

# Molecular Mechanisms of Esophageal Squamous Cell Carcinogenesis: Clues to Improve Treatment Outcomes

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Esophageal cancer is highly aggressive and has almost always been associated with a dismal prognosis until recently. Treatment and management have evolved in recent years, with dramatic advances in diagnostic techniques, the implementation of radical esophagectomy with extensive lymphadenectomy, and the development of chemo-radiotherapy.<sup>1-3)</sup> Although the prognosis of patients with this cancer has improved, early detection, as well as prevention, may still be the best way for them to avoid death from this aggressive cancer.

Esophageal cancers are classified into two major histological types; esophageal squamous cell carcinoma (ESCC) and adenocarcinoma. The incidence of these types shows remarkable variations in geographic distribution, which means that each area has particular environmental risk factors for esophageal carcinogenesis. Both cigarette smoking and alcohol consumption are well established risk factors for ESCC.<sup>4,5)</sup> We previously conducted a case-control study examining the risk of ESCC, and found that the odds ratio was 50.1 for people who drank heavily and smoked heavily, compared to those who neither drank nor smoked.<sup>6)</sup> This evidence has, therefore, encouraged us to continue studying the mechanisms underlying the smoking- and alcohol-induced carcinogenesis.

Various genetic abnormalities have also been investigated in ESCC, including alterations in cell-cycle regulation, growth factors and their receptors, and DNA repair systems.<sup>5)</sup> However, direct evidence showing a causal relationship

between cigarette smoking or alcohol consumption and the genetic abnormalities observed in ESCC is insufficient. To elucidate the mechanisms of carcinogenesis, we think that it is useful to examine the relationship of exposure to environmental risk factors with the genetic abnormalities that may cause ESCC.

The mutation spectrum of *TP53* is a useful tool for predicting the role of carcinogenic factors in specific types of cancer. Alterations in the *p53* tumor suppressor gene (*TP53*) have been reported to occur at an early stage of esophageal cancer, indicating the critical role of such alterations in esophageal carcinogenesis.<sup>7)</sup> We have reported that cigarette smoking and alcohol consumption are associated with *TP53* alterations in Japanese patients with both solitary ESCC<sup>8)</sup> and multiple ESCCs.<sup>9,10)</sup> Our mutational analysis indicated that the most frequent mutation in ESCC among Japanese subjects was a G:C to T:A transversion.<sup>11)</sup> These G:C to T:A transversions occur preferentially at defined codons known to be sites of adduct formation for the metabolites of benzo[a]pyrene, a major tobacco carcinogen.<sup>12)</sup> Therefore, it has been suggested that a point mutation, induced by environmental risk factors, might be the “first hit” in *TP53* in these subjects.

A loss of heterozygosity (LOH) is a possible event that may be responsible for the “second hit” in *TP53* mutant cancers. High-resolution fluorescence microsatellite analysis revealed that the LOH in ESCC was observable at a high frequency in multiple microsatellite markers,<sup>13)</sup> thus suggesting that LOH plays a role in esophageal squamous cell carcinogenesis. It has also been found that a close, positive correlation exists between *TP53* hot spot mutations and LOH at the *TP53* locus.<sup>14)</sup> These data suggest that the “two-hit” in *TP53*: (1) a mutation in one allele and (2) LOH through inactivation of the other allele, might be the dominant events in carcinogenesis.

The next question is how the LOH is generated during esophageal squamous cell carcinogenesis. There are several

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Received October 26, 2010; accepted for publication November 9, 2010  
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possible mechanisms involved in LOH.<sup>15)</sup> Generally, chromosomal partial deletion and total chromosomal loss have been regarded as major causes of LOH. Recently, analysis using single-nucleotide polymorphism (SNP) oligonucleotide genomic microarrays has permitted the detection of copy number and copy number-neutral changes.<sup>16)</sup> A copy-number-neutral LOH, from mitotic recombination, mitotic gene conversion, chromosomal deletion with duplication or from other means, has been frequently encountered in solid tumors,<sup>15)</sup> thus indicating that copy-number-neutral LOH can cause loss of an intact allele in *TP53* mutant ESCC. We will continue to elucidate the precise mechanisms of *p53*-associated carcinogenesis.

We, herein, briefly reviewed the current status of the molecular mechanisms involved in esophageal squamous cell carcinogenesis. The prognosis of patients with esophageal cancer is still not ideal. In order to improve the prognosis, early detection and prevention are critical. A better understanding of the causal relationship of risk factors with the genetic abnormalities in carcinogenesis should provide us with valuable clues to help us make improvements in the screening, treatment and prevention of esophageal cancer.

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