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
1) Chromosomal abnormalities

2) Proto-oncogene Ras

3) Tumor suppressor gene p53
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<th>H-Ras</th>
<th>p53</th>
<th>p16&lt;sub&gt;INK4a&lt;/sub&gt;</th>
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4) The INK4a locus

The INK4a locus codes for a family of cyclin-dependent kinase inhibitors (CDKIs) that are involved in the regulation of the cell cycle. INK4a is a tumor suppressor gene, and its loss can lead to the activation of the Ras signaling pathway. The expression of INK4a is regulated by the transcription factor SP1, which is upregulated by the transcription factor E2F1. The loss of INK4a expression leads to the activation of the Ras pathway, which in turn leads to the activation of the transcription factor SP1. This cycle is known as the INK4a-CDK4-SP1 feedback loop.

5) Allelic loss

Allelic loss refers to the loss of one of the two alleles of a gene. This can occur through various mechanisms such as gene deletion, gene amplification, or gene mutation. Allelic loss can lead to the loss of function of the gene, which can have significant consequences for the cell. In the case of the INK4a locus, the loss of one allele can lead to the activation of the Ras pathway, which in turn can lead to the activation of the transcription factor SP1. This can lead to the activation of the cell cycle, which can have significant consequences for the cell.
**Multiplex serial gene transfer**

*transduce multiple genes serially into normal keratinocytes using retroviral vectors*

- Seeding on dermis
- *Regeneration in vivo on SCID mice*
- Biopsy, Immunostaining

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**In vitro Experiments**

Y. Kubo et al.  *Molecular carcinogenesis of SCCs*
The Journal of Medical Investigation  Vol. 49  2002