Genetic alterations in cervical cancer

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In the pathogenesis of cervical cancer the role of human papillomavirus (HPV) infection is well established. However, other than HPV infection the genetics of cervical cancer remains poorly understood. In the pathogenesis of cervical cancer three major factors are involved, two of which are related to the presence of HPV and the third is the recurrent genetic alterations not linked to HPV infection. Several chromosomal regions with recurrent loss of heterozygosity (LOH) in cervical cancer have been identified. However, the putative tumor suppressor genes located in these chromosomal locations are yet to be identified. Recurrent amplifications have been mapped to the short arm of chromosome 3 in invasive cancer. Microsatellite instability and mutator phenotype do not play a major role in cervical carcinogenesis. As in other cancers, cervical cancer too requires the accumulation of genetic alterations for carcinogenesis to occur. Identification of these alterations could help to provide a better understanding of the disease and thus improve treatment.

Keywords: Cervical cancer, Genetic alterations, Human papilloma virus, Loss of heterozygosity (LOH), Microsatellite instability

Cervical cancer represents the fifth most common neoplasm worldwide and is second only to breast cancer as a cause of cancer mortality in women. According to the national cancer control program for India, it is the most common gynecological malignancy observed among Indian women. The World Health Organization estimates that India alone accounts for 18% of the approximately 900,000 cervical cancer victims each year. Introduction of the Papimicolaou (Pap) testing has reduced the incidence of cervical cancer cases in developed nations with good screening programs. The risk of cervical cancer in developing nations, however, remains high. World wide, an estimated 900,000 women are diagnosed with this malignancy each year. Three quarters of all the cervical cancers in the world occur in developing countries and over 90,000 occur in India alone. Associated mortality is exceeded only by that of breast cancer. In countries such as Nigeria, Liberia and Algeria cervical cancer represents about 30% of all female malignancies. The rate increases up to 50% in India and Korea. Countries with low rates of this disease include Israel, Kuwait, Spain and Ireland. Despite the considerable effort and costly health care resources expended on women with abnormal pap smears, the total contribution of cervical neoplasia to cancer related mortality may be the largest of any neoplastic process and thus still continues to present a significant challenge to the health care community. According to the national cancer control program for India, cervical cancer is the most common malignancy affecting women accounting for nearly 50% of all female malignancies. According to the data available from population based cancer registries at Bangalore, Mumbai, and Madras, the crude incidence rates are at 39.7, 15.4 and 46.5 per 100,000 females respectively. The data from the population based cancer registry functioning in Kolkata from 1997 reveals that of the 8028 cancer cases in females, 1537 were of cancers of the uterine cervix. Cervical cancer, thus, is a major public health problem in India, since not only is the incidence high, but 70% of the cases present with advanced stage of the disease.

Cervical neoplasia
Consistent with an origin in the transformation zone, most cervical cancers are squamous cell carcinomas, with adenocarcinomas and mixed adenosquamous tumors accounting for most of the remainder. Other histological types such as melanomas, sarcomas, and metastatic tumors are very rare. Squamous carcinomas of the cervix result from the progression of preinvasive precursor lesions called “cervical intraepithelial neoplasia (CIN)”.

Multistep pathogenesis of cervical cancer
A hypothetical scheme describing the multistep pathogenesis of cervical cancer is presented in Fig. 1.

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The earliest known step in cervical carcinogenesis is the transmission of human papillomavirus (HPV) infection\textsuperscript{10-14}. Cervical HPV infections can be monitored either by the molecular probes (DNA detection) or by immunohistological methods at microscopic level (low grade squamous intraepithelial lesion, SIL). Majority of the women with molecular evidence of HPV infection develop low grade SIL within four years of viral detection. Most HPV infections disappear within months to a few years of diagnosis. Although low grade lesions also tend to progress to cytologic normalcy, women with low grade SIL progress to high grade SIL with an absolute risk of about 15-25\% over 2-4 years. The three kinds of risk factors postulated to influence the risk of progression to high grade SIL are the same as those established primarily for cervical cancer: viral factors, host factors and environmental cofactors. The invasive potential of high grade SIL is very high and women with high grade SIL are less likely to have disease regression than those with low grade SIL.

**Risk factors for cervical cancer**

There exist several epidemiological reports relating to the various factors associated with a higher risk of developing cervical cancer\textsuperscript{15-17}. These include socio-demographic factors, early age sexual encounters, multiparity, oral contraceptives, failure to use barrier methods of contraception, dietary factors, genetic predisposition, immunosuppression, human papillomavirus infection and high-risk male partners. It has become clear that most cervical neoplasia is attributable in part to HPV infection. HPV infection although being the central unifying risk factor in cervical neoplasia, secondary factors such as smoking, immune response etc too are important. The mechanism involved in the interaction between HPV and host and environmental factors are poorly understood.

**Pathogenesis of cervical cancer**

Three major factors have been identified in the pathogenesis of cervical cancer, two of which are related to the HPV presence: (1) The consequences of HPV DNA integration in the cellular genome; (2) The effects of viral E6 and E7 proteins and (3) The accumulation of cellular genetic damage, not related to HPV, needed for tumor development. It has been reported that exposure to cooking by biofuel in women activate HPV\textsuperscript{18}.

**Consequences of viral DNA integration**—Viral DNA integrated into host genome is found in all cases
of cervical carcinoma\textsuperscript{19}, their metastasis and derivative cell lines\textsuperscript{20}. Cells carrying integrated viral DNA grow better in \textit{vitro}, and integration has been correlated with a poor prognosis, and development of resistance to treatment\textsuperscript{21,22}. The different consequences of HPV integration either on viral or cellular genome are outlined in Table 1.

The site of integration of the HPV DNA in the host chromosome is between is the viral regulatory genes \textit{E1} and \textit{L1}. Upon integration, the viral regulatory genes and the \textit{E6} and \textit{E7} genes are expressed from viral promoters, but with a different regulation, in which host factors might play an important role\textsuperscript{23,24}. From these hybrid viral-cellular aberrant RNA messages, normal \textit{E6} and \textit{E7} proteins are synthesized. The cellular DNA might undergo complex rearrangements or deletions\textsuperscript{25}.

**Effects of viral \textit{E6} and \textit{E7} proteins** — The effects of viral \textit{E6} and \textit{E7} genes have been extensively studied\textsuperscript{26}. These two viral genes are always retained and over-expressed in cervical cancer, and therefore are supposed to contribute to the tumor phenotype. The \textit{E6} and \textit{E7} proteins have been shown to induce immortalization of different cell types, such as fibroblasts\textsuperscript{27} and human keratinocytes\textsuperscript{28}. The \textit{E6} protein interacts with \textit{p53} tumor suppressor protein\textsuperscript{29} theoretically resulting in the functional sequestration of \textit{p53} and targeting it for degradation via the ubiquitin-dependant proteolytic pathway\textsuperscript{30}. The binding of \textit{E6} to \textit{p53} might thus contribute to accumulate additional mutations by allowing progression through the cell cycle before repair, by altering the control checkpoint for DNA integrity in the G1 phase before entering the S phase of the cell cycle. An additional consequence could be the inhibition of apoptosis by the partial effect of \textit{p53} levels and of \textit{pRb}.

The HPV \textit{E7} protein interacts either with \textit{pRb} and the \textit{p107-} or \textit{p130}-related proteins. This interaction dissociates these proteins from the transcription factor E2F. The free E2F factor can activate transcription of genes that will promote cell cycle progression and cell proliferation\textsuperscript{31}, \textit{E7} can also interact with cellular transcription factors such as AP-1\textsuperscript{32}. However, high levels of \textit{E6} and \textit{E7} expression can also be achieved from viral DNA in its extra-chromosomal form, therefore in cervical carcinoma there must be additional factors that contribute to the final tumor phenotype. Furthermore, other oncogenic viruses, such as adenovirus and SV40 have proteins, which interact with \textit{p53} and Rb even more efficiently than HPV proteins, yet they do not induce tumors in humans. The effects of \textit{E6} and \textit{E7} may thus be mediated by an as yet not identified mechanism.

**Inactivation of viral \textit{E2} gene by integration** — The \textit{E2} gene can be expressed in two forms, a complete protein that is a positive regulator, and a protein with only the DNA binding domain that functions as repressor\textsuperscript{33}. The \textit{E2} protein induces cell cycle arrest in the S phase, but allows the replication of viral DNA and at the same time resulting in an increase in cellular DNA. Thus the normal \textit{E2} increases the viral load of the infected cell and might alter its chromosomal number. In integrated viral DNA there is loss of both types of \textit{E2} proteins thus allowing the expansion of cells carrying genetic anomalies. The loss of \textit{E2} confers better growth properties to the cell\textsuperscript{34}. Disruption of \textit{E2} has been shown to be associated with poor prognosis and shortened disease-free survival\textsuperscript{35,36}.

**Table 1 — Characteristics of HPV DNA integration in host genome**

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<tr>
<th><strong>On viral gene structure</strong></th>
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<tr>
<td>Viral DNA is linearized between \textit{L1} and \textit{L2}</td>
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<td>Retention of regulatory region</td>
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<td>Retention of \textit{E6} and \textit{E7} genes</td>
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<td>Inactivation of \textit{E2} transcriptional regulator</td>
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<td>Loss or damage of all other viral genes</td>
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<th><strong>On viral gene expression</strong></th>
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<td>\textit{E6} and \textit{E7} expression modulated by flanking cellular sequences or cellular transcription factors</td>
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<td>\textit{E6} and \textit{E7} transcripts have altered message stability</td>
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<td>\textit{E6} and \textit{E7} expressed from hybrid viral cellular message produce normal proteins</td>
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<th><strong>On cellular genome</strong></th>
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<td>Initial integrations might be random resulting from recombination</td>
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<td>Selected integrations are near fragile sites or oncogenes</td>
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<td>Integration is recurrent at some locations: 8q24 and 12q14-15</td>
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<td>Frequent deletion of cellular sequences</td>
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<td>Altered cellular gene expression as consequence of nearby integration: N-MYC, JUN-B</td>
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\section*{Recurrent cellular genetic alterations in cervical carcinoma}

Cervical lesions must accumulate an increasing number of mutations as they progress towards malignancy and invasion. Therefore the identification of recurrent chromosomal alterations is of utmost importance for the understanding of the biology of this cancer. The recurrent genetic alterations might take several forms such as translocations, point
mutations, amplifications, viral DNA integrations, mutator phenotypes or LOH (loss of heterozygosity). LOH is generally thought of as an intermediate step in the inactivation of tumor suppressor genes such as p53 and Rb that require the inactivation of both alleles in order to display their phenotype. The presence of LOH at a particular chromosomal site therefore indicates the existence of a tumor suppressor(s) in that region.

**LOH in cervical cancer**

LOH studies in cervical cancer have revealed regions on chromosomes 3p, 4, 5p, 6p, 17p, 18 and 19 which are targets for LOH. On chromosome 3p a broad region between 3p12-24 has been found to have recurrent LOH in cervical carcinoma with a frequency of 48%. Several studies agree that within this region there are two subregions where the LOH is concentrated. These two regions are 3p14.2 and 3p21 suggesting that two tumor suppressors are likely to be located in this region. The tumor suppressor gene FHIT located at 3p14.2 is mutated in a wide variety of tumors such as lung and breast. This gene has been specifically studied in cervical cancer. Aberrant transcripts have been identified in cervical cancers, however in normal tissues similar aberrant transcripts were also detected indicating that FHIT exon skipping may not be a specific feature of the tumor cell. In the 3p21 region the affected genes are not known. One of the candidate genes present in this region is the β-catenin gene. Its involvement in cervical carcinoma is not yet known.

LOH studies have identified two regions on chromosome 4 that are frequently involved in this tumor, one of them at 4p16 and the other at 4q21-25. The genes affected have not been identified. The first evidence indicating that chromosome 5 might be implicated in cervical cancer was detected in the HeLa cell line. This cell line has an isochromosome 5p with integrated HPV 18. Cytogenetic studies of cervical cancer specimens have also revealed the presence of isochromosome 5p in a large number of cases.

Several studies have identified a very high incidence of LOH on the short arm of chromosome 6p21.3-p25. Among the candidate altered genes is TNF-α on 6p21.3. LOH within this gene has been observed in cervical cancer. Although there is still no functional evidence for the role of this gene in cervical cancer, its alteration is likely to make tumor cells less sensitive to the induction of apoptosis and therefore promote their survival. Evidence for the involvement of chromosome 11 in cervical cancer came from studies wherein HeLa cells fused with microcells containing human chromosome 11 resulted in the generation of cell hybrids that have lost their tumorigenic properties in nude mice. Two different regions with LOH have been identified in chromosome 11, one on each arm, one at 11p15 and the other at 11q23. The WT1 tumor suppressor gene located at 11p15 has been studied in cervical cancer, however no alterations were found in the gene ruling out its involvement in cervical carcinogenesis. The frequency of LOH at chromosome 17p13.3 is 24% but most often it does not affect the p53 gene located in this region, thus, suggesting the presence of another tumor suppressor in this region. In two other chromosomes, 18 and 19, LOH have been detected in two different regions. In chromosome 18 LOH was detected on regions 18q21 and in a smaller proportion in 18p11. In chromosome 19 LOH has been detected in regions 19q12-13 and 19p13. There is no information regarding the possible genes affected.

**Recurrent point mutations in cervical cancer**

There have been several studies attempting to detect mutations in genes well known to have point mutations in other tumors. Mutations have been detected in H-ras. The p15 and p16 genes, both on chromosome 9p21, are not mutated in cervical cancer. Mutations in the p53 gene have been found at a very low frequency in cervical cancer. Recently the role of mutations in p53, β-catenin, APC, bak and fas genes in cervical carcinomas was investigated in 46 cases of locally advanced cervical carcinomas (33 stage II and 13 stage III). Several mutations—point mutations and deletions—were detected in the p53, APC, β-catenin and Fas genes. The p53 genes were mutated in 19% (9/46) of the cases. There was a significant difference in stage II and III between wild type and mutant p53 patients (P<0.05) with p53 mutations more common in advanced stage cases. It was found that APC and β-catenin genes were mutated indicating a role for the Wnt signaling pathway in cervical carcinogenesis. The pro-apoptotic gene bak too was mutationally inactivated in 12% of the cases. Mutations of the fas gene were uncommon in the study.

**Recurrent amplification and chromosome gain**

Gene amplification and chromosome gain are two different mechanisms by which a tumor cell can increase a gene dosage. Gene amplification has not
been commonly seen in cervical cancer. In a study of 22 protooncogenes in 50 primary untreated squamous cell carcinomas of the uterine cervix, only 12 were found to have some amplification. Five fold or larger amplifications were found for MYCL1, SEK, CCND1, BCLI, GLL and ERBB2 genes. Gain of chromosome 3q has been shown to occur in dysplasia and more frequently in invasive carcinoma. The smaller common region of amplification has been reduced to band 3q24-28.

**Microsatellite instability and mutator phenotype**

Alterations in DNA repair genes result in the accumulation of mutations, some of which are important for tumor development. DNA repair genes belong to a family of genes designated as caretaker genes. The phenotype of mutations in this type of genes is detected by microsatellite instability (MI). The cell with a defect in any of these genes will invariably progress to develop a cancer. MI has been detected in a very small subset of cervical cancers indicating that it is not a feature of cervical carcinogenesis.

**Other factors: The role of the HLA system**

In the pathogenesis of HPV-infected cells there are several aspects that appear to be a consequence of the host immune response, such as reversion of lesions. The study of HLA haplotypes in a case control study has demonstrated that certain class II haplotypes are over represented. This observation might mean that certain haplotypes might be more efficient than others in triggering a host immune response that will eliminate the HPV-infected cells. The over represented HLA alleles might be those that are less effective in triggering a response against the infected cell. Thus the HPV infection starts to skew the representation of HLA alleles as the disease progresses. This might be a reflection of the host immune response to the presence of HPV. Therefore, the HLA haplotype is an important factor at the initial stage of the disease because it influences the point between reversion and progression of the HPV-induced lesion. Furthermore, in CC there is a down regulation of class I antigens in tumor cells, thus minimizing the consequences of a possible anti-tumor cell-mediated response by the host immune system.

**Radiotherapy and prognostic factors**

The main treatment for advanced stage uterine cervical cancer has been radiation therapy. However, the five-year survival rate is 40-60%. That rate indicates that some tumors respond to irradiation therapy effectively and others don’t. The inability of radiation therapy to locally control the growth of malignant tumors is still a major clinical problem leading to failure of the overall treatment program. It is of practical importance for the clinician to know if an individual’s tumor is particularly sensitive or resistant to radiation therapy, so that other treatment modalities, possibly recently developed effective chemotherapeutic regimens could be employed as an alternative. The wide variation in tumor response to radiation therapy might be explained by differences in tumor cell-death inducing effects or other factors influencing the radiosensitivity of the tumor. By understanding the mechanisms that govern the sensitivity of malignant cells, it may be possible to improve the probability of local tumor control. Various factors contributing to tumor radiosensitivity have been identified in experimental studies such as oncogene activation, tumor suppressor gene mutations, growth factor and cytokine signal transduction and apoptosis. Oncogene activation and tumor suppressor mutations are found predominantly in malignant tumors whereas growth factor and cytokine signal transduction and apoptosis occur in normal development, tissue response to injury, inflammation and malignant tumors.

Despite the rapid advances in knowledge of cellular functions that affect radiosensitivity, it is still not possible to account for most of the clinically observed heterogeneity of tumor responses to radiotherapy nor can we accurately predict which individual tumors will be locally controlled. Several studies have attempted to identify prognostic factors for radiotherapy in cervical cancers: some of them include oncogene activation, tumor suppressor inactivation, spontaneous apoptosis, radiation-induced apoptosis. However none of the studies have been able to conclusively identify any prognostic factor. In our recent study, no correlation was found between mutations in the p53, β-catenin, bak genes and response to radiotherapy.

**Concluding remarks and future perspectives**

Cervical cancer is the terminal manifestation of a multistep pathogenic process. The initial event in this process is HPV infection which can be detected even at the early stages with molecular probes and histopathological techniques as low grade squamous intraepithelial lesions. These lesions can disappear to
cytologic normality or progress upon influence of several risk factors to high grade grade squamous intraepithelial lesions and invasive cancers. Limiting exposure to the influencing risk factors is an important step in preventing these cancers.

As HPV is the early causative factor for this disease, one of the ways of preventing this disease will be by inhibiting the HPV infection. Identification of the cellular receptors for this virus and blocking these sites to prevent the initial stages of infection would be a major step in prevention of this disease. Another approach in preventing this disease will be by immunizing to have antibodies against HPV. Identification of viral antigens and cloning specific viral genes for these antigens would go a long way in this direction.

The next step in cervical cancer research would be the identification of the specific genes on different chromosomal regions involved in cervical carcinogenesis and determining the role they play in tumour progression. This knowledge would help to establish markers for tumour progression. Better understanding of the genetics of the disease would help devise better treatment strategies and improve patient care.

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