REVIEW

Molecular carcinogenesis of squamous cell carcinomas of the skin

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Abstract : Squamous cell carcinomas (SCCs) of the skin were suggested to develop through a multistep process that involves activation of proto-oncogenes and/or inactivation of tumor suppressor genes in the human skin keratinocytes. Exposure to ultra-violet (UV), especially UV-B, radiation is the most common cause for these genetic abnormalities in cells. We review causation of SCCs and genetic abnormalities in human SCCs with the current work. To elucidate the multistep process, we developed a method for examining the combinatorial function *in vivo* of plural genes in human keratinocytes. Using high efficiency retroviral transductions, we could express plural genes serially in normal human primary keratinocytes and use these cells to regenerate human skin on SCID mice. A combinatorial transduction of H-RasV12 and cyclin dependent kinase 4 (CDK4) produced human epidermal neoplasia resembling SCC. These findings were consistent with our previous results of mutation analysis in SCCs, one of which had both mutations of *H-Ras* gene and the *INK4a* locus. Therefore, it is suggested that a combination of these genetic abnormalities might be crucial to the carcinogenesis at least in a subset of SCCs. J. Med. Invest. 49 : 111-117, 2002

Keywords **:** *squamous cell carcinomas (SCCs), skin cancer, ultra-violet (UV) radiation, gene mutation, keratinocyte*

INTRODUCTION

Squamous cell carcinomas (SCCs) of the skin are one of the most common skin cancers associated with a substantial risk of metastasis (1). It is widely accepted that normal keratinocytes in the epidermis can convert to SCCs through a multistep process that involves activation of proto-oncogenes and/or inactivation of tumor suppressor genes (2, 3). In this study, we review the molecular carcinogenesis of SCCs.

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CAUSATION

Exposure to ultra-violet (UV) radiation is the most common cause of skin cancers (4, 5). In particular, UV-B radiation is mainly involved in the mutagenesis in the skin by two major photoproducts of a cyclobutane pyrimidine dimer and (6-4) photoproducts (6, 7). After UV-B radiation exposure, DNA damage in the keratinocytes would usually be repaired properly by means of DNA base excision repair. However, the abnormalities of genes would remain in the cells, if the cells fail to undergo DNA damage repair they could escape from apoptosis. Recently, tanning devices have been reported to be associated with odds ratios of 2.5 for SCCs in Caucasians (8).

The hypercarcinogenic state has been defined as the state that cells are susceptible to the occurrence and accumulation of gene mutations (9). Hypercarcinogenic

states for SCCs consist of inherited lesions, e.g., xeroderma pigmentosum that is defective in DNA base excision repair, and the acquired lesions, e.g., chronic ulcers, burn and posttraumatic scars, and Discoid lupus erythematosus. Among them, each of the candidate genes for all types of xeroderma pigmentosum has previously been identified, and the mechanism of DNA base excision repair has been elucidated (10). Although how gene mutations accumulate in the acquired lesions is poorly understood, the continually accelerated turnover of the cell cycle in chronic ulcers was suggested to be one of the most important factors for the initiation, promotion, and progression of carcinogenesis as the hypercarcinogenic state (9).

SCCs occur with high frequency in renal allograft recipients after prolonged immunosuppression (11). Human papillomavirus (HPV) infections are likely to be an important factor because they are often detected in these conditions (12, 13). In oncogenic types of HPV 16 and 18, which are frequently detected in uterocervical cancers, E6 protein inactivates the p53 tumor suppressor gene product and up-regulates hTERT, the reverse transcriptase of telomerase, and E7 protein inactivates Rb (Retinoblastoma) tumor suppressor gene product (14). It may be uncertain that HPV should mainly contribute to the development of SCCs because HPV 16 or 18 are not often detected in those on the immunosuppressive patients. However, E6 proteins of other types of HPV detected frequently in the skin also target and abrogate the function of Bak, an apoptosis-related protein that is induced by UV (15). Thus, HPV may contribute to the development of SCCs against apoptotic signals in keratinocytes.

Some gene polymorphisms related to the susceptibility of SCCs were reported in the general population of Caucasians recently. Greater than twenty polymorphisms were reported in the melanocortin-1 receptor (MC1-R), which has been associated with physiologic variation in hair and skin color. In particular, the variants Arg151Cys and Arg160Trp were strongly associated with fair skin and red hair, and carriers of the two variant alleles were at increased risk for developing SCCs (16). The DNA base excision repair gene XRCC1 Arg399Gln polymorphism was also reported to be associated with the occurrence of SCCs (17). These associations between gene polymorphisms and the occurrence of SCCs remain uncertain in the general Japanese population.

GENETIC ABNORMALITIES

1) Chromosomal abnormalities

The majority of a number of DNA ploidy studies reveal that aneuploidy is shown in some SCCs (18). Consistent with these findings, clonal chromosomal abnormalities have been reported in a subset of SCCs, although it is technically difficult to perform karyotypic analysis in solid tumors (19). Chromosomal instabilities may be critical on the carcinogenesis in a subset of SCCs, although chromosomal instabilities as a result of transformation or technical artifacts could not be completely excluded.

2) Proto-oncogene Ras

Ras genes consist of three different genes, *H-Ras*, *K-Ras*, and *N-Ras*, and activating *Ras* mutations are one of the most common genetic abnormalities in various human cancers (20). The Ras proteins are small G-proteins that transduce intracellular signal, and are constitutively activated by point mutations of codons 12, 13, and 61 of *Ras* genes (20, 21). Through the activated Ras pathway, many tumor-promoting effects, e.g., accelerating cell growth and inhibiting apoptosis, are induced (21). *Ras* mutations have been well characterized in the mouse skin two-stage carcinogenesis model, because the mutations are frequently detected after the initiation with the genotoxic carcinogen dimethylbenzanthracene (DMBA) (22, 23). However, the rates of *Ras* mutations in human SCCs vary between 0% and 46% (24, 25), and we also detected *Ras* mutations in only one of 21 SCC cases (Table 1) (26). Activating *Ras* mutations should be important on the carcinogenesis in a subset of SCCs, although the role of Ras activation in SCCs development remains unclear.

3) Tumor suppressor gene p53

Mutations of the *p53* gene have been found in approximately half the SCC cases in addition to various other human cancers (27-29). UV light-induced photoproducts at dipyrimidine sites should contribute to these mutations, because mutations of C to T or CC to TT predominate in SCCs that originate in the sunlight-exposed skin region (27-29). Known as "guardian of the genome" (30), p53 is involved in a number of important cellular control pathways, including G1 growth arrest and apoptosis, especially in response to DNA damage. p53 induces p21 and p53R2 for repairing DNA damage in the cells during G1 growth arrest (31, 32), and induces Bax and

Table 1. Summary of gene mutatios in 21 SCCs

Age (Gender)	Predisposing conditions	TNM	*H-Ras*	*p53*	*p16^{INK4a}*	*p14^{ARF}*
76 (M)		I	—	—	CC→T	CC→T
93 (F)		II	—	Y107X, C→G	—	—
79 (M)	Sun exposure	II	—	G244S, C→T	—	—
73 (M)		II	—	Q317X, C→T	—	—
93 (F)		II	—	R249T, C→G	—	—
63 (F)		II	G13R, C→G	—	21bp deletion	21bp deletion
48 (F)	Scar	III	—	Y234X, C→A	R80X, C→T	P94L, C→T
88 (F)	Scar	II	—	E326X, C→A	—	—
68 (M)	Radiation dermatitis	II	—	H178Q, H179Y CC→AT	—	—

p53AIP1 for rendering cells apoptotic if huge DNA damage remains in the cells (33, 34). The cells where the p53 functions are lost would render them resistant to cell growth arrest and apoptosis, and they would be susceptible to the occurrence and accumulation of gene mutations in addition to accelerated cell growth. Since mutations of the *p53* gene have been found in lesions of solar keratosis and apparently histological normal skin (35-38), the mutations might occur at an early stage in the development of SCCs.

4) The INK4a locus

The *INK4a* locus encodes two different tumor suppressor gene products, p16^{INK4a} and p14^{ARF} (39, 40). Each has its own promoter and exon 1, and shares the same exon 2 with different reading frames from each other (39, 40). p16^{INK4a} is involved in the function of cell growth suppression of Rb by binding cyclin dependent kinase 4/6 (CDK4/6) and inhibiting their enzyme activities (41), and p14^{ARF} is involved in the function of cell growth arrest and apoptosis of p53 by binding MDM2 and stabilizing p53 (40). Mutations of the *INK4a* locus have been reported in up to 20% of SCCs (42, 43). They have so far been detected in exon 2, which is common to both *p16^{INK4a}* and *p14^{ARF}* (42, 43). Although expression of the catalytic component of telomerase, hTERT, alone is sufficient for immortalizing human fibroblasts, both Rb/ p16^{INK4a} inactivation and hTERT are required to immortalize human ketatinocytes (44). These findings suggest that Rb/ p16^{INK4a} inactivation might have some relevance to the carcinogenesis in some of SCCs

5) Allelic loss

Tumor suppressor genes have been revealed by the study of hereditary human cancers (45). Although these genes render carriers heterozygous and so appear in pedigrees, as dominantly inherited disorders, they were suggested to be recessive in carcinogenesis (45). "Knudson's two-hit hypothesis" that inactivation of both maternal and paternal alleles should be essential in carcinogenesis is widely accepted. In many instances, one allele is mutated and another allele is lost although there are exceptions. Allelic loss can be detected in tumor tissues by means of PCR assays based on microsatellite sequences, which are widely dispersed throughout the genome and usually highly informative. Although allelic loss in SCCs has been found on many chromosomes, the rates of allelic loss are relative high, in approximately 20% to 40% of SCCs, on 3p, 9p, 9q, 13q, 17p, and 17 q (46-48). The *INK4a* locus, *Rb* gene, and *p53* gene are located on 9p, 13q, and 17p, respectively. Recently, the gene responsible for multiple self-healing squamous epithelioma syndrome (Ferguson-Smith) was mapped on 9q22, which is expected to be identified (49).

THE MULTI-STEP PROCESS IN CARCINOGENESIS

Although many studies regarding chromosomal and genetic abnormalities in SCCs have been reported, the multi-step process in carcinogenesis of SCCs is still unclear. We have been trying to examine the combinatorial function of activation of proto-oncogenes and inactivation of tumor suppressor genes in normal human keratinocytes (Figure 1), especially activation of *H-Ras* and inactivation of the *INK4a* locus, because we found one SCC with both mutations of these two genes (26). Since neither dominant nega-

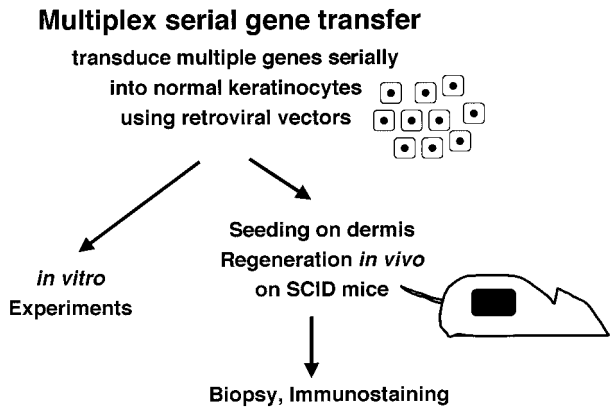

Fig. 1. Experimental procedure.

tive mutant $p16^{INK4a}$ nor $p14^{ARF}$ in the *INK4a* locus were found, activation of CDK4 and inactivation of p53 were substituted for inactivation of $p16^{INK4a}$ and $p14^{ARF}$, respectively. Using high efficiency retroviral transductions in normal human primary keratinocytes (50), we expressed H-RasV12 (an activated mutant H-Ras), CDK4, p53W248 (a dominant-negative mutant p53), and hTERT either singly or in combination and used these cells to regenerate human skin on SCID mice.

A combination of H-RasV12 and CDK4 produced human skin tumors with histologic features of SCC at 7 weeks after grafting, although a combination of H-RasV12 and p53W248 showed no specific effects compared with normal controls (Figure 2) (51). The tumors derived from the cells where both H-RasV12 and CDK4 were transduced (Ras-CDK4 tumors), similar to human SCCs, expressed increased levels of Cyclin D1 and VEGF. Cyclin D1 was necessary but not sufficient for Ras-CDK4 tumors, because a combination of Cyclin D1 and CDK4 failed to induce tumors while an anti-sense Cyclin D1 retrovector that suppressed D1 tissue protein expression abolished Ras-CDK4 tumors (51). In addition, CDK4 synergy with H-RasV12 is dependent on intrinsic CDK4 kinase function because the kinase-dead N158 CDK4 point mutant failed to induce tumors when co-expressed with H-RasV12 (51). These findings identify Ras and CDK4 as capable of converting normal human epidermal tissue into invasive neoplasia and suggest that functional CDK4 and Cyclin D1 is necessary for this process. Thus, it is suggested that a combination of Ras activation and Rb/ $p16^{INK4a}$ inactivation might be crucial to the carcinogenesis at least in a subset of SCCs.

CONCLUDING REMARKS

Squamous cell carcinomas (SCCs) of the skin are one of the most common skin disorders, and sometimes recur or metastasize after surgical excision. Advanced SCCs are often resistant to radiation treatment and chemotherapy. We hope that molecular carcinogenesis of SCCs of the skin would be elucidated in the near future to establish some markers for the prognosis of SCCs and a novel effective therapy for advanced SCCs.

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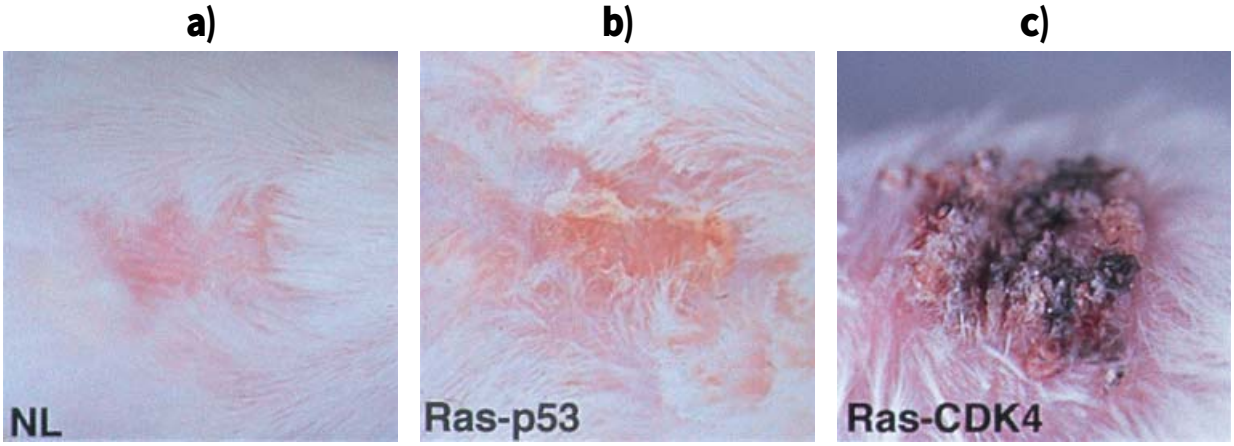

Fig. 2. Clinical features at 7 weeks after grafting. a) green fluorescent protein, b) both of H-RasV12 and p53W248, and c) both of H-RasV12 and CDK4 were transduced into keratinocytes for regenerating human skin on SCID mice, respectively. Note a) the smooth appearance and b) the slightly scaly surface of the skin in contrast to c) the large tumor.

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