Molecular Biology Developments in Head and Neck Cancer

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Molecular biology of carcinogenesis

The common head and neck cancers in Hong Kong are nasopharyngeal carcinoma (NPC), head and neck squamous cell carcinoma of oral cavity, oropharynx, hypopharynx and larynx (HNSCC) and thyroid carcinoma. The aetiology, pathology and treatment response differ among these three common head and neck cancers. Their underlying genetic aberrations and carcinogenesis pathways are also different.

The development of cancer involves multiple genetic abnormalities. A stepwise carcinogenesis process is sometimes found in HNSCC in which 5-20% pre-malignant dysplastic leukoplakia and erythroplakia lesions will develop into carcinoma in-situ and invasive cancer. Field cancerisation is also commonly observed in patients with HNSCC. There are already presence of aberrant genetic abnormalities in the apparently normal looking mucosa in upper aerodigestive tract due to wide-field carcinogenic effects of chronic smoking, drinking and betal leave chewing of HNSCC patients. Multiple upper aerodigestive tract carcinomas can develop in 10-20% of HNSCC patients in their life time.

In the early stage of carcinogenesis process, there are increased cellular proliferations and reduction of apoptosis (programmed cell death). Further development of invasive carcinoma will require the proliferation of blood vessels to supply sufficient nutrients to growing tumours (angiogenesis), breaking down of surrounding tissues for local invasion, lymphangiogenesis for regional nodal metastasis and reduced cellular adhesion for distant metastasis. These malignant cellular biologic properties are dictated by specific gene activation or inactivation. Aberrant upregulation or activation of gene function can be due to molecular mechanisms of gene overexpression (increased transcription), amplification (multiplication of gene copy), translocation (transfer of a gene to another chromosome), down-regulation of miRNA (reduced breakdown of RNA and reduced inactivation of protein production). Downregulation or inactivation of gene function can be due to molecular mechanisms of mutation (dysfunctional protein), deletion (absence of the gene), hypermethylation of gene promoter (inactivate gene transcription at its starting site) or overexpression of miRNA (increased breakdown of RNA and inactivate protein production). The genes responsible for the carcinogenesis of common head and neck cancers are shown in Table 1.

Molecular markers for screening early nasopharyngeal carcinoma

There is lack of consistent early symptom in most head and neck cancers and 50% patients in our clinic are already in stage III and IV at the time of presentation. Molecular screening of early cancers in high risk population is an important issue of current research.

DNA, protein and RNA materials are released from cancer cells either by active secretion from living cells or liberated from disintegrated cells upon cell death. These genetic materials can be detected in local tissues, exfoliated cells or local body fluids. These cellular materials are also absorbed into the systemic circulation. The development of technology has enabled us to detect the presence of a few copies of aberrant DNA materials using polymerase chain reaction (PCR) in tissue, exfoliated cell, local body fluid and peripheral blood.

Hong Kong has the highest incidence of NPC in the world. Screening of NPC has been carried out for decades using serum EBV IgA level as tumour marker. The sensitivity of detection of early stage I-II NPC is 81% for the serum EBV VCA or EBNA1 IgA antibodies. The EB virus proliferates inside the NPC cancer cells and the EB virus DNA is absorbed into systemic circulation. The plasma EBV DNA can be detected by using PCR method. The sensitivity of plasma EBV DNA is 90% for early stage I-II NPC using 60 copies of EBV DNA per ml of plasma as cut off reference. There are many aberrantly methylated genes for NPC and these methylated DNAs can also be used as specific plasma markers for detection of NPC. The sensitivity is however much lower than EBV DNA and requires up to 4 markers including E-cadherin, DAPK, p16, RASSF1A to enhance its sensitivity to 80-90%.

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It may be difficult to enhance the sensitivity of tumour markers in blood because of the tremendous dilution factor by the 5000 ml of blood for the small quantity of absorbed genetic materials from early stage NPC. The alternative approach is to retrieve small quantity of exfoliated cancer cells and their genetic materials directly from nasopharynx non-invasively using brush or swab. The nasopharyngeal swab EBV DNA has sensitivity of 87-96% and specificity of 96-99% for primary NPC. The serum EBV DNA has significant value for prediction of distant metastasis, its sensitivity for detection of local and
Targeted molecular therapy

With increasing knowledge of the genetic abnormalities of cancers, there are high hopes for the development of targeted molecular therapy of cancers. Although there is still no well-proven successful molecular therapy available in the market for head and neck cancers, some of the clinical trial results are worth noting.

Among the many targeted therapy in clinical trials, anti-EGFR targeting the overexpressed EGFR of head and neck cancers is most promising. EGFR regulates multiple cellular functions including cell proliferation, differentiation, apoptosis, cell motility and angiogenesis. Anti-EGFR can be achieved by using monoclonal antibody (Cetuximab) or tyrosine kinase inhibitor (Gefitinib, Erlotinib). The anti-EGFR monoclonal antibody competitively binds to the extracellular domain of the receptor preventing its activation by other growth factors. The EGFR tyrosine kinase inhibitor binds to the intracellular domain of the receptor to block its downstream signaling cascade effectors. A phase III randomised trial has shown that combined Cetuximab and radiotherapy is better than radiotherapy alone for primary HNSCC (median survival 49 versus 29 months). Phase III randomised study has shown that combined Cetuximab and cisplatin has improved response than cisplatin alone for recurrent or metastatic HNSCC, but there is no survival benefit. Phase II study of gefitinib (Iressa) alone has shown only modest response of 10% for recurrent or metastatic HNSCC. Anti-EGFR is well tolerated and toxicity is limited to cutaneous reaction and diarrhea.

There are many other potential molecular therapeutic targets that have already entered into various phases of clinical trials for head and neck cancers including demethylating therapy to reactivate the tumour suppressor genes and anti-angiogenesis therapy to inhibit growth of cancers. Since cancers have multiple genetic abnormalities, multi-targeting therapy is perhaps necessary to enhance the successful cure or palliation. Further research studies are necessary to evaluate the role of various molecular therapies for head and neck cancers.

Table 1. Comparison of genetic abnormalities of common head and neck cancers

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<tr>
<th>Cancer biologic properties</th>
<th>Cisplatin plus placebo</th>
<th>Cisplatin plus cetuximab</th>
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<tr>
<td>Prognostic significance</td>
<td>Increased proliferation and reduced apoptosis</td>
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<tr>
<td>Prognostic significance</td>
<td>Hypermethylation of p16, p14, RASSF1A &amp; RASSF1C, DAPK, RIZ1, MLI1, HIN1, THBS1, mutation</td>
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<td>Prognostic significance</td>
<td>Reduced cellular adhesion</td>
<td>Reduced cellular adhesion</td>
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<td>Prognostic significance</td>
<td>Hypermethylation of E-cadherin, hemidesmosome</td>
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<td>Prognostic significance</td>
<td>Increased invasion</td>
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<td>Prognostic significance</td>
<td>MMP-2,9</td>
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References


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