patients. MF often advances through the following phases. First, a premycotic phase with a scaly, red rash appears in areas of the body that are usually not exposed to the sun. The rash does not cause symptoms, and may be present for months or years.[26] It is frequently difficult to diagnose the rash as MF during this phase. Second, a patch phase occurs with a thin, reddened, eczema-like rash. Third, a plaque phase occurs, manifested by small raised papules and nodules/plaques on the skin. Fourth, the tumor phase occurs; the skin tumors may develop ulceration and the skin may become secondarily infected. The following tests and procedures are utilized for the diagnosis of MF and SS: A clinical history and physical examination in particular; a complete blood count with differential; a peripheral blood smear examination; and a skin biopsy augmented with immunohistochemistry (IHC) special stains.[26] The IHC immunophenotyping represents a process used to identify and classify cells, based on the specific antigens present on their surfaces or within their cytoplasms. Other testing may include IHC staining of leukemic cells. Other testing involves conducting a T cell receptor (TCR) gene rearrangement test to see if genetic changes have occurred that lead to the production of a clonal population of T lymphocytes. Other testing includes flow cytometric analysis that can measure:

1. The number of cells in a sample of blood,
2. The percentage of live cells in the sample,
3. Specific characteristics of the cells such as their sizes and shapes, and
4. The presence of tumor markers on their surfaces.

In SS, multiallelic and monoallelic deletions of the tumor necrosis TNFAIP3 have been identified.[26] Also, A20 is a potent anti-inflammatory signaling molecule that restricts multiple intracellular signaling cascades. In mycosis fungoides and folliculotropic MF, a combination of skin-directed therapy and low-dose immunomodulators such as interferon or bexarotene may be effective. A better understanding of the pathogenic and biologic markers (including the altered TSG) is needed to improve treatments directed against other specific markers.

BCC and TSG in the skin

BCC represents the most common human neoplastic disease. BCC is a type of skin cancer that begins in the pluripotent basaloid cells of the epidermis. BCC often appears as a waxy bump, though it can take other forms; it primarily affects photoexposed areas, most often on the head and the neck. BCC rarely appears on the genital and the perigenital zones. A general warning sign of skin cancer is a sore that will not heal. However, BCC may also appear as a pearly white or waxy bump, often with visible blood vessels on the face, ears, or neck. The bump may bleed and develop a crust. In darker-skinned people, this type of cancer may be brown or black. Other forms can present as a flat, scaly, brown, or flesh-colored patches on the chest; over time, these patches can grow quite large. BCC may also present as a white, waxy scar; this may be a sign of a particularly invasive and disfiguring variant, termed morpheaform BCC. Almost all BCCs occur on parts of the body excessively exposed to the sun, especially the face, ears, neck, scalp, shoulders, and back. On rare occasions, however, the tumors develop on unexposed areas. In a few cases, contact with arsenic, exposure to radiation, chronic inflammatory skin conditions, and complications of burns, scars, infections, vaccinations, or even tattoos are contributing factors. BCC usually progresses slowly; metastases are rare and found in less than 0.5% of the cases. However, considerable local destruction, damage, and mutilation may be observed if treatment is not performed. In advanced cases, large reconstructive plastic surgeries are needed to address the tumor.[27] Diverse histologic variants of BCCs have been defined including nodular, cystic, micronodular, superficial, and pigmented presentations.[27] After the physician's examination, the diagnosis of BCC is confirmed with a biopsy, and a clinical staging of BCC may be performed according to the tumor-node-metastasis (TNM) classification system; however, this classification is often not used in practice due to the rarity of BCC involvement beyond the skin. Multiple therapeutic methods have been established for the successful treatment of BCCs. Thus, early diagnosis leads to improved prognosis.[27] People who have had one BCC are at risk of developing others over time, either in the same area or elsewhere on the body. Therefore, regular visits to a dermatologist should be kept so that not only the site(s) previously treated, but the entire skin surface can be examined. BCCs on the scalp and nose are especially troublesome, with reappearances typically taking place within the first 2 years following

surgery. Should a cancer recur, the physician might recommend a different type of treatment. Some methods, such as Mohs micrographic surgery, may be highly effective. In addition, topical medications such as fluorouracil (5-FU), imiquimod 5%, and vismodegib may be utilized. Other therapeutic modalities include curettage and electrodissecation, laser surgery, radiation, cryosurgery, and photodynamic therapy. Expression of the altered TSG products B-cell lymphoma 2 gene (Bcl-2), BCL2-associated X protein (BAX), and p53 have been noted as BCCs; specific mutations of p53 have been described in Korean patients with BCCs.[27] [Table 1]. In addition, Bcl-2 and p53 expression have been negatively correlated to clinical BCCs.[27]

NF-1 TSG and the skin

NF-1 (Online Mendelian Inheritance of Man No. 162200, http://www.omim.org/entry/162200, accesses February, 19, 2015), formerly known as von Recklinghausen disease, is an autosomal dominant disorder that affects approximately 1 in 3,500 persons.[28,29] It is caused by mutations in the NF-1 TSG, which encodes a GTPase-Activating Protein (GAP) that negatively regulates p21-RasNF1 in a relatively common inherited disorder. Patients have a predisposition to develop both benign and malignant tumors. Although many manifestations of NF-1 affect the nervous system, other organs and tissues can also be affected. Café au lait spots, neurofibromas, freckles, Lisch nodules, brain hamartomas, seizures, mental retardation, plexiform neurofibromas, and peripheral nerve sheath tumors are common. The development of malignant nerve tumors and neurofibromas occurs frequently in NF1. However, little is known about the molecular mechanisms mediating the genesis and the progression of these complex tumors, or the identity of the specific cell types that give rise to dermal or cutaneous neurofibroma. Due to the variable clinical features inherent to this disorder, patients can present to different medical and surgical specialists and consequently, the association of clinical symptoms with NF1 may not be initially easily to discern.[28,29] Accordingly, for prompt diagnosis and providing optimum care for patients with NF1, clinicians should be aware of the diverse clinical features of this disorder. NF1 may present solely with learning disabilities, speech disorders, glomus tumors, or a variety of skeletal manifestations such as short stature, osteopenia/osteoporosis, and lytic bone lesions. Glomus tumors are benign but painful tumors of the fingertips and toes. Affected individuals often present with the triad of severe paroxysmal pain, cold intolerance, and localized tenderness.[29] Half of the patients with NF1 have inherited their NF1 mutation. The NF1 gene is located on human chromosome 17q11.2, spanning approximately 280 kb of genomic DNA. The NF1 gene also has a high frequency of *de novo* mutations.[28,29] Interestingly, numerous clinical syndromes with disease-causing mutations in genes for proteins of the Ras signaling pathway have phenotypes overlapping with those of NF1. These syndromes include Noonan syndrome, LEOPARD syndrome, cardiofaciocutaneous syndrome, Costello syndrome, and Legius syndrome. Genetic testing is thus very important because the eventual penetrance of NF1 is 100%, meaning that all patients with NF1 mutation will eventually present with clinical NF1. Plexiform neurofibromas are common NF1 tumors carrying a risk of malignant transformation, which is typically fatal. Some recent studies have shown a population of $GAP43^+$ PLP^+ precursors in embryonic nerve roots as the cells of origin for these tumors. A multidisciplinary approach to care, entailing a devoted team of specialists throughout the lifetime of the patient is needed; knowledge of TSGs and swift implementation of new effective treatments are also essential.[28,29] Surgery is often utilized to remove the NF1 tumors. NF1 has no cure; however, the quality of life of the patients can be greatly improved. In most cases, neurology, psychiatry, dermatology, clinical genetics, oncology, nursing, psychology, behavioral therapy, and internal medicine specialists are able to make a positive impact of the quality of life of the patients and their families. It is important to keep in mind that overall, NF1 has pronounced variability in phenotypic expression, course progression, and multiple organ involvement. NF1 often also requires patient group support. Finally, the NF1 gene is genetically heterogeneous with a high mutation detection rate.

Myhre syndrome (MS) and TSG in the skin

MS is a rare disorder whose diagnosis is primarily clinical. MS is characterized by abnormal growth of the skeleton, muscles, and joints and manifested by short stature, brachydactyly, altered facial features, pseudomuscular hypertrophy, intellectual deficiency, joint use limitation, and hearing loss. Characteristic facial features may include abnormally narrow skin folds (palpebral fissures) between the upper and the lower eyelids (blepharophimosis), underdevelopment of the upper jaw bone (maxillary hypoplasia), and an unusually prominent jaw (prognathism). Recently, mutations in the mothers against decapentaplegic/DPP homolog 4 (SMAD4) gene has been cited as the cause of MS.[30,31] SMAD4 is a 552-amino acid protein involved in cell signaling. It belongs to the Darwin family of proteins, which modulate members of the transforming growth factor beta (TGF-β) protein superfamily. Other alterations described in MS include delayed speech, moderate psychomotor retardation, thick calvaria, broad ribs, hypoplastic iliac wings, and short tubular bones. Other common

features include a "muscular" habitus and behavioral problems. Health complications including obesity, arterial hypertension, bronchopulmonary insufficiency, laryngotracheal stenosis, pericarditis, and early death may occur.[30,31] Ataxia and cerebellar atrophy may also occur. The skin may display streaks with areas of patchy thickening, suggestive of genetic mosaicism. Some recent studies have also described *de novo* heterozygous SMAD4 mutations, presenting with laryngotracheal stenosis, arthropathy, prognathism, and short stature syndrome (LAPS). Sometimes, the presence of skewed X-chromosome inactivation in patient DNA may be seen in MS.[30,31] Life-threatening complications often occur in the course of the disease. An association of MS with advanced paternal age at patient birth suggests an autosomal dominant mutation as the cause of MS. SMAD4 mutations have also been identified in the primary MS differential diagnosis, specifically LAPS. The SMAD4 data thus supports the clinical heterogeneity in MS and a clinical overlap with LAPS.[30,31] Most MS treatments are palliative; for example, treatment of recurrent, progressive, proximal tracheal stenosis required partial tracheal resection, laser treatment, and eventually tracheotomy. Other frequent palliative treatments include addressing recurrent pericarditis and/or pulmonary infections.

Conclusion

TSGs encode proteins that decrease the risk of a eukaryotic cell line becoming tumorigenic. When TSPs are sequestered away from their normal functional locations within the cell by retroviral tumor antigens, the loss of their normal suppressor functions may result in cellular transformation. Some common TSGs are altered in many skin conditions and our knowledge of these genes is constantly increasing.

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